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ORIGINAL RESEARCH

Identification of the first signs or symptoms in different spondyloarthritis subtypes and their association with HLA-B27: data from REGISPONSER and RESPONDIA registries

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ABSTRACT

Objective To describe and analyse the initial symptoms attributable to patients with spondyloarthritis (SpA) and their association with HLA-B27 status.

Methods This was an observational, cross-sectional and multicentre study with patients who fulfilled the European Spondyloarthropathy Study Group criteria for SpA from the Registry of Spondyloarthritis of Spanish Rheumatology (REGISPONSER) and Ibero-American Registry of Spondyloarthropathies (RESPONDIA) united registries. Differences in the first sign(s) or symptom(s) were compared across diagnoses and between HLA-B27 status. The diagnostic delay between patients who start the disease with musculoskeletal manifestations (MMs) and extra-MMs (EMMs) was compared.

Results A total of 4067 patients were included (2208 from REGISPONSER and 1859 from RESPONDIA) (ankylosing spondylitis (AS): 68.3%, psoriatic arthritis (PsA): 19.9%, undifferentiated SpA: 11.8%). Overall, 3624 (89.1%) patients initiated the disease with MMs and 443 (10.9%) with EMMs. Low back pain (61.7%) and lower-limb arthritis (38.5%) were the most frequent initial symptoms. In AS patients, the absence of HLA-B27 seems to be related to an increase in the probability of starting the disease with cervical pain and peripheral manifestations. In PsA, the onset of arthritis and psoriasis was more prevalent in HLA-B27-negative patients, while initiation with axial manifestations was more predominant in HLA-B27-positive patients. The diagnostic delay was longer in patients with initial MMs than in those with EMMs (7.2 (34.8) vs 4.5 (7.6) years, respectively).

Conclusion In this SpA population, MMs were the most prevalent initial symptoms, with differences across diagnoses and depending on the presence of the HLA-B27 antigen.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early diagnosis of spondyloarthritis (SpA) is crucial for minimising the impact of the disease. However, this early diagnosis can be difficult, as there is no agreement on what constitutes the initial symptom.

WHAT THIS STUDY ADDS

⇒ This study suggests that SpA usually starts with musculoskeletal manifestations, which differ based on the diagnosis and HLA-B27 status.

⇒ The diagnostic delay was longer in patients with musculoskeletal manifestations as the first symptom.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study demonstrates that SpA can start with a huge variety of symptoms.

⇒ Clinicians and general practitioners should be aware of the need to accurately recognise rheumatic symptoms due to the longer diagnostic delay in patients who initiate the disease with musculoskeletal manifestations.

INTRODUCTION

Spondyloarthritis (SpA) encompasses a heterogeneous group of inflammatory rheumatic disorders characterised by axial skeleton and sacroiliac joint involvement, peripheral symptoms, extra-articular manifestations (psoriasis, uveitis and inflammatory bowel disease (IBD), among others), and a strong association with the HLA-B27 antigen. Classically, SpA patients have been categorised into several subtypes depending on the presence of peripheral and/or extramusculoskeletal manifestations (EMMs), such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), IBD-associated SpA (IBD-SpA), reactive

arthritis (ReA), undifferentiated SpA (u-SpA) and juvenile SpA (Juv-SpA).[1 2]

Despite the increase in knowledge about this disease, studies have established a mean delay of 2–6 years between symptom onset and the definitive diagnosis of SpA.[3] Early diagnosis of SpA is important to minimise disease burden by establishing early treatment.[4] Reasons for diagnostic delay are multifactorial, one of which is the difficulty of identifying SpA at an early stage.[5 6] Recently, the Assessment of Spondyloarthritis International Society (ASAS) defined 'early axial SpA' as patients with a diagnosis of axial SpA with a duration of axial symptoms less than or equal to 2 years.[7] However, this definition has only been developed for axial SpA because of the low rate of studies exploring other types of SpA.[8] The definition for early SpA should imply the correct identification of the initial symptom of SpA. However, what should we consider as an initial symptom? There is currently no consensus on whether only musculoskeletal manifestations (MMs) or EMMs should be considered the onset in the whole spectrum of SpA. A matter of debate is whether to consider the appearance of uveitis or psoriasis as the initial symptom of SpA or only consider that SpA begins with the appearance of MMs. In addition, we do not know how the onset of symptoms differs depending on the diagnosis and presence of the HLAB-27 antigen.

Our starting hypothesis was that MMs (inflammatory low back pain, arthritis, enthesitis or dactylitis) is the most frequent form of disease onset and that this may vary depending on the diagnosis and the presence of HLA-B27 antigen. However, we believe that the disease may also begin with EMMs and should take these factors into account and screen for MMs in those patients who present for early diagnosis.

The purpose of this study was to: (A) describe the initial sign or symptom (either MMs or EMMs) in the different SpA subtypes based on the clinical diagnosis by the rheumatologist; (B) describe the initial symptom stratified by the clinical diagnosis and by the presence of HLA-B27 and determine if HLA-B27 may influence the form of onset of the disease; (C) quantify the mean time that separates the appearance of the EMMs from the MMs among patients who start the disease with EMMs; (D) compare the diagnostic delay between patients who start the disease with EMMs or MMs and (E) analyse the clinical factors associated with different forms of initiation.

PATIENTS AND METHODS

Design

This was an observational, cross-sectional and multicentre study that included patients from the REGISPONSER (Registry of Spondyloarthritis of Spanish Rheumatology) and RESPONDIA (Ibero-American Registry of Spondyloarthropathies) registries. Despite being a cross-sectional registry, both REGISPONSER and RESPONDIA recorded the onset date of each symptom, so that temporal sequence could be determined, and they shared the same variables so that the two registries could be united.

Patients

REGISPONSER is a national and multicentre registry that incorporated consecutive SpA patients who fulfilled the European Spondyloarthropathy Study Group (ESSG)[9] criteria for SpA between March 2004 and March 2007. Thus, patients could have a diagnosis according to their rheumatologist of AS, PsA, IBD-SpA, ReA, u-SpA or Juv-SpA. The study was conducted by Spanish Group for the Study of Spondyloarthritis of the Spanish Rheumatology Society with 31 participating centres. More information about the design, sampling and recruitment of patients is detailed in a previous publication.[10]

RESPONDIA has a similar design and shares the case report form and all of the variables studied with REGISPONSER.[11] It was conducted between 2006 and 2007. Thirty-three centres from eight Latin American countries participated in this registry. The inclusion criteria were the same as in REGISPONSER. Consecutive patients with SpA according to the criteria of the ESSG were included.

The overall population included 4410 patients (2366 from REGISPONSER and 2044 from RESPONDIA). However, for this specific analysis, we focused on patients with a diagnosis of AS, PsA or u-SpA with the aim of having a more homogeneous population and because these were the more prevalent groups, resulting in 4067 patients (2208 from REGISPONSER and 1859 from RESPONDIA) (online supplemental figure 1). The AS and u-SpA nomenclature was maintained because it was the one used in both registries at the time that they were carried out.

Collected variables

From the REGISPONSER and RESPONDIA registries, we collected the following variables:

1. Sociodemographic data: age, sex and race.
2. Data on symptom onset: symptoms that have appeared in the patient throughout their disease (inflammatory low back pain, buttock pain, coxitis, cervical pain, enthesitis, dactylitis, psoriasis, lower and upper-limb arthritis, uveitis and IBD). Participants'answers to the question 'indicate the first sign or symptom attributable to the disease' were recorded, as well as the year of the first MMs and EMMs, allowing us to determine the first symptom(s) in each patient. It must be considered that patients could start the disease with more than one symptom. Patients who started the disease with MMs and EMMs at the same time were considered as starting with EMMs, with the aim of comparing them with those who started the disease only with MMs.
3. Clinical data: diagnosis according to the rheumatologist (AS, PsA and u-SpA), presence of HLA B27 antigen, family history of SpA, C reactive protein and erythrocyte sedimentation rate were collected. Disease duration (years between the date of the SpA diagnosis

and study visit) and symptom duration (years between the date of symptom onset and the study visit) were recorded. Finally, we defined diagnostic delay as the difference between symptom duration and disease duration.

The Bath Ankylosing Disease Activity Index[12] and Ankylosing Spondylitis Disease Activity Score[13] were collected in all patients to evaluate disease activity. Function was evaluated through the Bath Ankylosing Spondylitis Functional Index,[14] and structural damage was evaluated using the Bath Ankylosing Spondylitis Radiology Index for the spine and total axial skeleton (which includes the spine and sacroiliac joints).[15]

4. Treatment: Data from concomitant and/or previous treatments were analysed, such as the use of oral corticosteroids, non-steroidal anti-inflammatory drugs, conventional disease-modifying anti-rheumatoid drugs (DMARDs) (sulfasalazine, methotrexate or leflunomide) and biological DMARDs (anti-TNF treatment).

Statistical analysis

First, a descriptive analysis of the clinical and sociodemographic characteristics of the two populations included in the study (REGISPONSER and RESPONDIA) and in the whole population was carried out. Descriptive data are expressed as the mean and SD for quantitative variables and absolute and relative frequencies for qualitative variables.

Second, we evaluated the percentage of patients who started the disease with each one of the symptoms in the overall population and per diagnosis. Subsequently, within each diagnosis, the prevalence of each onset symptom was stratified based on the HLA-B27 status (among patients with available data for HLA-B27 antigen) to evaluate whether the presence of this antigen influences the onset of the disease. Differences in the first symptom across diagnosis and between HLA-B27 carriers were compared using the χ^2/Fisher's exact test.

Among the patients who started the disease with EMMs, we quantified the average time that separates the appearance of the different EMMs from the MMs, and we compared this average between HLA-B27-positive and HLA-B27-negative patients using the Mann-Whitney U test.

Next, we compared the diagnostic delay between patients who started the disease with EMMs versus those starting with MMs using the Mann-Whitney U test to evaluate whether the initiation of the disease with EMMs led to a shorter diagnostic delay. In addition, cumulative probability plots were used to display the cumulative distribution in diagnostic delay stratified by the first symptom (EMMs or MMs).

Finally, factors associated with the most prevalent initial symptom were evaluated using χ^2/Fisher's exact tests for qualitative variables and Student's t-test/Mann-Whitney U tests for continuous variables.

All tests were two tailed, and a $p<0.05$ was considered to indicate significance. Data were collected, processed and analysed using IBM SPSS Statistics V.25 (SPSS) and RStudio V.4.0.4.

RESULTS

Description of the population

A total of 4067 patients were included in the analysis (2208 from REGISPONSER and 1859 from RESPONDIA), including 68.3% AS (n=2778), 19.9% PsA (n=808) and 11.8% u-SpA (n=481). Descriptions of the clinical and sociodemographic characteristics of the two populations included in this study (REGISPONSER and RESPONDIA) are presented in table 1. A total of 67.2% of the patients were men, their mean age was 46.9 (14.7) years, and their mean age of onset was 27.1 (36.4) years. The majority of the population was HLA-B27 positive (69.5%).

Initial sign or symptom

Overall, 3624 (89.1%) patients initiated disease with MMs, 251 (6.1%) patients started disease with both MMs and EMMs at the same time, and 192 (4.7%) patients started disease with only EMMs. The prevalence of the initial symptom in the overall population was as follows (in descending order): low back pain (61.7%), lower-limb arthritis (38.5%), buttock pain (35.8%), upper-limb arthritis (21.1%), cervical pain (20.4%), psoriasis (15.3%), coxitis (11.2%), dactylitis (8.3%), uveitis (2.7%) and IBD (2.2%) (figure 1).

The percentage of patients who started the disease with each symptom according to the diagnosis is represented in figure 1.

Initial sign or symptom according to HLA-B27

A total of 2703 patients had available data for HLA-B27 antigen status (online supplemental figure 1). The association between HLA-B27 antigen and disease onset according to diagnosis is represented in table 2. In AS patients, the absence of HLA-B27 seems to be associated with an increase in the probability of initiating the disease with cervical pain (24.2% vs 15.6%), peripheral manifestations (lower-limb arthritis, upper-limb arthritis, enthesitis and dactylitis), psoriasis (8.5% vs 1.8%) and IBD (4.2% vs 1.4%) in comparison with HLA-B27-positive patients. In PsA, the initiation of upper-limb arthritis (61% vs 38.4%) and psoriasis (62.1% vs 37%) was more prevalent in HLA-B27-negative patients, while the initiation of low back pain (22.1% vs 38.4%) and buttock pain (13.6% vs 28.8%) was more prevalent in HLA-B27positive patients.

Time separating EMMs from MMs

In patients who initiated the disease with EMMs (N=443) (either EMMs and MMs at the same time (n=251) or only EMMs as the first symptom(s) (n=192)), the average time that separated the appearance of EMMs from MMs was 11.5 (9.2) years. The shortest average time that separated the appearance of EMMs from MMs was in the case of uveitis (5.8 (6.2) years), followed by IBD (6.2 (6.7) years) and finally psoriasis (11.8 (9.2) years). Patients with

Table 1 Demographic and clinical characteristics of the of the two populations included in the study: REGISPONSER and RESPONDIA

Variables	Total N=4067, n (%)	REGISPONSER N=2208, n (%)	RESPONDIA N=1859, n (%)
Sex (male)	2732 (67.2)	1502 (68)	1230 (66.2)
Age, years (SD)	46.9 (14.7)	47.6 (13.2)	43.8 (17.7)
Race (Caucasian)	2151/2991 (71.9)	1132/1148 (98.6)	1019/1843 (55.3)
Disease duration, years (SD)	16.5 (12.5)	18 (12.8)	12.6 (10.7)
Diagnostic delay, years (SD)	6.6 (31.1)	6.4 (8.6)	7 (47.7)
Inflammatory low back pain	3388/4054 (83.6)	1809/2205 (82)	1579/1849 (85.4)
Lower-limbs arthritis	2201/4054 (54.3%)	1020/2201 (46.3)	1181/1853 (63.7)
Enthesitis	1681/4023 (41.8)	661/2191 (30.2)	1020/1832 (55.7)
Dactylitis	619/4046 (15.3)	251/2197 (11.4)	368/1849 (19.9)
Psoriasis	1068/4043 (26.3)	544/2198 (24.7)	524/1845 (28.4)
Uveitis	682/4031 (16.9)	353/2191 (16.1)	329/1840 (17.9)
Buttock pain	2071/4030 (51.4)	1158/2182 (53.1)	913/1848 (49.4)
IBD	158/4040 (3.9)	96/2198 (4.4)	62/1842 (3.4)
SpA family history	691/3839 (18)	369/2029 (18.2)	322/1810 (17.8)
HLA-B27 negative	824/2703 (30.4)	536/1946 (27.5)	345/935 (36.8)
Sacroilitis	3031/4029 (75.2)	1671/2196 (76.1)	1360/1833 (74.2)
CRP mg/dL, mean (SD)	8.7 (15.9)	8.5 (13.3)	9.2 (19.7)
ESR mm/hour, mean (SD)	20.7 (17.9)	18 (15.7)	24.2 (19.9)
BASDAI, mean (SD)	4.1 (2.4)	4 (2.3)	4.3 (2.4)
BASRI total, mean (SD)	5.8 (4.4)	5.3 (4.3)	6.5 (4.4)
BASRI spine, mean (SD)	5 (3.6)	4.7 (3.6)	5.5 (3.5)
BASFI, mean (SD)	3.8 (2.8)	3.5 (2.6)	4.2 (2.8)
ASDAS, mean (SD)	2.5 (1.1)	2.6 (1)	2.5 (1.2)
NSAIDs	2405/3080 (78.1)	1640/2193 (74.8)	765/887 (86.2)
cDMARDs (ever)	1175/3048 (38.5)	612/2161 (28.3)	563/887 (63.5)
bDMARD (ever)	424/3030 (14)	332/2147 (15.5)	92/883 (10.4)

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; bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; REGISPONSER, Registry of Spondyloarthritis of Spanish Rheumatology; RESPONDIA, Ibero-American Registry of Spondyloarthropathies.

negative HLA-B27 had more years of separation between the EMMs of the MMs ones 12.0 (9.9) vs 7.9 (7.1) years in comparison with HLA-B27 positives.

Association between the first symptom and the diagnostic delay

Overall, the diagnostic delay was longer in patients with initial MMs than in those with initial EMMs (7.2 (34.8) vs 4.5 (7.6) years, p=0.000). Similarly, in patients with AS, the diagnostic delay was longer in patients who initiated the disease with an MMs in comparison with those who initiated with an EMMs (8.3 (39.1) vs 6 (8.6) years, p=0.028). Conversely, in patients with PsA, the diagnostic delay was longer in patients who initiated the disease with an EMMs (2.67 (4.7) vs 3.91 (7) years, p=0.009). Finally, no differences were found in patients with u-SpA. Figure 2 shows the cumulative probability plots representing the diagnostic delay according to whether the first symptom was MMss or EMMs.

Factors associated with different onset symptom

Back pain versus buttock pain as initial symptom

In the population, factors associated with low back pain versus buttock pain (table 3) as the first symptom were male sex (71.6% vs 64.8%), lower-limb arthritis (42.9% vs 33.7%) and uveitis (20.9% vs 15.2%).

Cervical pain versus low back pain as initial symptom

Factors associated with cervical pain versus low back pain (table 4) as the first symptom in the overall population were cutaneous psoriasis (38.5% vs 14.4%), negative HLA-B27 (44.5% vs 24.1%) and peripheral involvement

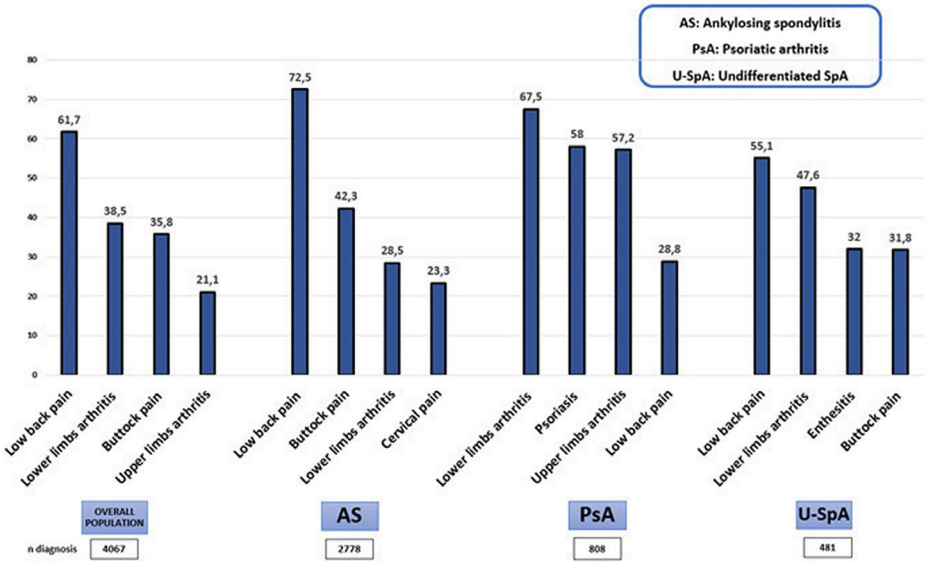

Figure 1 Description of the first symptoms according to the SpA diagnoses. SpA, spondyloarthritis.

(arthritis (54.8% vs 39.2%) and dactylitis (25.9% vs 9.8%)).

Upper-limb versus lower-limb arthritis as the initial symptom

Finally, factors associated with upper-limb arthritis versus lower-limb arthritis (online supplemental table 1) as the first symptom were female sex (48.7 vs 39.2%), cutaneous psoriasis (66.4% vs 30.8%), HLA-B27 negativity (63.6% vs 33%) and absence of axial symptoms (low back pain (50.9% vs 75.4%) and buttock pain (28.8% vs 44.6%)).

DISCUSSION

In this study, we aimed to identify and characterise the first symptoms of SpA for an early diagnosis of the disease. This study suggests that MMs (ie, low back pain, buttock pain and lower-limb arthritis) are the initial symptom of SpA in the majority of cases, with differences across diagnoses and depending on the presence of the HLA-B27 antigen. In addition, our results may imply that the initiation of the disease with MMs led to a

Table 2 Influence of the HLA-B27 gene on disease onset according to diagnosis

	AS*			PsA*			u-SpA*		
First symptom	HLA-B27+ N=1579, n (%)	HLA-B27- N=426, n (%)	P value	HLA-B27+ N=73, n (%)	HLA-B27- N=272, n (%)	P value	HLA-B27+ N=227, n (%)	HLA-B27- N=126, n (%)	P value
Low back pain	1151 (72.9)	319 (74.9)	0.410	**28 (38.4)**	**60 (22.1)**	**0.005**	126 (55.5)	71 (56.3)	0.879
Buttock pain	676 (42.8)	193 (45.3)	0.357	**21 (28.8)**	**37 (13.6)**	**0.002**	69 (30.4)	45 (35.7)	0.306
Cervical pain	**246 (15.6)**	**103 (24.2)**	**0.000**	11 (15.1)	29 (10.7)	0.296	17 (7.5)	12 (9.5)	0.505
Coxitis	**137 (8.7)**	**59 (13.8)**	**0.001**	**8 (11)**	**9 (3.3)**	**0.007**	7 (3.1)	5 (4)	0.761
Lower-limb arthritis	**360 (22.8)**	**121 (28.4)**	**0.016**	45 (61.6)	190 (69.9)	0.181	95 (41.9)	50 (39.7)	0.692
Upper-limb arthritis	**91 (5.8)**	**51 (12)**	**0.000**	**28 (38.4)**	**166 (61)**	**0.001**	31 (13.7)	27 (21.4)	0.059
Enthesitis	**192 (12.2)**	**82 (19.2)**	**0.000**	15 (20.5)	41 (15.1)	0.260	57 (25.1)	37 (29.4)	0.386
Dactylitis	**32 (2)**	**23 (5.5)**	**0.000**	14 (19.2)	47817.3)	0.706	16 (7)	8 (6.3)	0.803
Psoriasis	**29 (1.8)**	**36 (8.5)**	**0.000**	**27 (37)**	**169 (62.1)**	**0.000**	1 (0.4)	3 (2.4)	0.132
Uveitis	49 (3.1)	7 (1.6)	0.105	1 (1.4)	0 (0)	0.212	10 (4.4)	4 (3.2)	0.777
IBD	**22 (1.4)**	**18 (4.2)**	**0.000**	0 (0)	1 (0.4)	1	**2 (0.9)**	**7 (5.6)**	**0.012**

Statistical significance based on $\chi 2$ or Fisher's exact test.
Bold values: significant differences.
*Patients with available data for HLA-B27 status.
IBD, inflammatory bowel disease.

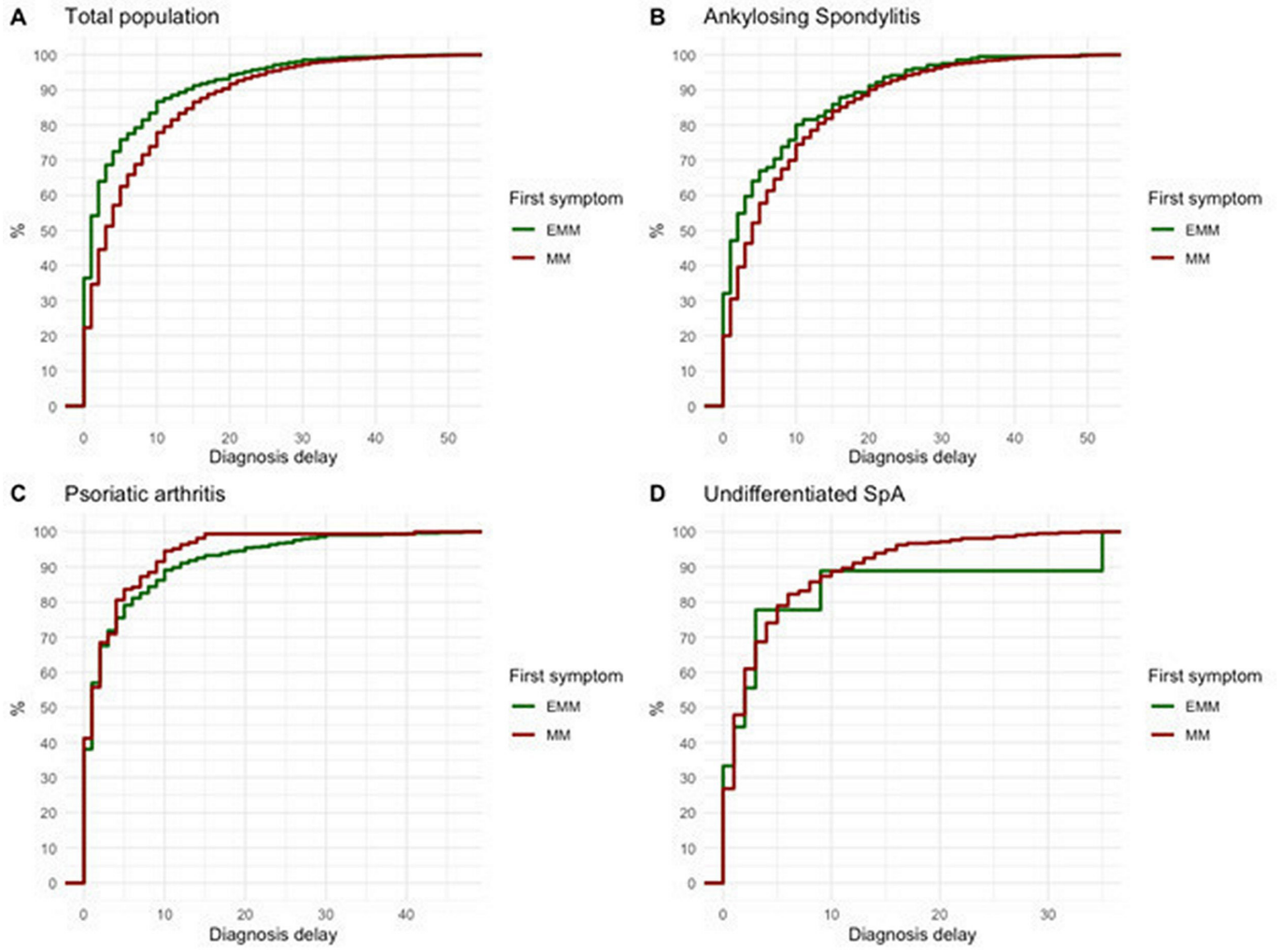

Figure 2 Probability plot showing the cumulative distribution of the diagnostic delay according to the first symptom (musculoskeletal or extramusculoskeletal). The green line represents patients who initiated the disease with extramusculoskeletal manifestations (EMM), and the red line represents patients who initiated the disease with a musculoskeletal manifestation (MM). The horizontal axis represents the diagnostic delay, and the vertical axis represents the cumulated percentage of patients. SpA, spondyloarthritis.

longer diagnostic delay compared with EMMs as initial symptoms.

Among all the onset symptoms, low back pain stands out as the most prevalent in our population. Its higher frequency can be explained by the fact that most patients have an AS diagnosis whose characteristic onset symptom is low back pain and that it is the central symptom of all subtypes of SpA. Low back pain was also the initial onset symptom in a previous study conducted in the REGISPONSER-early cohort,[6] with patients whose inclusion criteria were a disease course of ≤2 years from the onset of symptoms or the appearance of the first sign of disease. One difficulty in the early diagnosis of SpA is the high frequency of low back pain in the general population. It is necessary to look for features of SpA in those patients with chronic low back pain that, if present, increase the suspicion of SpA.[16]

When stratifying according to diagnosis, we observed in our population that in those pathologies in which axial symptoms predominate (AS and u-SpA), their initial symptom was low back pain. Conversely, in those with predominant peripheral symptoms (PsA), the initial symptom was lower-limb arthritis. Surprisingly, in this cohort, psoriasis was the second most frequent onset symptom in PsA, although in previous literature, the majority of PsA patients start with cutaneous psoriasis.[17 18] In an Italian study,[19] it was observed that 26.1% of seronegative rheumatoid arthritis patients had nail lesions and skin psoriasis previously unrecognised by their rheumatologist when evaluated by a dermatologist. These lesions can be minimal and are sometimes only recognised by dermoscopy or ultrasound. This could mean that an active search for psoriasis is recommended for seronegative arthritis, and if it is not visible, an evaluation by a dermatologist may be necessary.

In this analysis, we also tested whether HLA-B27 may be related to the early-onset form of the disease. We found that the absence of this antigen in AS patients was associated with the initiation of cervical pain and peripheral involvement. Similarly, HLA-B27-negative PsA patients

Table 3 Factors associated with low back pain versus buttock pain as the initial symptom

	Low back pain N=1447, n (%)	Buttock pain N=390, n (%)	P value
Sex (male)	**1036/1447 (71.6)**	**253/390 (64.8)**	**0.010**
Age of onset, years (SD)	**29.4 (13.1)**	**27.3 (11.8)**	**0.000**
Diagnostic delay, years (SD)	7.1 (8.7)	6.5 (8.7)	0.159
Psoriasis	241/1441 (16.7)	68/385 (17.7)	0.663
IBD	52/1440 (3.6)	21/388 (5.4)	0.108
Lower-limbs arthritis	**618/1440 (42.9)**	**131/389 (33.7)**	**0.001**
Dactylitis	141/1439 (9.8)	35/389 (9)	0.635
Enthesitis	564/1428 (39.5)	141/386 (36.5)	0.289
Sacroiliitis	**1183/1432 (82.6)**	**358/387 (92.5)**	**0.000**
Inflammatory low back pain	**1404/1446 (97.1)**	**357/387 (92)**	**0.000**
Buttock pain	**645/1436 (44.9)**	**299/389 (76.9)**	**0.000**
Uveitis	**300/1437 (20.9)**	**59/387 (15.2)**	**0.013**
HLA-B27 negative	233/1021 (22.8)	58/307 (18.9)	0.145
CRP mg/dL, mean (SD)	9.1 (14.7)	8.6 (13.1)	0.936
ESR mm/hour, mean (SD)	**20.9 (18.4)**	**18.6 (17.4)**	**0.027**
ASDAS, mean (SD)	**2 (0.9)**	**1.9 (0.9)**	**0.037**
BASDAI, mean (SD)	**4.2 (2.3)**	**3.9 (2.3)**	**0.022**
BASFI, mean (SD)	**4 (2.7)**	**3.2 (2.6)**	**0.000**
BASRI total, mean (SD)	**6.7 (4.3)**	**5.4 (3.8)**	**0.000**
BASRI spine, mean (SD)	**5.8 (3.5)**	**4.9 (3.2)**	**0.000**
csDMARDs (ever)	**335/1064 (31.5)**	**83/335 (24.8)**	**0.019**
bDMARDs (ever)	136/1058 (12.9)	30/333 (9)	0.059

Statistical significance based on $\chi 2$, Fisher's exact test or Mann-Whitney or Student's t-test.
Bold values: significant differences.
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; bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs.

seem to initiate the disease predominantly with peripheral symptoms, while HLA-B27-positive PsA patients seem to initiate the disease with axial symptoms (ie, low back pain, buttock pain and coxitis). These results in PsA patients are in line with previous literature showing that patients with HLA-B27-positive PsA have a higher risk of developing axial symptoms than HLA-B27-negative patients.[20 21] Although studies comparing axial PsA with axSpA show a higher prevalence of HLAB27 positivity in those with axSpA,[22] HLA-B27-positive PsA individuals showed a worse prognosis and more radiographic damage, and it is the only associated common risk factor found between the two.[23 24]

A total of 10.9% of patients initiated the disease with EMMs. Among these, the meantime separating EMMs from MMs was approximately 11 years. When stratifying according to the presence of the HLA-B27 antigen, the number of years increases in the HLA-B27-negative forms, meaning that HLA-B27-negative patients may need more time to fully develop the clinical picture of SpA; this finding agreed with previous studies in the DESIR cohort.[20] Studies have shown that up to 50%, 30% and 3%–10% of patients with acute anterior uveitis, psoriasis and IBD, respectively, will develop SpA at some point in their lives.[25–27] Although the number of patients who initiated the disease with EMMs is low, these patients require a multidisciplinary team (ophthalmologists, gastroenterologists, dermatologists) who, during the follow-up, remember to consider the possibility of a rheumatic disease and, in the event of a suspicious symptom of SpA, refer the patient to a rheumatologist and vice versa for early diagnosis.

Our results also show that the form of initiation of the disease could be associated with the diagnostic delay. We found that patients who started the disease with MMs had a longer diagnostic delay than those who initiated with EMMs. Possibly, when a patient initiates an EMMs, such as psoriasis, uveitis or IBD, an active search for a disease suggestive of SpA is performed. However, because low back pain-type MMs are so common in the general

Table 4 Factors associated with low back pain versus cervical pain as the initial symptom

	Low back pain N=1841, n (%)	Cervical pain N=159, n (%)	P value
Sex (male)	1304/1841 (70.8)	103/159 (64.8)	0.109
Age of onset, years (SD)	**28.4 (12.2)**	**34 (16.4)**	**0.000**
Diagnostic delay, years (SD)	**7 (8.7)**	**5.8 (8.7)**	**0.027**
Psoriasis	**264/1829 (14.4)**	**60/156 (38.5)**	**0.000**
IBD	81/1828 (4.4)	8/157 (5.1)	0.699
Lower limbs arthritis	**720/1835 (39.2)**	**86/157 (54.8)**	**0.000**
Dactylitis	**160/1829 (8.7)**	**40/157 (25.5)**	**0.000**
Enthesitis	675/1819 (37.1)	63/156 (40.4)	0.417
Sacroiliitis	**1580/1827 (86.5)**	**111/157 (70.7)**	**0.000**
Inflammatory low back pain	**1799/1838 (97.9)**	**137/158 (86.7)**	**0.000**
Buttock pain	**1056/1824 (57.9)**	**59/156 (37.8)**	**0.000**
Uveitis	358/1828 (19.6)	23/156 (14.7)	0.141
HLA-B27 negative	**343/1420 (24.1)**	**37/83 (44.5)**	**0.000**
CRP mg/dL, mean (SD)	8.3 (13.7)	12.2 (25.2)	0.184
ESR mm/hour, mean (SD)	19.7 (17.2)	20.8 (15.6)	0.149
ASDAS, mean (SD)	2 (0.9)	2 (0.9)	0.726
BASDAI, mean (SD)	4.2 (2.3)	4.2 (2.5)	0.991
BASFI, mean (SD)	3.9 (2.7)	4.2 (2.6)	0.199
BASRI total, mean (SD)	6.3 (4.2)	6.8 (4.6)	0.220
BASRI spine, mean (SD)	5.5 (3.4)	6 (3.8)	0.185
csDMARDs (ever)	**422/1435 (29.4)**	**50/106 (47.2)**	**0.000**
bDMARDs (ever)	**195/1423 (13.7)**	**22/103 (21.4)**	**0.032**

Statistical significance based on $\chi 2$, Fisher's exact test or Mann-Whitney or Student's t-test.
Bold values: significant differences.
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; bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs.

population, it may take several years for a patient to be diagnosed. Interestingly, inverse results were found in PsA patients, in whom the diagnostic delay was longer in those who initiated the disease with EMMs (mainly psoriasis). This can be explained because the joint manifestations of PsA can often be confused with osteoarthritis. Another possible explanation is that patients with PsA have atypical forms of low back or neck pain that do not raise suspicion of axial involvement. These findings demonstrate the importance of the implementation of screening tools and questionnaires for detecting patients with suspicion of PsA in dermatology clinics.

Buttock pain has been described as a very typical symptom of axial SpA. In fact, 42.3% of patients with a diagnosis of AS started the disease with such symptoms. For this reason, we considered it worthwhile to evaluate the characteristics of patients who started the disease with buttock pain in comparison with lumbar pain. We found that lumbar pain was associated with male sex, lower limb arthritis and uveitis, whereas patients initiating with buttock pain were more frequently female and younger than those who initiated with lumbar pain. On the other hand, factors associated with cervical pain versus low back pain as the first symptom were cutaneous psoriasis, negative HLA-B27 status and peripheral involvement (arthritis and dactylitis), confirming that cervical pain could represent the initiation of PsA with axial involvement. In fact, it is not uncommon to find radiological cervical involvement in patients with PsA (35%–75%). Radiographic manifestations can affect the upper or lower cervical spine, with the upper involvement resembling that caused in rheumatoid arthritis with erosions or atlantoaxial subluxation and the lower involvement resembling SpA with syndesmophytes, ossification of the anterior longitudinal ligament, and facet joint arthritis.[28 29] Finally, factors associated with upper-limb arthritis versus lower-limb arthritis as the first symptom were female sex, cutaneous psoriasis, HLA-B27 negativity and absence of axial symptoms. This means that many patients initiate the disease in the upper limbs, as they

may have a diagnosis of PsA. This is in line with what has been found in the recent ASAS-PerSpA study,[30] in which patients with PsA had predominantly upper limb and small joint involvement.

Our study has some limitations and strengths. One limitation is the possibility of recall bias that patients may have when remembering the first symptom with which the disease began, and this should be considered when interpreting the results. There is also a high number of patients with missing information for HLA-B27 antigen. The analysis on association with HLA-B27 has been done in patients with available data for HLA-B27 leading to possible underestimation of patients with PsA in this subanalysis (who fit the profile of patients in which HLA-B27 is not always evaluated). Another limitation of this study is the inability to make causal assumptions when interpreting numerous statistically significant results and having a very large sample that may favour them. In addition, the diagnostic groups were not homogeneous in the number of patients, with a greater number of patients with AS and having to eliminate patients with IBD-SpA and Juv-SpA diagnoses because of the low number of patients in these groups. However, this is in line with current clinical practice, in which IBD-SpA and Juv-SpA show a very low frequency in comparison with other diagnoses. Finally, the last limitation is the use of the ESSG as an inclusion criterion, which enables the inclusion of patients with a diagnosis of u-SpA and prevents the identification of those with non-radiographic axSpA. One strength of this study is the large number of patients and the representation of the whole spectrum of SpA thanks to joining both registries (RESPONDIA and REGISPONSER). Although this is a cross-sectional study, the availability of the dates of each symptom initiation allowed us to establish the sequence of events and to determine the initial symptom. Future prospective studies are necessary to avoid memory bias and to be able to use the current ASAS classification criteria.

In summary, the findings of our study suggest that SpA commonly initiates with MMs, with low back pain likely being the most prevalent initial symptom within the AS and u-SpA populations, and lower-limb arthritis being prominent in PsA cases. However, these initial symptoms may vary according to the presence of HLA-B27. It should be noted that the diagnostic delay was greater in those patients who started the disease with MMs in our study, emphasising the correct recognition of rheumatic symptoms by general practitioners.

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