UNIVERSITAT DE BARCELONA

Exploring phenotypic heterogeneity across spondyloarthritis

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Doctoral thesis dissertation presented by **Xabier Michelena Vegas** to apply for the degree of doctor at the University of Barcelona.

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TABLE OF CONTENTS

FIGURES AND TABLES RELATIONSHIP

Each of the manuscripts contains the main figures within the text and the supplementary figures in the supplementary materials. This figure and tables legend refers to the rest of the figures and tables within the text (introduction).

GLOSSARY

AS: Ankylosing Spondylitis

ASDAS: Ankylosing Spondylitis Disease Activity Score

ASAS20: ASAS response criteria 20

ASAS: Assessment of Spondyloarthritis International Society

axSpA: axial Spondyloarthritis

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

BASMI: Bath Ankylosing Spondylitis Metrology Index

bDMARDs: biological Disease-modifying anti-rheumatic drugs

BMI: Body Mass Index

BME: Bone Marrow Edema

CRP: C-reactive protein

CBP: Chronic Back Pain

CASPAR: ClASsification criteria for Psoriatic ARthritis

DISH: Diffuse Idiopathic Skeletal Hyperostosis

EMMs: Extra-musculoskeletal manifestations

GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

IBP: Inflammatory Back Pain

IBD: Inflammatory Bowel Disease

MRI: Magnetic Resonance Imaging

mNYc: modified New York Criteria

nr-axSpA: non-radiographic axial spondyloarthritis

NSAIDs: Non-steroidal anti-inflammatory drugs

pSpA: Peripheral Spondyloarthritis

PsO: Psoriasis

PsA: Psoriatic Arthritis

r-axSpA: radiographic axial Spondyloarthritis

RCT: randomised controlled trials

ReA: Reactive arthritis

SIJ: Sacroiliac Joint

STIR: short tau inversion recovery

SpA: Spondyloarthritis

TNFi: TNF inhibitors

uSpA: Undifferentiated Spondyloarthriti

LIST OF ARTICLES IN THE THESIS

Thesis in compendium of publications format

The thesis consists of 4 objectives and 4 articles:

1.

Michelena X, Zhao SS, Marco-Pascual C, Almirall M, Collantes E, Font-Ugalde P, López-Medina C, Wei JC, Morgan AW, Rodríguez J, Juanola X, Vázquez-Mellado J, Marzo-Ortega H.

Diagnostic delay is associated with uveitis and inflammatory bowel disease in AS: a study of extra-musculoskeletal manifestations in SpA

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2.

Michelena X, Zhao SS, Dubash S, Dean LE, Jones GT, Marzo-Ortega H.

Similar biologic drug response regardless of radiographic status in axial Spondyloarthritis: data from the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis registry.

Rheumatology (Oxford). 2021 Dec 1;60(12):5795-5800.

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3.

Michelena X, López-Medina C, Erra A, Juanola X, Font-Ugalde P, Collantes E, Marzo-Ortega H.

Characterising the axial phenotype of psoriatic arthritis: a study comparing axial psoriatic arthritis and ankylosing spondylitis with psoriasis from the REGISPONSER registry.

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4.

Michelena X, Sepriano A, Zhao SS, López-Medina C, Collantes E, Font-Ugalde P, Juanola X, Marzo-Ortega H.

Exploring the unifying concept of Spondyloarthritis: a latent class analysis of the REGISPONSER registry.

Submitted

Summary Table of the Thesis

Aims	Methods	Chapters	Output
To identify the current understanding of the literature including areas of unknown knowledge and unmet needs.	PubMed search for the available scientific literature on pathogenesis and clinical characteristics of Spondyloarthritis (SpA).	**Background literature review** (Introduction)	• *Michelena X, Poddubnyy D, Marzo-Ortega H.* Axial Psoriatic Arthritis: A Distinct Clinical Entity in Search of a Definition. *Rheum Dis Clin North Am. 2020;46(2):327-41.* • *Michelena X, López-Medina C, Marzo-Ortega H.* Non-radiographic versus radiographic axSpA: what's in a name?. *Rheumatology (Oxford). 2020 Oct 1;59(Suppl4):iv18-iv24*. • *Michelena X, Marzo-Ortega H*. Axial spondyloarthritis: time to stop the split 10 years on. *Nature Reviews Rheumatology. 2020;16(1):5-6.*
To determine the prevalence of EMMs (uveitis, psoriasis and IBD) in large cohorts of AS (r-axSpA) and PsA across the world and its relationship with diagnostic delay.	Multicentre observational cohort study (RESPONDIA, Bellvitge, Leeds)	**Materials, Methods, Results: Study 1**	• EULAR 2019: THU0394: The Prevalence Of Extra-Articular Manifestations In Axial Spondyloarthritis And Psoriatic Arthritis Is Associated To Disease Duration: Results From The Leeds Specialist Spondyloarthritis Service • Michelena X, Zhao SS, Marco-Pascual C, Almirall M, Collantes E, Font-Ugalde P, López-Medina C, Wei JC, Morgan AW, Rodríguez J, Juanola X, Vázquez-Mellado J, Marzo-Ortega H. Diagnostic delay is associated with uveitis and inflammatory bowel disease in AS: a study of extra-musculoskeletal manifestations in SpA. *Rheumatology (Oxford). 2023 May 15:kead225. doi: 10.1093/rheumatology/kead225*
To explore the baseline characteristics of r-axSpA and nr-axSpA and to evaluate the level of disease control according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) and the drug survival of first biologic disease modifying anti-rheumatic drug (bDMARD) at one year.	Longitudinal prospective epidemiological study	**Materials, Methods, Results: Study 2**	• EULAR 2020. FRI0287. Biologic Drug Response Does Not Appear Related To Radiographic Status In Axial Spondyloarthritis: Data From The BSRBR-AS Registry • Michelena X, Zhao SS, Dubash S, Dean LE, Jones GT, Marzo-Ortega H. Similar biologic drug response regardless of radiographic status in axial spondyloarthritis: data from the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis registry. *Rheumatology (Oxford). 2021 Dec 1;60(12):5795-5800*
To explore the axial phenotype of PsA regarding its clinical and radiological characteristics and compare it with ankylosing spondylitis (r-axSpA) with psoriasis.	Cross-sectional study on multicentre registry (REGISPONSER)	**Materials, Methods, Results: Study 3**	• Michelena X, De Marco G, Dubash S, McGonagle D, Marzo-Ortega H. Comment on: Is axial psoriatic arthritis distinct from ankylosing spondylitis with and without concomitant psoriasis? *Rheumatology (Oxford). 2021 Jan 5;60(1):e24-e25*. • Michelena X, López-Medina C, Erra A, Juanola X, Font-Ugalde P, Collantes E, Marzo-Ortega H. Characterising the axial phenotype of psoriatic arthritis: a study comparing axial psoriatic arthritis and ankylosing spondylitis with psoriasis from the REGISPONSER registry. *RMD Open. 2022 Dec;8(2):e002513. doi: 10.1136/rmdopen-2022-002513.*
To identify through unsupervised methods the potential distinct phenotypes within a broad SpA population.	Latent class analysis on multicentre registry (REGISPONSER)	**Materials, Methods, Results: Study 4**	• Michelena X, Sepriano A, Zhao SS, López-Medina C, Collantes E, Font-Ugalde P, Juanola X, Marzo-Ortega H. Exploring the unifying concept of Spondyloarthritis: a latent class analysis of the REGISPONSER registry. *(Submitted)*

RESUM DE LA TESI (Català)

Títol: Explorant l'heterogeneïtat fenotípica de les espondiloartritis.

Introducció: Les espondiloartritis (EspA) són un grup de malalties articulars inflamatòries cròniques amb característiques clíniques, història natural, fisiopatologia i epidemiologia comuns. Tot i que es tracta d'un tema controvertit, es sol considerar que l'espondiloartritis axial (incloent l'espondilitis anquilosant), l'artritis psoriàsica (APs), l'artritis relacionada amb la malaltia inflamatòria intestinal (MII), l'artritis reactiva (ARea) i l'espondiloartritis indiferenciada formen part de les EspA. El debat sobre si agrupar o dividir el grup de malalties conegudes com EspA és complex, però conèixer millor analizant la interacció entre les múltiples manifestacions extramusculoesquelètiques (MMEs), la resposta al tractament de les diferents EspA i ooptmitzar la caracterització de l'fectació axial de la APs pot contribuir a resoldre'l.

Hipòtesi: L'heterogeneïtat en les característiques clíniques, incloent les MMEs i les característiques d'imatge dels fenotips axial i perifèric dins de les EspA (principalment espondiloartritis axial -EspaAx- i APs) poden orientar a possibles diferències endotípiques que ajuden a comprendre l'espectre de malaltia en les EspA.

Objectius:

- Determinar la prevalença de les MMEs (uveïtis, psoriasi i MII) en grans cohorts de Espondilitis anquilosant -EA- (EspAax-r) i APs arreu del món i la seva relació amb el retard en el diagnòstic.

- Explorar les característiques basals de l'EspaAx radiogràfica (EspAax-r) i no radiogràfica (EspAax-nr) i avaluar el grau de control de la malaltia segons l'Ankylosing Spondylitis Disease Activity Score (ASDAS) i la supervivència del primer fàrmac biològic modificador de la malaltia antireumàtica (FAMEb) al cap d'un any.

- Explorar el fenotip axial de l'APs pel que fa a les seves característiques clíniques i radiològiques i comparar-lo amb l'espondilitis anquilosant (EspAax-r) amb psoriasi.

-Identificar, a través de mètodes no supervisats, els possibles fenotips distintius dins d'una àmplia població de EspA.

Mètodes: Aquesta tesi inclou 4 estudis basats en cohorts de pacients amb EspA tant amb EspAax com APs. El primer treball és un estudi retrospectiu de cohorts que comprèn dues cohorts unicèntriques a Europa (Leeds i Barcelona) i una cohort multicèntrica a Amèrica Llatina (RESPONDIA). Es va calcular la prevalença crua de les MMEs (uveïtis, MII i psoriasi) en les diferents zones geogràfiques i es va ajustar per estandarditzaciό directa. Es van realitzar un estudi multivariable de Cox per avaluar l'associació entre el retard diagnòstic i la incidència de les MMEs. El segon treball es va realitzar a la cohort multicèntrica britànica BSRBR-AS que inclou participants amb EspaAx que compleixen criteris ASAS (Assessment of SpondyloArthritis international Society) de forma prospectiva. A l'anàlisi d'aquesta tesi, es van comparar les dades basals dels pacients que començaven amb FAMEb dividits per EspaAx-r i EspAax-nr. Per avaluar la resposta al tractament es van utilitzar els índexs ASDAS per definir l'estat de baixa malaltia, la millora clínicament important (CII) i la milloria major (MI) a 1 any . Es va realitzar un anàlisi multivariant de Cox després d'ajustar-se per factors de confusió clínicament rellevants. El tercer i quart treball de la tesi es basa en estudis tranversals del registre multicèntric nacional REGISPONSER. El criteri d'entrada per la inclusió de pacients en aquest registre fou complir criteris ESSSG. En el tercer treball es realitza un estudi comparatiu de les característiques clíniques, de laboratori i imatge entre aquests pacients amb un diagnòstic primari d'APs axial i aquells amb un diagnòstic d'EA amb psoriasis. Inclou també un sub-anàlisi en què es divideix el pacients segons estat de HLA-B27. El quart treballes basa en un anàlisi no supervisat de classes latents (Latent Class analysis) utilitzant una sèrie de variables clíniques i radiogràfiques predefinides per identificar els fenotips latents en una cohort àmplia d'EspA.

Resultats principals: La prevalença global d'uveïtis fou del 22,9% (IC del 95% 21,1-24,8) en EA i del 3,8% (IC del 95% 2,9-5,0) en APs; 8,1% (IC del 95% 7,0-9,4) i 2,1% (1,3-2,9) respectivament per a la MII; 11,0% (IC del 95% 9,7-12,4) i 94,6% (93,0-95,9) per a la psoriasi; amb MMEs que sovint es presenten abans de la afectació articular. En el model multivariable, un major retard diagnòstic (≥5 anys) es va associar amb més presència d'uveïtis (HR 4,01, IC del 95% 3,23-4,07) i esdeveniments de MII (HR 1,85, IC del 95% 1,28-2,67) en EA. El retard diagnòstic no es va associar significativament amb uveïtis o MII en APs. A la cohort BSRBR-AS es va observar una major prevalença masculina, edat

més avançada i durada més llarga de la malaltia al subgrup d'EspAax-r. Dos terços dels pacients van assolir un índex d'activitat de la malaltia baix segons l'ASDAS al primer any, independentment de l'estat radiogràfic (EspaAx-nr 64,2% vs EspAax-r 66,1%). Les corbes de probabilitat de supervivència de FAMEb van ser similars per a ambdos subgrups i la Hazard ratio per EspaAx-nr/EspAax-r era de 0,94 (IC del 95% 0,69, 1,28) després d'ajustar-se per sexe, edat, ASDAS-PCR inicial, tabaquisme, durada de la malaltia, HLA-B27 i FAMEb prescrit. A la cohort REGISPONSER, en el grup d'EA amb psoriasi eren més freqüentment homes, amb un major retard diagnòstic i més prevalença d'uveïtis anterior que aquells amb APs axial que tenien més afectació perifèrica i malaltia ungueal. Els pacients amb APs axial HLA-B27 negatiu tenien menys dolor inflamatori i dany estructural en comparació amb l'EA amb psoriasi. En canvi, la APs axial HLA-B27 positiva compartia característiques clíniques similars a l'EA amb psoriasi, encara que amb una puntuació BASRI més baixa. En l'anàlisi multivariable, els pacients amb EA i psoriasi estaven associats independentment amb la positivitat de HLA-B27 (OR 3,34, IC del 95% 1,42-7,85) i dany estructural lumbar puntuat per BASRI (OR 2,14, IC del 95% 1,4-3,19). Finalment, l'anàlisi no supervisat de la cohort REGISPONSER va identificar com a millor model aquell amb 5 classes. Les classes anomenades 'axial amb dany a columna' i 'axial amb dany sacroilíac' mostren un fenotip predominantment axial definit per dolor lumbar inflamatori i alta prevalença de HLA-B27. Els pacients de la classe 'axial + perifèric' mostren una distribució similar de variables a les classes anteriors, però també tenen una major probabilitat d'afectació perifèrica (artritis perifèrica/dactilitis) i entesitis, representant per tant un subtipus mixt (axial i perifèric). Les classes 'Perifèric + psoriasi' i 'Axial + perifèric + psoriasi' són indicatives d'EspA perifèrica (i/o APs) amb alta probabilitat de psoriasi, afectació perifèrica, dactilitis, malaltia de les ungles, i baixa prevalença de HLA-B27, mentre que la classe 'Axial + perifèric + psoriasi' també mostra més probabilitat d'afectació axial tant clínic com radiològicament.

Conclusions: La prevalença d'uveïtis i MII és més elevada a l'EA en comparació amb l'APs, però presenten una història natural similar, apareixent principalment abans del diagnòstic de l'EspA. Un major retard diagnòstic s'associa amb una major probabilitat d'uveïtis i MII en casos d'EA. Les característiques demogràfiques, clíniques i radiogràfiques, així com la resposta a la medicació, mostren una semblança notable

entre l’EspaAx-r i l’EspaAx-nr. Pel contrari, l'APs axial presenta diferències en termes de característiques clíniques i radiogràfiques respecte a l’EspAax amb psoriasi sent en gran mesura independent de HLA-B27. Finalment, L’anàlisi no supervisat revela entitats clíniques úniques d’EspA, definides per una combinació de manifestacions axials i perifèriques, que es veuen modificades per la presència de psoriasi. S’observa una superposició considerable entre els fenotips axials i perifèrics en SpA. En general, l'espectre d’EspA presenta una heterogeneïtat i complexitat significatives que cal considerar detalladament per millorar el diagnòstic i el tractament dels pacients afectats per aquestes condicions.

INTRODUCTION

The Spondyloarthritis Concept

The spondyloarthritis (SpA) are a group of inflammatory chronic conditions with common clinical findings, natural history, pathophysiology and epidemiology (1). Controversy exists, but axial spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-related arthritis, reactive arthritis (ReA), and undifferentiated spondyloarthritis are considered part of the SpA group (2) as seen in Figure 1. Moll and Wright were pioneers in grouping these diseases together based on their observations in clinical practice (3). They found that these patients were mainly seronegative for rheumatoid factor and shared clinical similarities with ankylosing spondylitis (AS). Furthermore, familial aggregation of these diseases and a clear genetic association with HLA-B27 was observed. Finally, characteristic radiographic findings were noted in both axial and peripheral joints that differentiated these diseases from other inflammatory arthritis (3). This concept was adopted by rheumatologists worldwide and the term SpA encompassed a clinical picture consistent of axial inflammation (sacroiliac joints and spine); peripheral arthritis that was commonly asymmetric, oligoarticular and predominantly in the lower limbs; enthesitis; dactylitis; uveitis; psoriasis (PsO); IBD and association with the HLA-B27 (4).

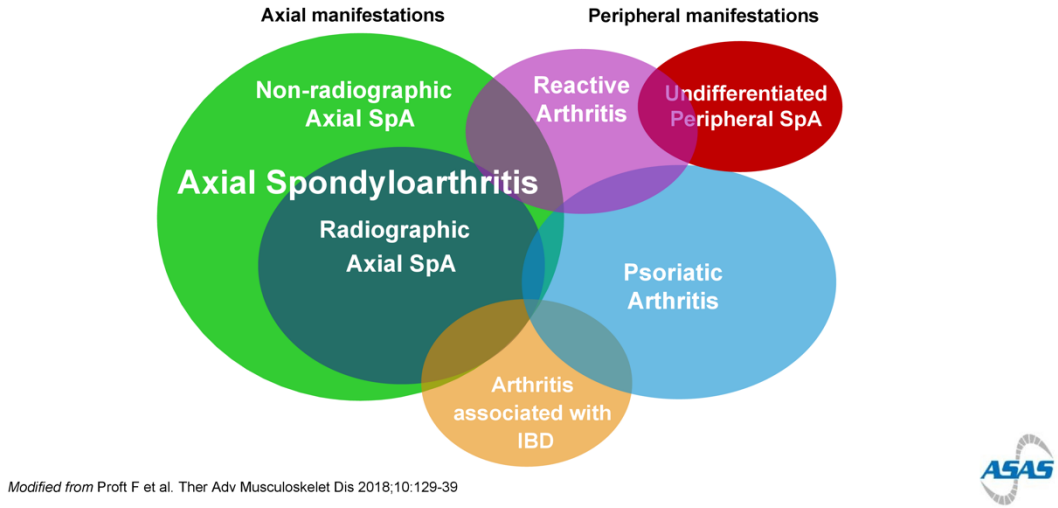

Figure 1. The concept of Spondyloarthritis

SpA Diagnosis: An historical perspective on the criteria

AS was described as a disease before the concept of SpA was established, and it played a pivotal role in defining the SpA group (5). AS served as a model disease to describe the features shared by other SpA, and the first classification criteria for AS were proposed at the European Congress of Rheumatology in Rome in 1961 (Rome Criteria)(6). This were followed by the New York Criteria in 1966 (7) that were further modified in 1984 (8). Table 1 shows the items that these criteria included mainly based in clinical findings and radiographic involvement of the sacroiliac joints.

Table 1: Criteria developed for AS (Rome, New York and Modified New York)

Criteria	**Rome 1961**	**New York 1966**	**Modified New York (mNYc) 1984**
Clinical Criteria	- Low back pain and stiffness for >3 months, which is not relieved by rest. - Pain and stiffness in the thoracic region. - Limited motion in the lumbar spine. - Limited chest expansion. - History or evidence of iritis or its sequelae.	- Limitation of motion of lumbar spine in all three planes, anterior flexion, lateral flexion, and extension. - History or presence of pain at dorsolumbar junction or lumbar spine. - Limitation of chest expansion to 1 inch (2.5 cm), at the fourth intercostal space.	- Inflammatory low back pain for >3 months. - Limitation of lumbar motion. - Limitation of chest expansion PLUS radiological criteria
Radiological Criteria	X-ray showing bilateral sacroiliac changes characteristic of AS (this would exclude bilateral osteoarthritis of sacroiliac joints).	- Definite AS: Grade 3-4 bilateral sacroiliitis with at least one clinical criterion OR Grade 3-4 unilateral or grade 2 bilateral sacroiliitis with clinical criterion 1 or with both clinical criteria 2 and 3. - Probable AS: Grade 3-4 bilateral sacroiliitis with no clinical criteria	Sacroiliitis grade >2 bilaterally or 3 unilaterally.

In the 1990s, the Amor criteria (9) and the European Spondyloarthropathy Study Group (ESSG) (10) criteria were developed to classify the whole spectrum of SpA, including undifferentiated SpA. The ESSG criteria mandate the presence of inflammatory back pain (IBP) or synovitis as entry conditions. On the other hand, the Amor criteria do not require any specific features for classification, but they assign different weight to different features of SpA. Details of both classification criteria are shown in Table 2.

Table 2: ESSG and Amor Criteria for SpA.

	ESSG Criteria	**Amor Criteria**
Criteria	Inflammatory spinal pain or synovitis (asymmetric or predominantly in the lower limbs) PLUS at least one of the following: - positive family history - psoriasis - inflammatory bowel disease - urethritis, or acute diarrhea - alternating buttock pain - enthesopathy - sacroiliitis as determined from radiography.	Diagnosis of SpA requires a score of >6. - Lumbar pain at night or lumbar morning stiffness:1 - asymmetric oligoarthritis:2 - buttock pain (or bilateral alternating buttock pain):2 - sausage-like toe or digit(s):2 - heel pain or other well-defined enthesitis: 2 - iritis: 2, - nongonococcal urethritis/cervicitis within 1 month of onset: 1 - acute diarrhea within 1 month of arthritis onset:1 - psoriasis, balanitis, or inflammatory bowel disease (Crohn's or ulcerative colitis): 2 - sacroiliitis (bilateral grade 2 or unilateral grade 3): 2 - HLA-B27 positive or positive family history of a spondyloarthropathy: 2 - rapid (<48 h) response to NSAIDs: 2

The addition of “undifferentiated SpA” (uSpA) in the SpA spectrum and these broader criteria permitted the diagnosis of AS or what soon was denominated axial spondyloarthritis (axSpA) (11) in earlier stages without the need of definite structural changes in the sacroiliac joints as demanded by the mNYc for AS (8). In 2009 (12) and 2011 (13), the Assessment of Spondyloarthritis International Society (ASAS) developed new classification criteria for axSpA and peripheral SpA (pSpA) mainly driven by the arising of new imaging techniques such as the magnetic resonance imaging (MRI) of the

sacroiliac joints (14,15). The ASAS criteria consolidated the axSpA concept and the term “non-radiographic axSpA" (nr-axSpA) was created to include patients with clinical features of axSpA but without radiographic sacroiliiitis. This allows for earlier diagnosis and treatment of the disease. Nr-axSpA can be identified using either the "imaging arm" of the ASAS criteria, which involves MRI detection of inflammatory lesions in the sacroiliac joints (SIJ), or the "clinical arm," which considers the presence of HLA-B27 positivity in the absence of MRI findings (12). Radiographic axSpA (r-axSpA) was also introduced as a term to describe those who had definite radiographic findings in the SIJ and that has been found to be a comparable term of AS (16). On the other hand, the pSpA ASAS criteria describe the full range of SpA diseases that affect primarily the peripheral skeleton including psoriatic arthritis (13). Both axSpA and pSpA ASAS criteria, outperformed the previous ESSG and Amor criteria with a sensitivity of 82.9% and a specificity of 84.4% (12,13). Details of the axSpA and pSpA ASAS criteria can be found in Figure 2 and 3.

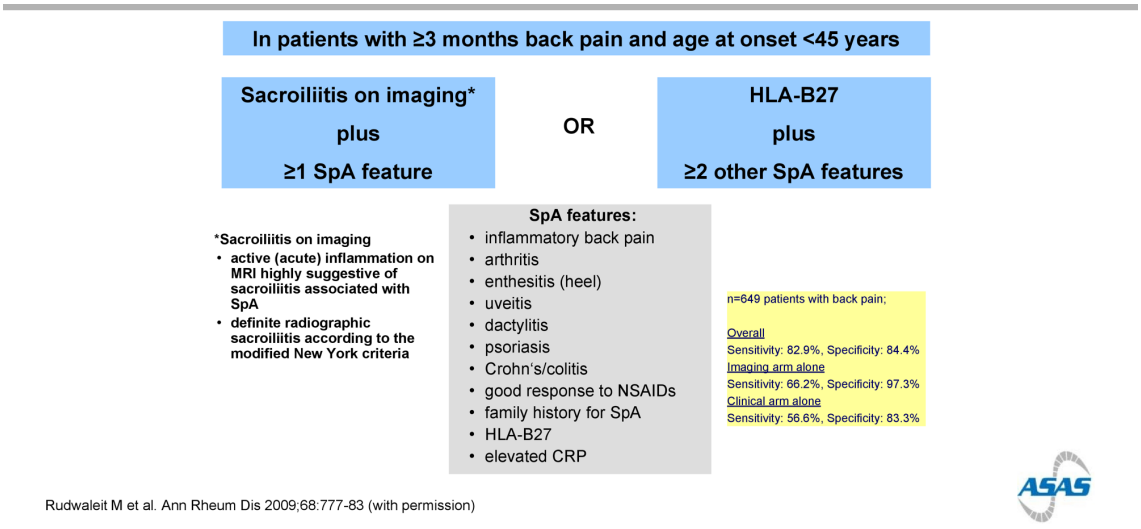

Figure 2: ASAS classification criteria for Axial Spondyloarthritis (axSpA)

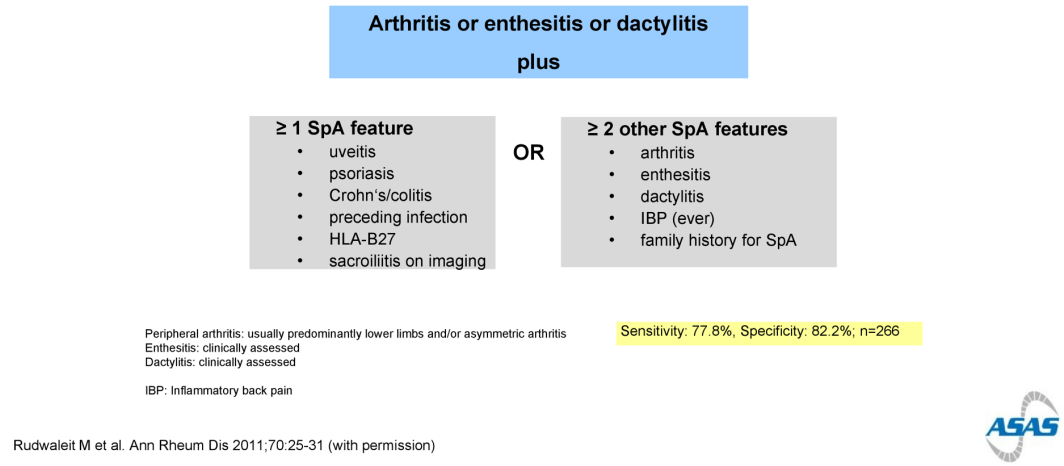

Figure 3: ASAS Classification Criteria for peripheral SpA.

Diagnostic delay in SpA

Despite increased awareness and advancements in diagnostic techniques during the past twenty years, there is still a notable unaddressed issue of delayed diagnosis in SpA compared to other chronic inflammatory arthritides. The diagnosis of axSpA remains challenging due to the often-insidious onset of this condition, where initial presentation may not immediately indicate an inflammatory disease. Furthermore, although chronic back pain (CBP) lasting over three months is a key characteristic of axSpA, it frequently occurs in many patients with non-inflammatory back pain (79). In a recent meta-analysis, the median diagnostic delay in axSpA ranges between 2 and 6 years (80). Factors associated with this diagnostic delay were found to be gender and family history of SpA, although without enough strong evidence to draw any conclusions. When it comes to PsA, there are few studies examining diagnostic delay. Although diagnosing PsA may appear easier than axPsA due to visible skin or nail psoriasis, a delayed diagnosis can result in more severe radiographic and destructive joint damage (81). The most recent study evaluating diagnostic delay in PsA outlines a median delay of 2.5 years (82). There is great heterogeneity in this numbers as another study done in Spain showed a median diagnostic delay of 4 years (83). Factors associated with diagnostic delay (>2 years) in PsA were earlier age at onset of PsA symptoms, higher Body Mass Index (BMI) and

enthesitis (82). Aside from the elements contributing to the diagnostic delay, the paramount inquiry pertains to the potential effects of such diagnostic delays on the progression of axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) as well as incidence of EMMs which is thoroughly explored in this thesis.

Magnetic resonance imaging in SpA: The diagnostic milestone

In the context of axSpA, a significant quantity of scientific evidence backs the efficacy of MRI in diagnosing and monitoring disease progression (11). This efficacy is associated with its ability to simultaneously generate images of both inflammatory and structural lesions in the SIJs and the spine. This imaging technique incorporates a T2-weighted sequence sensitive to free water, such as short tau inversion recovery (STIR), as well as a T1-weighted sequence. Notably, the application of gadolinium contrast to identify active inflammatory lesions in adults is not recommended due to its lack of added diagnostic value in axSpA (17).

MRI of the SIJs is advised for patients with suspected axSpA who do not display clear radiographic sacroiliitis, as recommended by EULAR and the European Society of Skeletal Radiology (ESSR) (18). This recommendation is especially pertinent for younger patients or those with brief symptom duration, for whom MRI should be the primary imaging modality. Studies from the late 1990s revealed that inflammation in the SIJs could be identified through MRI before the structural changes become apparent on SIJ radiographs (19).

The sensitivity of MRI-SIJ in diagnosing axSpA varies from 35 to 91%, contingent on the clinical context (20). If the initial MRI of a patient with chronic back pain suspected of axSpA is negative, the likelihood of a positive MRI after 3 months to 2 years is relatively low (5–15%), and almost non-existent in female or HLA-B27-negative patients. Therefore, the utility of repeated MRI of the SIJs for diagnostic purposes is limited to

certain cases (21,22). Caution in interpretation is needed, particularly in patients under a full dose of non-steroidal anti-inflammatory drugs (NSAIDs), which can potentially lessen the visibility of inflammatory MRI lesions in patients with established SpA. However, the effect of NSAIDs on diagnostic investigations in patients with suspected axSpA remains unexplored.

The question is what constitutes positive MRI and what does this mean in a diagnostic setting. In 2009, the ASAS not only promulgated the classification criteria, but also introduced a definition for an ASAS-positive MRI. According to this definition, for an MRI to be ASAS-positive and thus indicative of axSpA, it must exhibit bone marrow edema (BME) in an anatomical location typically associated with the disease. Furthermore, the MRI manifestation should be strongly suggestive of axSpA. The definition also stipulates specific criteria concerning the distribution of BME. It requires the presence of BME in at least two consecutive slices or in more than one location within a single slice (12).

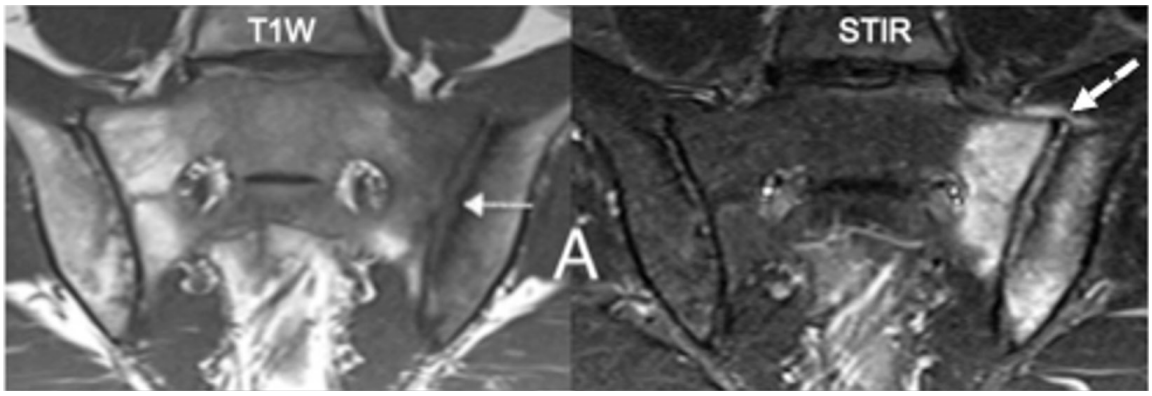

Figure 4. MRI scans of a patient with axSpA. Extensive bone marrow oedema in the left iliac and sacral subchondral bone marrow is depicted as bright signal on the STIR MRI scan meeting the ASAS definition of a positive MRI. There is loss of the bone marrow fat signal in the corresponding location on the T1-weighted (T1W) scan and erosion of the entire vertical height of the left iliac cortical bone with loss of adjacent marrow matrix leading to an appearance of widening of the joint space (arrow). This meets the ASAS definition for erosion. The dashed arrow points to bright signal in the anterosuperior joint capsule on the STIR scan meeting the ASAS definition of capsulitis. Extracted from Maksymowych WP, Lambert RG, Østergaard M, et al. Ann Rheum Dis. 2019 Nov;78(11):1550-1558.

The definition of an ASAS-positive MRI has been a subject of considerable discussion. The reasoning behind this definition is multifaceted. First, early axSpA is typified by active inflammation of the axial skeleton, which is detectable via imaging in over 95% of cases at the sacroiliac joints (SIJ), with less than 5% showing inflammation confined to the spine (23). This explains why the spine is not central to the definition. Second, x-ray imaging adequately captures structural lesions, with well-established criteria already in place. The capacity of MRI to detect structural lesions was uncertain when these criteria were formulated. SIJ osteitis is the most predictive sign of early, non-radiographic axSpA and signifies a higher likelihood of progression to AS or r-axSpA and subsequent requirement for biologic therapy (24). Small, focal areas of edema or edema-like lesions often lack specificity or are mere artifacts. Up to 40% of healthy subjects can present BME in the SIJ MRI(25). Hence, a minimum quantity of osteitis must be evident. The definition acknowledges the importance of a comprehensive interpretation, where the collective findings—including the distribution of changes and other factors (particularly structural lesions in the SIJ)—should strongly imply the existence of inflammatory sacroiliitis.

In essence, inflammatory changes in the SIJ adjacent to the cartilaginous surface of the joint (excluding the ligamentous part) are mandatory. These should be accompanied by an adequate amount of BME that cannot be attributed to artifacts or other causes. The distribution should suggest axSpA, without being limited or excessively present in the most ventral part of the joint. Structural lesions, such as the presence of erosions or fat lesions, should be taken into account as they lend support to the suspicion of axSpA. The aggregate of these findings must strongly suggest axSpA. Only when these conditions are met can the MRI be termed 'ASAS-positive'. It's important to stress that "bone marrow edema on two consecutive MRI slices" alone is insufficient, and has never been adequate, to fulfill the criteria for an ASAS-positive MRI.

In 2019, the definitions were revised but no changes were made to the current ASAS definition of a positive SIJ MRI (26). Ultimately, the diagnosis of axSpA heavily relies on a comprehensive interpretation of both imaging results and clinical presentation. There

is a substantial risk of overdiagnosis in individuals solely exhibiting a positive MRI, underscoring the importance of a holistic assessment approach.

Non-radiographic axial SpA: Is it a separate disease?

The purpose of introducing the terms nr-axSpA and r-axSpA was not to create two distinct conditions, but rather to encompass the entire spectrum of axSpA and facilitate research in this area by staging the disease. It is important to note that classification criteria are not intended to be used for diagnosis, but rather as a tool to aid in diagnosis. However, the misuse of these criteria has caused controversy over whether nr-axSpA is truly a different condition or simply an early stage of axSpA. Those who argue for separating believe that many cases are diagnosed without inflammatory signs or damage ("clinical arm"), making it difficult to classify them using objective evidence (for example, MRI). Additionally, a significant number of patients with nr-axSpA may never develop radiographic sacroiliitis (27). The research community has investigated the similarities and distinctions between these two subgroups (nr-axSpA and r-axSpA), with the primary findings summarised in the subsequent sections.

From a demographic perspective, the reported prevalence of AS (r-axSpA) exhibits considerable heterogeneity, ranging from 0.007% to 0.54%, with no studies focusing exclusively on nr-axSpA (28). However, when examining the entire axSpA group, the prevalence rises to 1.4% (29). Additionally, an equal percentage of patients with a family history of SpA has been observed in both nr-axSpA and r-axSpA, which supports the notion of a shared genetic foundation (30). A common misconception has long persisted that axSpA primarily affects males. However, the male-to-female ratio has declined in recent times, with research showing nearly equal prevalence, especially in nr-axSpA cohorts(31). Women exhibit distinct clinical manifestations, such as more extensive pain in the neck and upper thoracic regions, which may not align with established definitions of IBP, and less radiographic damage (32). These factors may contribute to a longer diagnostic delay for females compared to males (33). Despite a higher overall disease

burden in women (31), this has not resulted in a corresponding increase in biologic prescriptions (34).

In terms of symptom onset and diagnosis, nr-axSpA exhibits a shorter disease duration and is identified earlier, consistent with the continuum concept (35). Notably, r-axSpA manifests at an earlier age (36), as demonstrated by a recent meta-analysis (30). The nature of low back pain presentation in both subgroups remains underexplored; however, similar percentages of inflammatory back pain have been observed in a referral study (37). Peripheral manifestations show mixed results based on the inclusion criteria in the two available meta-analyses (30,38). The largest study reported a higher prevalence of peripheral arthritis, enthesitis, and dactylitis in the nr-axSpA population, which may be due to selection bias, as noted by the authors (30).

Regarding serum biomarkers, the primary difference lies in C-reactive protein (CRP) levels, which are higher in r-axSpA (30). Interestingly, a post-hoc analysis of ABILITY-1 indicated that a significant number of nr-axSpA patients with initially negative CRP levels exhibited elevated CRP at week 12(39). If verified, this may imply that CRP levels increase as the disease progresses, particularly in patients with a more "severe" phenotype who may develop radiographic features over time.

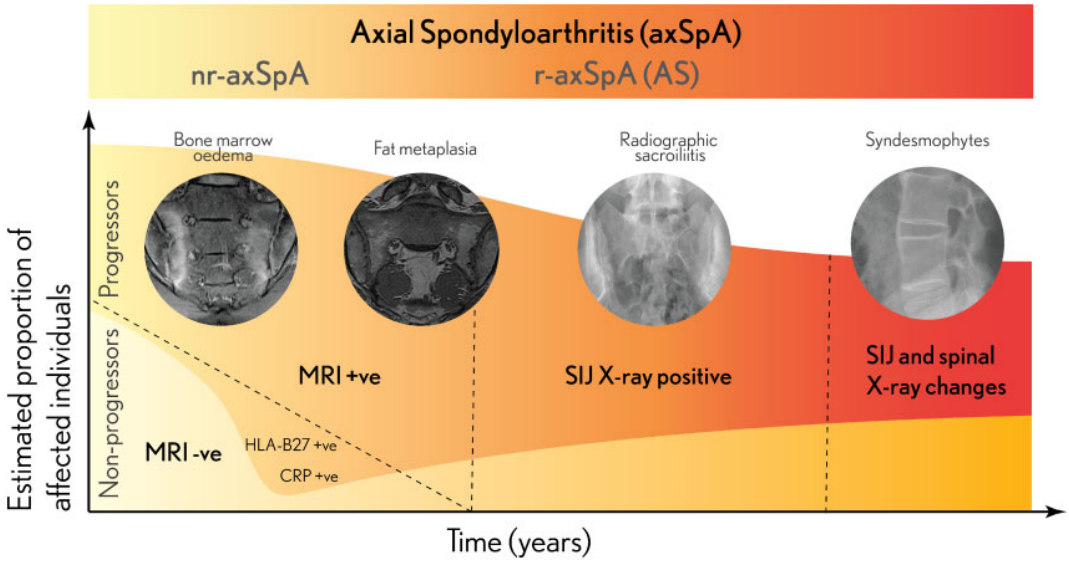

Figure 5. Axial spondyloarthritis continuum. Nr-axSpA, which may or may not be identified with and without bone marrow oedema as seen by MRI, may evolve over the years to r-axSpA previously known as AS, which is characterized by established changes of sclerosis, ero- sions and/or fusion in the sacroiliac joints and syndesmophytes or vertebral fusion in the spine in a proportion of cases. These changes are represented with the different colour grading (yellow/red) to illustrate the nr-axSpA–r- axSpA continuum. Those who will develop radiographic changes are represented as 'progressors' with risk factors such as a previously positive MRI, raised CRP and positive HLA-B27. A proportion of HLA-B27 positive subjects with negative MRIs may develop a raised CRP, placing them in the more severe or 'progressor' category. With time and a possible treatment effect, the number of 'non-progressors' can increase as shown. Fat metaplasia is represented as a post-inflammatory lesion after bone marrow oedema occurs and is a possible precursor of radiographic structural lesions. nr-axSpA: non-radiographic axial spondyloarthritis; r-axSpA: radiographic axSpA. Extracted from: Michelena X, López-Medina C, Marzo-Ortega H. Non-radiographic versus radiographic axSpA: what's in a name? Rheumatology (Oxford). 2020 Oct 1;59(Suppl4):iv18-iv24. doi: 10.1093/rheumatology/keaa422. PMID: 33053190; PMCID: PMC7566325.

Disease burden seems similar across radiographic statuses, with disease activity measures such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) showing comparable results in various observational (36) and randomized clinical trials (40,41). The Ankylosing Spondylitis Disease Activity Score (ASDAS) also performs similarly in both nr and r-axSpA (42). As expected, radiographic axSpA is associated with higher Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing

Spondylitis Metrology Index (BASMI) (43), which can be attributed to more severe radiographic involvement.

Apart from its academic significance, the classification into nr-axSpA and r-axSpA holds considerable therapeutic implications, as some organizations have established distinct treatment recommendations based on this categorisation (44).

Non-steroidal anti-inflammatory drugs (NSAIDs) serve as the foundation for axSpA treatment. No notable differences have been observed in clinical response or NSAID usage between r-axSpA and nr-axSpA patients, reinforcing the similarities in response rate and disease burden (45).

A number of randomised controlled trials (RCTs) have shown the effectiveness of biological disease-modifying anti-rheumatic drugs (bDMARDs) in both r-axSpA and nr-axSpA, with varying response rates likely due to diverse inclusion criteria across studies(46). The ESTHER trial, which examined both r-axSpA and nr-axSpA patients treated with etanercept versus sulfasalazine, revealed comparable efficacy and safety data for both groups up to four years, suggesting a similar disease course (40). Although adalimumab has proven effective in both r-axSpA and nr-axSpA, no studies have directly compared the two groups in terms of adalimumab response (47). The RAPID-AS trial assessed the effectiveness of certolizumab against a placebo for both r-axSpA and nr-axSpA patients by implementing stratified randomization for both groups. A direct comparison at the six-month mark demonstrated similar ASAS40 responses (41). For golimumab, significant improvements were observed in separate RCTs for r-axSpA and nr-axSpA patients (48,49). However, in the nr-axSpA trial, patients with negative MRI and normal CRP levels at baseline exhibited no difference in response rate between golimumab and placebo treatment. Additionally, studies with IL-17A blockers, such as secukinumab and ixekizumab, have demonstrated effectiveness in both r-axSpA and nr-axSpA patient groups (50–52).

Real-world data remains limited, with only a few studies published so far. The DANBIO registry (53) and two smaller studies (54,55) show similar TNFi survival data and response rates in both nr-axSpA and r-axSpA groups, while the Swiss Clinical Quality Management (SCQM) Cohort (36) observed higher response rates in the r-axSpA group.

Psoriatic arthritis: a journey on its own

As discussed in the prior section, while PsA is categorised within the SpA spectrum, research and pharmacological advancements have increasingly recognised PsA as a distinct disease entity. The clinical features of PsA were first described in 1973, also by Moll and Wright (56), describing five clinical subtypes: oligoarticular, polyarticular, distal interphalangeal joints involvement, arthritis mutilans and axial involvement (57). A recent meta-analysis determined that the prevalence of psoriatic arthritis (PsA) is 133 per 100,000 individuals, with an incidence rate of 83 per 100,000 person-years (58). Of particular importance, the prevalence of PsA among patients with psoriasis can be as high as 30% (59), making it the most reliable biomarker to date for identifying PsA patients. Furthermore, approximately 15% of psoriasis patients under the care of dermatologists have undiagnosed arthritis (60). In order to standardise research on PsA, the ClASsification criteria for Psoriatic ARthritis (CASPAR) were established in 2006 (see Figure 4). Since then, CASPAR has facilitated an increased amount of research on PsA, including RCT evaluating pharmacological treatments for this condition(61). Also, in 2003 the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) was founded with the aim of improving the domain assessment of psoriatic arthritis and to develop treatment recommendations for this disease (62).

This inevitably helped reinforcing the idea that PsA was not part of the SpA spectrum and that specific treatment and management guidelines were needed for this disease. Although the European Alliance of Associations for Rheumatology (EULAR) made an effort to integrate PsA inside the treatment recommendations of peripheral SpA in 2017 (63), the importance of PsA-specific guidelines from EULAR remained prominent (64).

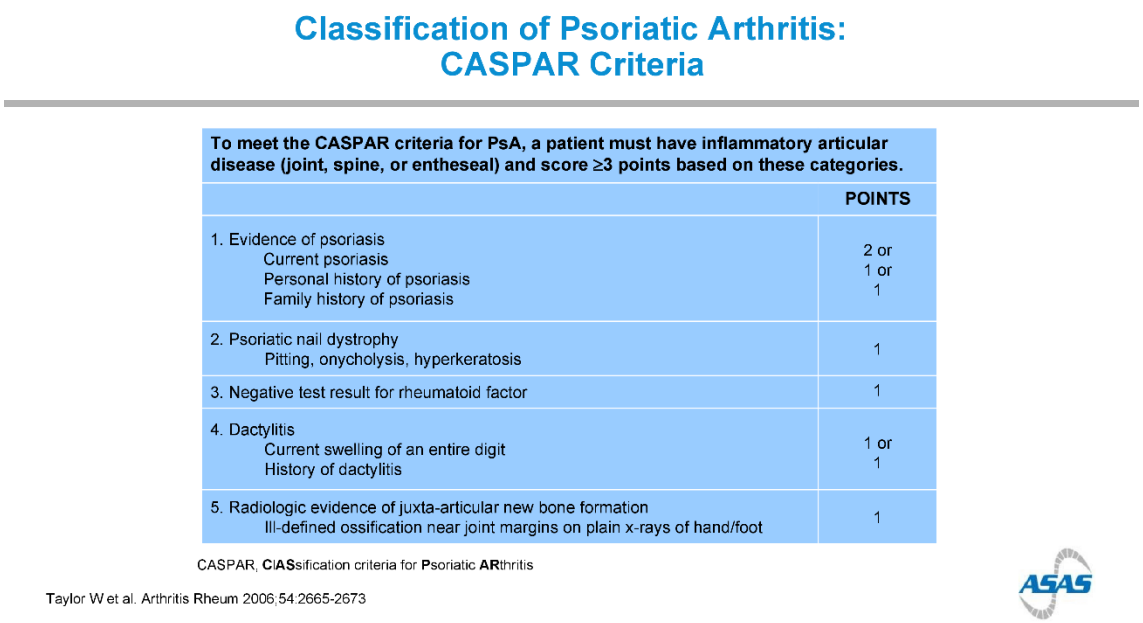

Figure 6. CASPAR Criteria for Psoriatic Arthritis.

From a pathophysiological point of view, there are not many differences between PsA and axSpA (65,66). Both PsA and axSpA have immune-mediated pathogenesis, with a crucial role of T-helper cells in driving inflammation. In PsA, the interleukin 23 (IL-23) and T-helper-17 (Th17) cell pathway play a significant role. While earlier studies focused on CD4-positive T cells producing TNFα, current research emphasizes Th17 cells, IL-23, and IL-17. Naive T cells differentiate into Th17 cells under the influence of various cytokines, which then produce a range of proinflammatory cytokines (67). The frequency of Th17 cells is increased in the circulation of PsA patients and even more so in synovial fluid, where they display a highly differentiated and polyfunctional phenotype. IL-17-positive CD8-positive T cells in synovial fluid are associated with erosive disease (68). Accumulation of IL-17-producing cells in joints causes inflammation, angiogenesis, and increased osteoclastogenic activity. Single-nucleotide polymorphisms in genes involved in Th17 cell differentiation are linked to PsA susceptibility (69). Th17 cells produce many cytokines, including IL-22. However, a subset of CD4-positive T cells, called Th22 cells, produce only IL-22 independently of IL-17A (70). IL-22 levels are higher in synovial fluid than in peripheral blood in PsA patients and are reduced following TNF inhibitor therapy (71). The differential expression of these T-cell subsets at disease sites suggests that Th17 and Th22 cells may have distinct roles in joint and skin disease. IL-22 can activate

fibroblast-like synoviocytes, induce osteoclastogenesis, and promote the proliferation, migration, and osteogenic differentiation of mesenchymal stem cells (70). Also, type 3 innate lymphoid cells are more abundant in synovial fluid of PsA patients compared to rheumatoid arthritis. These cells show increased expression of CCR6 and NK-p44 and produce significant amounts of interleukin 17A (IL-17A) (72).

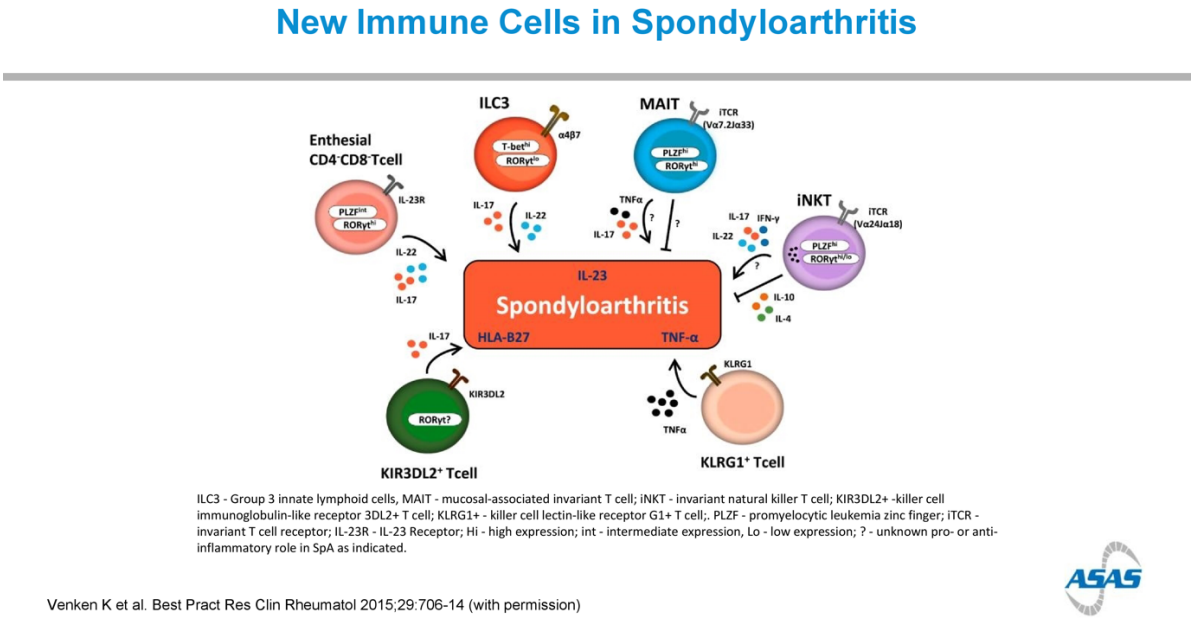

Figure 7. Overview of immune cells participating in the spondyloarthritis pathogenesis.

Similarly, in axSpA, IL-23R-positive T cells are stimulated to produce IL-17 (73). The role of IL-17 in axSpA has been rapidly recognised, with increased levels found in serum, synovial fluid, joints, and CD4+ (Th17) cells from patients (74). Genome-wide association studies have identified IL-17-related genes as risk factors for AS development (75). IL-17 production and cell types that produce IL-17 are the focus of current research. A multitude of IL-17-producing cells have been implicated in AS, including myeloid cells, adaptive lymphocytes, innate-like lymphocytes, and innate lymphocytes (65). IL-17 upregulation in patients with AS is not cell-specific, likely reflecting a global dysregulation of IL-17-producing type 3 immune cells (76). The relative contribution of IL-17 derived from various type 3 immune cells has yet to be determined but might be tissue-specific. It is unclear whether all type 3 immune cells are pathogenic, as some may promote tolerance to gut microorganisms or maintain epithelial integrity (77).

PsA and axSpA also have overlapping extra-musculoskeletal manifestations (EMM), including uveitis, inflammatory bowel disease, and the hallmark symptom of skin psoriasis. Recent meta-analyses have highlighted that the occurrence of uveitis, IBD and psoriasis is more frequent in axSpA compared to PsA. The pooled prevalence rates for these conditions are 23%, 6.4% and 10.2% respectively in axSpA while it is only 3.2% for uveitis and IBD each in PsA (38,78). Despite the lower prevalence in PsA, data in the literature is sparse. This might have therapeutic implications, and it is still unknown if specific subgroups of patients from the PsA spectrum with similar characteristics to axSpA might exhibit different behaviours regarding EMMs.

Are axSpA with psoriasis and axial PsA the same disease?

The question of whether axSpA accompanied by psoriasis and axial PsA represent identical conditions, as well as their distinguishing features, has become a prevailing subject of debate in contemporary research. This issue is central to unravelling the heterogeneity observed within the spectrum of SpA, thereby enhancing our understanding of its multifaceted nature.

The current understanding of axial PsA has been hindered by the lack of a definition to facilitate research. In fact, there are several terms utilized interchangeably in the medical literature to describe spinal involvement in the context of PsA, including "psoriatic spondyloarthropathy" (84), "axial psoriatic arthritis" (85), and "psoriatic spondylitis" (86). However, axial PsA is preferred as “psoriatic spondylitis” may imply exclusive spine impact (without SIJ involvement) and “psoriatic spondyloarthropathy” includes an outdated term ("spondyloarthropathy") now substituted by spondyloarthritis. This difficulty in the definition is clearly seen in the heterogeneity in the prevalence of axial involvement in PsA which ranges from 12.5% to 78% depending on the series (87).

When exploring differences between axial PsA and axSpA, the most compelling evidence may lie in genetic associations. There is a clear overlap between axial PsA and axSpA with the associations with HLA-B27 genes. HLA-B27 prevalence can be as high as 80% in AS

whilst being around 20% in patients with PsA (88). While the prevalence of HLA-B27 can increase by up to 30% in axial PsA, there remains a significant disparity, indicating the involvement of other genetic factors (89). The effect of HLA-B27 has been explored in some cohorts suggesting that a smaller subset of axPsA, which has been confirmed through imaging and is HLA-B27 positive, exhibit more pronounced radiographic bilateral sacroiliac joint (SIJ) damage and/or MRI findings of acute inflammatory lesions similar to those observed in HLA-B27-positive axSpA (90,91). These findings suggest the presence of two distinct subtypes of the axial phenotype within the already heterogeneous PsA population, influenced at least partially by HLA-B27 (87).

In this line, some researchers argue against HLA-B27 being a definitive marker of axial PsA, as no specific HLA association was found in their cohorts (92). Additionally, a recent study demonstrated that HLA-B0801 exhibited the strongest correlation with radiographic sacroiliitis. However, when the cohort was divided, HLA-B0801 was associated with unilateral sacroiliitis, while HLA-B27 was linked to bilateral sacroiliitis. These findings support the existence of distinct clinical phenotypes in axial PsA and radiographic axSpA (93).

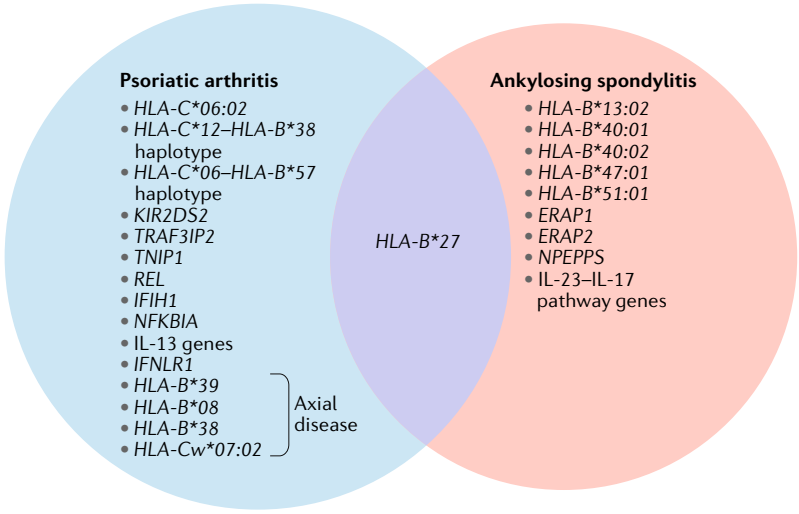

Figure 8. Genetic commonalities between psoriatic arthritis and ankylosing spondylitis. Adapted from Feld J, Chandran V, Haroon N, Inman R, Gladman D. Axial disease in psoriatic arthritis and ankylosing spondylitis: a critical comparison. Nat Rev Rheumatol. 2018 Jun;14(6):363-371.

Furthermore, polymorphisms in the IL-23 receptor provide additional evidence that AS and axPsA may have different genetic backgrounds. For example, rs12401432 GG homozygosity has been associated with axial involvement in PsA, while rs11209032 has been previously linked to AS(94). Other HLA associations have also been reported, including HLA-Bw38, HLA-Cw*0802, HLA Cw2, DRw52, HLA-B39, and HLA-B17/Cw6 (87). Notably, HLA-B46 was found to be associated with radiographic sacroiliitis in a Japanese cohort, although this finding has not been investigated in the white population (95).

From a clinical perspective, phenotypic manifestations are overall very similar when comparing axial PsA and axSpA. To provide clarity to the reader, clinical and imaging characteristics have been summarised in a table dividing both diseases according to HLA-B27 status.

Table 3. Clinical and imaging characteristics of axial Psoriatic arthritis and axial Spondyloarthritis according to HLA-B27 status.

	Axial PsA		**axSpA**	
	HLA-B27+	**HLA-B27-**	**HLA-B27+**	**HLA-B27-**
Estimated prevalence	23-43% of axPsA	57-77% of axPsA	≈ 90% of axSpA	10% axSpA
Age of presentation	Younger (<40 years old)	Older (>40 years old)	Younger (≈ 30 years old)	Older (≈ 35 years old)
Female:Male ratio	1:7[18]	1:1	51-96%	37-95%
Radiographic features	Bilateral symmetrical sacroiliitis	Asymmetrical sacroiliitis	More radiographic sacroiliitis.	Less radiographic sacroiliitis.
Concomitant spondylitis	Sacroiliitis with spondylitis	Isolated spondylitis	Sacroiliitis with spondylitis	Sacroiliitis with spondylitis
Pattern of spinal involvement	Lumbar spine, SIJ less cervical involvement	More cervical involvement	Lumbar spine, SIJ, rare isolated cervical involvement. No HLAB27 subset data available.	Lumbar spine, SIJ, rare isolated cervical involvement.
Radiographic progression	More radiographic progression	Less radiographic progression	Heterogeneity in results: HLA-B27+ men progress more	Heterogeneity in results: HLA-B27- men progress less
MRI features	More BMO	Less BMO	More BMO	Less BMO
Extra-articular manifestations	More uveitis. IBD* data not available.	Less uveitis	More Uveitis, less Pso. No evidence in IBD.	Less uveitis, more Pso. No evidence in IBD.

Data included in the table are extracted from these references (28,85,90,91,93,96–100)

Imaging characteristics have also been crucial to differentiate axial PsA from axSpA. Spondylitis without radiographic changes in the SIJs is observed in approximately 35% of axPsA patients, despite it being the defining feature of axSpA (96). The asymmetrical and predominantly unilateral SIJ involvement in axial PsA, as described by McEwen et al. in 1971 (101), has been observed in subsequent cohorts. Complete SIJ ankylosis is infrequent in axPsA (96). Regarding spinal involvement, AS exhibits more severe changes, particularly in the lumbar spine (102). Conversely, axial PsA primarily affects the cervical spine (98). A study focusing on this segment reported a 70% frequency of cervical radiological involvement in PsA patients with an average disease duration of 10 years. Additionally, a high frequency of posterior elements fusion (zygo-apophyseal or facet joints) was observed. Syndesmophyte morphology also differs between the two diseases. Axial PsA is characterized by non-marginal, asymmetrical, and "chunky" syndesmophytes, whereas established r-axSpA or AS is associated with marginal, symmetric, and well-delimited syndesmophytes (102).

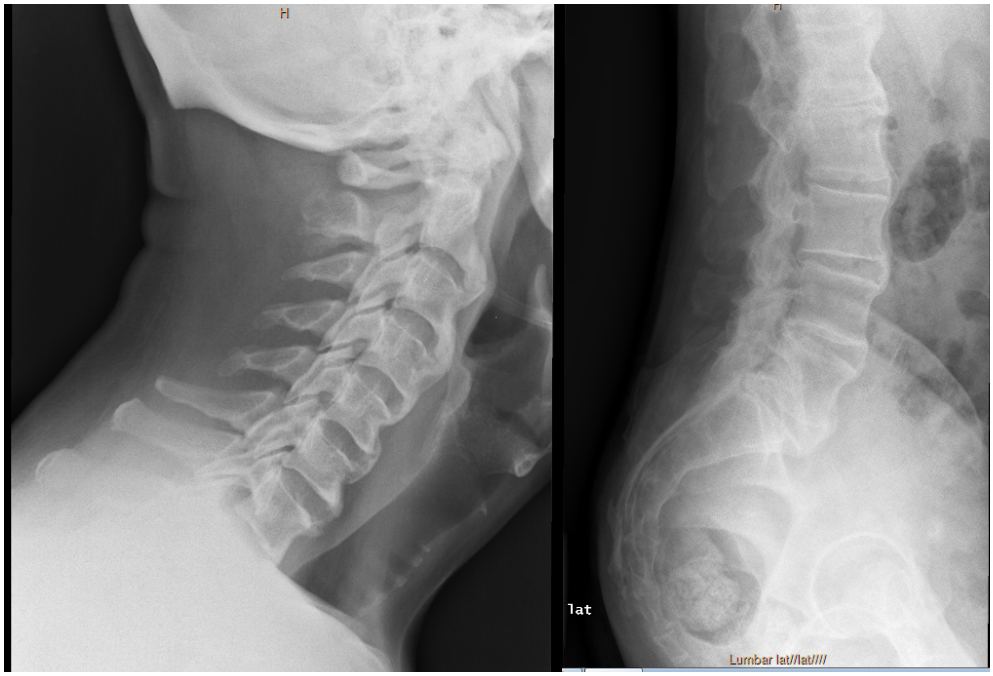

Figure 9. Cervical and lumbar x-rays of a patient with axial involvement and psoriatic arthritis. Shared with permission of the patient.

One of the key diagnostic challenges in axial PsA is differentiating it from another common condition with similar syndesmophyte appearance: diffuse idiopathic skeletal

hyperostosis (DISH). Haddad et al. conducted a study showing that both diseases can coexist, with an 8.3% prevalence of DISH in PsA patients, similar to the general population (103). The underlying pathophysiology of DISH remains unclear, and shared mechanisms of aberrant new bone formation in both diseases have not yet been identified.

MRI data in axial PsA are limited. A study conducted on the Toronto cohort, which included 125 patients, revealed that spinal MRI scans in PsA patients were primarily requested due to suspected inflammatory disease (51.1%) (104). The most commonly observed features were erosions (15.6%) and bone marrow edema (18.5%). Among cases with inflammatory back pain (IBP), only 44.6% of the scans exhibited changes consistent with spondyloarthritis. Two additional studies have explored the role of MRI in axial PsA, but yielded conflicting results. Williamson et al. performed SIJ MRI on 103 PsA patients and detected abnormalities in 38% of cases, but found no correlation with clinical signs or HLA-B27 status (105). In contrast, Castillo-Gallego et al. reported a significant association between HLA-B27 and the extent of bone marrow edema in axial PsA patients, suggesting that HLA-B27 serves as a marker of disease severity and progression, similar to what has been demonstrated in axSpA (91). The discrepancies between these studies may stem from differences in methodologies, as the first study employed a binary assessment of abnormal or normal scans, while the latter employed a semi-quantitative scoring system for the lesions.

An essential aspect to consider is the treatment response of patients with axial PsA. The most recent recommendations from GRAPPA provide treatment guidance for axial involvement based on studies conducted in axSpA(106). While the available data are limited, primarily derived from observational studies, they suggest that TNF inhibitors show efficacy in axial PsA. The MAXIMISE trial, the only randomized controlled study conducted thus far, investigates the effectiveness of an IL-17 inhibitor in axPsA and demonstrates positive outcomes(107). Secukinumab 300 mg and 150 mg significantly improved ASAS response criteria (ASAS20) response versus placebo at week 12 (63% and 66% vs 31% placebo). As for IL-12/23 inhibition, initial post-hoc analysis of pivotal studies

showed significant improvement in BASDAI and ASDAS in PsA patients with physician-reported spondylitis (108). However, subsequent placebo-controlled trials failed to demonstrate efficacy in axSpA (109). Post-hoc analysis of guselkumab trials suggests a beneficial effect of this IL-23 inhibitor on axial involvement in PsA patients (110). Nonetheless, confirmation through a dedicated randomized controlled trial, which is currently recruiting, is necessary (111). In the following table, I outline the most relevant trials in axial PsA and their inclusion criteria.

Table 4. Studies evaluating treatment response in Axial Psoriatic arthritis.

	Lubrano et al. Clin Exp Rheumatol (112)	**Lubrano et al.** J Rheumatol. 2016 (113)	**Haroon et al.** Arthritis Res Ther. 2018 (114)	**Baraliakos et al**. Ann Rheum Dis. 2021 (107)
Design	Multi-center observational study	Single-center observational study	Single-center open-label controlled trial	Muti-centre RDBCT phase 3 trial
Inclusion criteria	CASPAR criteria IBP AND/or radiological axial involvement Eligible for TNFi according to local guidelines	CASPAR criteria IBP AND/or radiological axial involvement Eligible for TNFi according to local guidelines	CASPAR criteria OR mNYC criteria IBP with spinal VAS score ≥ 4 and BASDAI ≥ 4 MRI proven SIJ BMO Naïve to bDMARDs	CASPAR criteria IBP with spinal VAS score ≥ 4 and BASDAI ≥ 4 Inadequate response to 2 NSAIDs Naïve to bDMARDs
Sample size	32	58	15 axPsA, 15 AS, 10 controls (chronic LBP)	503
Primary outcome	BASDAI 50 response at Week 52	BASDAI 50 response at Week 52	Mean change in ASDAS at week 2	ASAS20 response with SEC 300 at week 12
Intervention	Etanercept 50 mg s.c. w	Adalimumab 40 mg eow OR Etanercept 50 mg w OR Golimumab 50 mg mo	Triamcinolone acetonide 80 mg i.m depot	Arm 1: Secukinumab 300 mg Arm 2: Secukinumab 150 mg Arm 3: Placebo
Results	72% patients achieved BASDAI 50	Percentages of patients achieving: BASDAI 50 31.2% CPDAI < 4 35.4% DAPSA ≤ 3.3 22.9% PR 22.9% MDA 50%	Mean change in ASDAS: axPsA: 1.43 ±0.39 AS: 1.03 ±0.30 Controls: 0.81±0.26	63.1% responders with SEC 300 vs 31.3% with placebo with an OR 3.81 (p <0.0001)

To Lump or To Split SpA?

The debate over whether to lump or split the group of diseases known as SpA is a complex one, with compelling arguments on both sides as seen in the introduction of this thesis. Those in favor of lumping argue that the similarities in underlying pathophysiology, shared genetic markers like HLA-B27, and commonalities in clinical symptoms among the various forms of SpA (including AS, PsA, ReA, arthritis associated with IBD and uSpA) warrant a unified approach to diagnosis and treatment. On the other hand, those who advocate for splitting argue that significant differences exist in the clinical manifestations, prognosis, and response to treatment across these diseases. They posit that a more nuanced classification system would lead to more personalized treatment regimens, improve patient outcomes, and facilitate more focused research efforts. A better understanding of the clinical phenotypes together with future research in genetic drivers might erase artificial splits and identify the correct splits that will ultimately help a better management and treatment of SpA patients.

HYPOTHESIS

Heterogeneity in clinical characteristics including extra-musculoskeletal manifestations, and imaging features of axial and peripheral phenotypes within the spondyloarthritis group of diseases (mainly axial spondyloarthritis and psoriatic arthritis) may point towards potential endotypic differences that could help understand the spondyloarthritis disease spectrum.

OBJECTIVES

The main objectives of this thesis were:

1. To determine the prevalence of EMMs (uveitis, psoriasis and IBD) in large cohorts of AS (r-axSpA) and PsA across the world and its relationship with diagnostic delay.
2. To explore the baseline characteristics of r-axSpA and nr-axSpA and to evaluate the level of disease control according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) and the drug survival of first biologic disease modifying anti-rheumatic drug (bDMARD) at one year.
3. To explore the axial phenotype of PsA regarding its clinical and radiological characteristics and compare it with ankylosing spondylitis (r-axSpA) with psoriasis.
4. To identify through unsupervised statistical analysis methodology, the potential distinct phenotypes within a broad SpA population.

MATERIALS, METHODS AND RESULTS

Study 1. Diagnostic delay is associated with uveitis and inflammatory bowel disease in AS: a study of extra-musculoskeletal manifestations in SpA.

Michelena X, Zhao SS, Marco-Pascual C, Almirall M, Collantes E, Font-Ugalde P, López-Medina C, Wei JC, Morgan AW, Rodríguez J, Juanola X, Vázquez-Mellado J, Marzo-Ortega H.

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Clinical science

Diagnostic delay is associated with uveitis and inflammatory bowel disease in AS: a study of extra-musculoskeletal manifestations in SpA

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Abstract

Objectives: To examine the prevalence of extra-musculoskeletal manifestations (EMM) and the association between diagnostic delay and their incidence in AS and PsA.

Methods: This was a retrospective, cohort study comprising two single centre cohorts in Europe and one multicentre cohort in Latin America (RESPONDIA). Crude prevalence of EMMs (uveitis, IBD and psoriasis) was calculated across geographic area and adjusted by direct standardization. Cox proportional hazard analysis was performed to assess the association between diagnostic delay and EMM incidence.

Results: Of 3553 patients, 2097 had AS and 1456 had PsA. The overall prevalence of uveitis was 22.9% (95% CI: 21.1, 24.8) in AS and 3.8% (95% CI: 2.9, 5.0) in PsA; 8.1% (95% CI: 7.0, 9.4) and 2.1% (1.3, 2.9), respectively, for IBD; and 11.0% (95% CI: 9.7, 12.4) and 94.6% (93.0, 95.9), respectively, for psoriasis. The EMM often presented before the arthritis (uveitis 45.1% and 33.3%, and IBD 37.4% and 70%, in AS and PsA, respectively). In the multivariable model, longer diagnostic delay (≥5 years) associated with more uveitis (hazard ratio [HR] 4.01; 95% CI: 3.23, 4.07) and IBD events (HR 1.85; 95% CI: 1.28, 2.67) in AS. Diagnostic delay was not significantly associated with uveitis (HR 1.57; 95% CI: 0.69, 3.59) or IBD events (HR 1.59; 95% CI: 0.39, 6.37) in PsA.

Conclusion: EMMs are more prevalent in AS than PsA and often present before the onset of the articular disease. A longer diagnostic delay is associated with the '*de novo*' appearance of uveitis and IBD in AS, highlighting the need to enhance diagnostic strategies to shorten the time from first symptom to diagnosis in SpA.

Keywords: AS, PsA, psoriasis, uveitis, IBD, diagnostic delay

Rheumatology key messages

- The prevalence of uveitis and IBD is higher in AS when compared with PsA.
- Uveitis or IBD may present before the onset of the SpA diagnosis in a significant proportion of people with AS and PsA.
- A longer diagnostic delay is associated with a higher probability of uveitis and IBD in AS.

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Introduction

Axial spondyloarthritis (axSpA) encompassing AS, also known as radiographic axSpA (r-axSpA), and PsA are two distinct chronic inflammatory diseases under the umbrella of the spondyloarthritides (SpA) [1, 2]. The different SpAs share common clinical and genetic characteristics including inflammation of axial (spine/sacroiliac) and peripheral joints with extra-musculoskeletal manifestations (EMMs). EMMs strongly linked to the SpA disease group are uveitis, IBD and psoriasis [3]. Their prevalence has been outlined in recent meta-analyses as higher in axSpA (pooled prevalence of uveitis, IBD and psoriasis of 23%, 6.4% and 10.2%, respectively) than PsA (pooled prevalence of 3.2% for uveitis and 3.3% IBD of 3.2%) [4, 5].

In axSpA, EMMs have been shown to impact the disease course with a recent report revealing increased cardiovascular risk that appears proportional to the number of EMMs in addition to higher axSpA disease activity and functional impairment [6, 7]. By contrast, this relationship with functional disability was not seen in the OASIS cohort after 12 years of follow-up [8]. The relationship between disease duration and EMM incidence has been confirmed in several studies [8–11]. Also, HLA-B27 positivity has been shown to be associated with uveitis in several axSpA cohorts [11, 12].

Despite greater awareness and improved diagnostic techniques over the last two decades, delay to diagnosis remains a significant unmet need in SpA when compared with other chronic inflammatory arthritides. This is particularly the case in axSpA with consequent impact on disease outcome [13]. Longer diagnostic delay may also lead to higher incidence of EMMs, a hypothesis that has not been fully investigated yet. The aims of this study are to examine the prevalence of EMM and the effect of diagnostic delay in their appearance in large cohorts of AS and PsA.

Methods

We performed a retrospective, multicentre, cohort study across three geographic areas comprising two single centre cohorts in Europe (Chapel Allerton Hospital, Leeds, UK and Hospital Universitari de Bellvitge, Barcelona, Spain) and one multicentre cohort in Latin America (RESPONDIA Cohort comprising Argentina, Brazil, Chile, Costa Rica, Mexico, Peru, Uruguay, Venezuela) [14]. Data from patients older than 18 years with a primary clinician diagnosis of AS or PsA were included in the analyses. All participants provided informed written consent and the study was approved by the Hospital Universitari de Bellvitge Research Ethics Committee (Approval Number PR004/20). Individual cohort ethics and inclusion criteria details are shown in Supplementary Materials, available at *Rheumatology* online. Protocol design in each cohort predated the development of ASAS and CASPAR classification criteria, and hence the original nomenclature utilized in the different studies referring to ankylosing spondylitis rather than r-axSpA will be utilized in this report.

Age, sex, date of onset of musculoskeletal symptoms, date of diagnosis, date of last follow-up, disease duration (calculated as time from diagnosis to last available follow-up date), HLA-B27 status, history of uveitis, IBD (including Crohn's disease, ulcerative colitis and undifferentiated IBD) and psoriasis (as confirmed by a physician) together with their onset dates were collected as variables. Data from all cohorts were collected at the inclusion time point with missing values retrieved from clinical notes at a later time point.

Statistical analysis

Demographic characteristics were compared by disease (AS and PsA) and across the three geographic cohorts. Student's *t* or Mann–Whitney *U* tests for continuous variables and the chi-square test for categorical variables were used as appropriate. Prevalence of EMM was calculated (with 95% CI) overall and for each of the three geographic areas and by disease. Crude prevalence was adjusted for age by direct standardization using the WHO World standard population as reference [15].

Diagnostic delay was defined as the time between date of musculoskeletal symptom onset and date of diagnosis. To examine the relationship between diagnostic delay and appearance of EMM, only EMMs that occurred after the date of diagnosis were considered. Only uveitis and IBD were analysed as psoriasis predated the majority of PsA diagnoses (~85%). Only patients with available EMM onset date were included.

Diagnostic delay was categorized by the median, that is, 5 years or more delay in AS and 3 years or more in PsA. An additional sub-analysis using 5 years or more in PsA was also performed. Time-to-event analysis was performed and defined as time from disease diagnosis (AS or PsA) to onset of EMM or to the last available follow-up date and described using Kaplan–Meier plots and log-rank test. Cox proportional hazard analysis was performed adjusting for sex, age of onset and geographical location to assess the association between diagnostic delay on incidence of EMM. The proportional hazards assumption was examined using statistical (Schoenfeld residuals) and graphical approaches. All analysis was conducted using Stata version 16.1 (StataCorp, College Station, TX, USA).

Results

Demographic characteristics of cohort populations

Data from 3553 patients were analysed comprising 2097 with AS and 1456 with PsA. Demographic characteristics of the different cohorts are presented for AS and PsA in Table 1. Subjects with AS in Latin America were younger, with correspondingly shorter disease duration, at the time of enrolment (last available follow-up) compared with the Barcelona and Leeds Cohorts. Similar diagnostic delay was observed in the three cohorts.

For PsA, the vast majority of patients presented with PsA after psoriasis with similar proportions in all cohorts. A longer delay between psoriasis and PsA onset was seen in the Barcelona cohort, which also had longer disease duration and older age of onset when compared with the Leeds and Latin America cohorts (Table 1). Missing data proportions of the different variables are shown in Supplementary Tables S1 and S2, available at *Rheumatology* online.

Overall prevalence of extra-musculoskeletal manifestations by geographical location and diagnosis

The overall prevalence of uveitis in the three cohorts was 22.9% (95% CI: 21.1, 24.8) in AS and 3.8% (95% CI: 2.9, 5.0) in PsA; 8.1% (95% CI: 7.0, 9.4) and 2.1% (95% CI: 1.3,

Table 1. Demographic characteristics of AS and PsA patients from the respective geographical cohorts

	Latin America	Barcelona	Leeds	*P*-value
AS[a]				
n	1169	472	456	
Age, mean (S.D.), years	45.6 (14.6)	56.5 (15.8)	51.4 (14.5)	<0.001
Sex, male, *n* (%)	867 (74.2)	335 (71.1)	324 (72.8)	0.44
HLA-B27 positive, *n* (%)	–	347 (77.6)	251 (81.8)	0.17
Age at symptom onset, median (IQR), years	26.0 (19.0, 36.0)	25.0 (20.0, 33.0)	24.0 (18.0, 32.0)	<0.001
Disease duration, median (IQR), years	7.0 (4.0, 13.0)	19.5 (10.0, 35.0)	13.5 (7.0, 24.0)	<0.001
Diagnostic delay, median (IQR), years	4.0 (1.0, 10.0)	3.0 (1.0, 8.0)	5.0 (2.0, 10.0)	<0.001
PsA[b]				
n	392	442	622	
Age, mean (S.D.), years	53.5 (13.6)	59.6 (14.1)	53.5 (13.2)	<0.001
Sex, male, *n* (%)	201 (51.3)	214 (48.4)	298 (50.6)	0.68
HLA-B27 positive, *n* (%)	–	46 (11.8)	57 (18.8)	0.01
Age at symptom onset, median (IQR), years	42.0 (32.0, 51.0)	41.0 (30.0, 51.0)	38.0 (27.0, 48.0)	<0.001
Disease duration, median (IQR), years	6.0 (3.0, 10.0)	13.0 (7.0, 24.0)	10.0 (6.0, 13.0)	<0.001
Diagnostic delay, median (IQR), years	1.0 (0.0, 5.0)	2.0 (1.0, 6.0)	1.0 (0.0, 2.0)	<0.001
Psoriasis duration, median (IQR), years	16.0 (9.0, 26.0)	29.0 (17.0, 40.0)	22.0 (12.0, 34.0)	<0.001
PsA diagnosed after psoriasis, *n* (%)	203 (85.7)	366 (88.0)	376 (87.9)	0.65
Psoriasis-PsA delay, median (IQR), years	6.0 (1.0, 15.0)	9.0 (2.0, 19.0)	7.0 (1.0, 20.0)	0.026

[a] Missing data proportion is included in Supplementary Table S1, available at *Rheumatology* online.
[b] Missing data proportion is included in Supplementary Table S2, available at *Rheumatology* online. IQR: interquartile range.

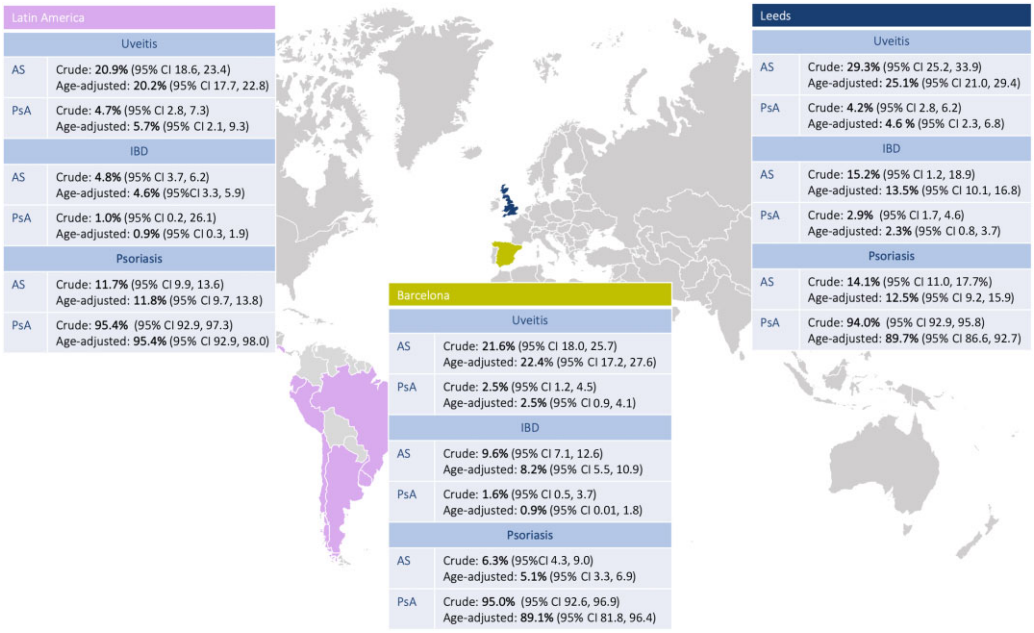

Figure 1. Crude and age-adjusted prevalence of extra-musculoskeletal manifestations divided by location and disease

2.9), respectively, for IBD, and 11.0% (95% CI: 9.7, 12.4) and 94.6% (95% CI: 93.0, 95.9), respectively, for psoriasis. Crude and age-standardized prevalence are presented across geographical locations and disease (Fig. 1).

Relationship between extra-musculoskeletal manifestations onset and SpA diagnosis

Divided by diagnosis, EMMs were more prevalent in the AS population (28.9%, $n = 600/2073$ uveitis and/or IBD *vs* 5.8%, $n = 74/1284$ in the PsA group). For AS patients with uveitis, the first episode of uveitis occurred before AS diagnosis in 45.1%. Of patients with uveitis, 33.3% reported a first episode of uveitis before the diagnosis of PsA. Regarding IBD, 37.4% of AS patients with concomitant IBD were diagnosed with IBD before the AS diagnosis and 70% of patients with PsA and concomitant IBD were diagnosed with IBD before the PsA diagnosis.

Diagnostic delay and extra-musculoskeletal manifestations

For the time-to-event analysis, only EMMs that happened after the diagnosis of SpA (AS/PsA) were considered. Demographic variables and their relationship to incidence of uveitis and IBD (incidence rate ratios) after diagnosis of SpA are presented in Supplementary Table S3a and b, available at *Rheumatology* online. Kaplan–Meier graphs are presented for each EMM (uveitis and IBD) divided by diagnosis (AS or PsA) according to diagnostic delay (Fig. 2). In the multivariable Cox model, AS

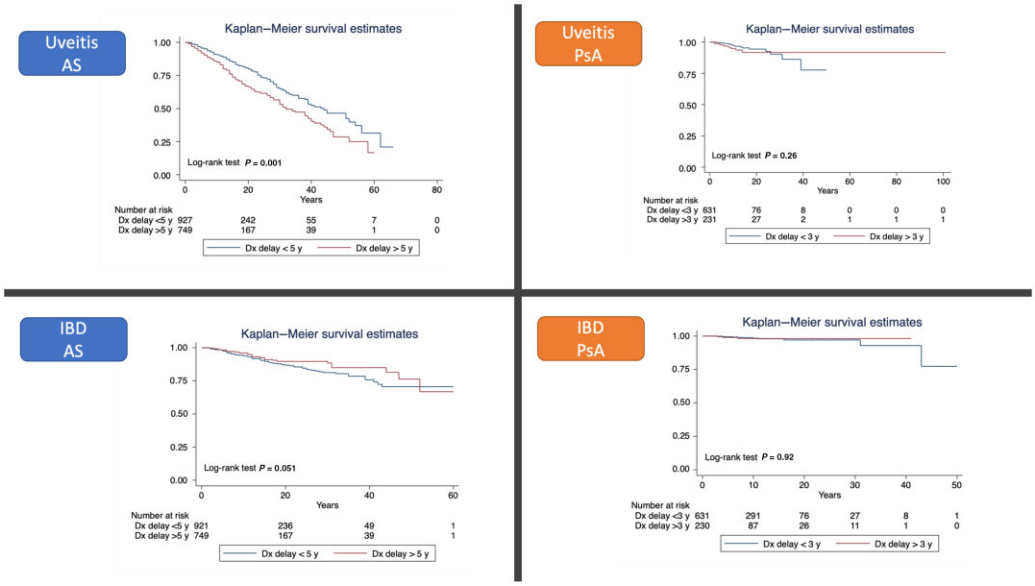

Figure 2. Kaplan–Meier survival curves divided by disease and extra-musculoskeletal manifestation. Dx: Diagnostic; y: years

patients with longer diagnostic delay (≥5 years) had more uveitis events (hazard ratio [HR] 4.01; 95% CI: 3.23, 4.07) when adjusted for age of onset, sex and location. This was also observed in AS patients with IBD (HR 1.85; 95% CI: 1.28, 2.67). HRs for diagnostic delay were not significant for uveitis (HR 1.57; 95% CI: 0.69, 3.59) or IBD events (HR 1.59; 95% CI: 0.39, 6.37) in PsA. No differences were seen in additional analyses on PsA patients divided by a 5-year diagnostic delay cut-off (Supplementary Fig. S1, available at *Rheumatology* online).

Discussion

This study examined the prevalence of EMMs in different SpA (AS and PsA) cohorts and their relationship with diagnostic delay. Our results show that, despite some differences in demographic factors, the prevalence of uveitis and IBD is higher in AS when compared with PsA. Interestingly, when exploring the characteristics of SpA patients with EMMs, we found that a significant proportion presented with uveitis or IBD before the onset of the SpA diagnosis. Furthermore, longer diagnostic delay was associated with a higher probability of uveitis and IBD in AS, suggesting that longer time of uncontrolled inflammation might influence the incidence of EMMs.

In our study, the combined prevalence of uveitis, IBD and psoriasis in AS was 22.9%, 8.1% and 11.0%, respectively, in line with previous publications [4]. Similarly, in PsA, the combined prevalence of uveitis, IBD and psoriasis was 3.8%, 2.1% and 94.6%, respectively, also consistent with results published in a recent meta-analysis [5]. There were some differences across geographic cohorts, such as higher prevalence of uveitis and IBD seen in the Leeds cohort when compared with the other cohorts in this study and a prior AS meta-analysis, which may be explained by a longer disease duration as previously shown [4, 16]. Interestingly, IBD prevalence in AS was significantly lower in the Latin American population compared with the other two cohorts. This is consistent with a recent report of the multi-country observational study PROOF including axSpA patients, outlining an IBD prevalence of just 2.3% in Latin America [17]. Access to prompt secondary care or perhaps differential genetic factors underlying the populations might partly explain this difference when compared with the European cohorts.

Overall, 35% of AS and up to 70% of PsA patients in our study presented with IBD before the SpA diagnosis was made. We decided to exclude these patients in the time-to-event analysis for a number of reasons. Firstly, individuals with a pre-existing history of EMMs are more likely to experience subsequent events or flares, which may confound the results of the analysis. Secondly, longer diagnostic delay may influence the risk of subsequent episodes of flares of EMMs, and excluding patients with prior EMMs can help mitigate this potential confounding factor. Additionally, diagnostic delay was defined as the time from onset of articular (peripheral joint or spinal symptoms) to SpA diagnosis, and thus including patients with pre-existing EMMs may bias the results, as EMMs may have occurred before the onset of joint symptoms. Although our decision to exclude a considerable number of patients may be viewed as a limitation, it is noteworthy that our findings align with previous literature. Specifically, a recent analysis from the Swedish Registry demonstrated that patients with IBD were diagnosed with SpA both before and after their IBD diagnosis. Notably, this association was most pronounced during the 2-year period preceding and following the diagnosis of IBD [18]. Nevertheless, the cumulative incidence of SpA kept increasing in the first 10 years following the diagnosis of IBD particularly in those with Crohn's disease. In line with our findings, the strongest association in IBD was found with incident PsA (HR 12.0; CI: 10.8, 13.4) outlining that most PsA diagnoses happen after the IBD diagnosis. In the same manner, our data show that in ∼40% of patients, uveitis occurred before the SpA diagnosis. These findings highlight gastroenterology and ophthalmology clinics as potential stages for earlier identification of PsA and axSpA. Indeed, awareness of the need for early referral strategies from ophthalmology to rheumatology is increasing. The SENTINEL study enrolled 798 patients with anterior uveitis that were thoroughly assessed by a rheumatologist finding a prevalence of 50% for axSpA and 17.5% for peripheral SpA [19]. Referral strategies in IBD are also being explored to

identify undiagnosed SpA [20]. Yet, our data show that long diagnostic delays remain an unmet need and influence the appearance of uveitis and IBD, which highlights the need for multi-specialty collaborative work at the clinical level in order to improve and enhance referral strategies between ophthalmology, gastroenterology, dermatology and rheumatology.

To our knowledge, this is the first study using data from cohorts across two continents to show that diagnostic delay is associated with a greater probability of uveitis and IBD in AS patients. In line with our findings, Bilge *et al.* used data from a Turkish cohort including rheumatoid arthritis and SpA patients to show that delay to diagnosis was associated with uveitis in the bivariate analysis [10]. Similarly, Gevorgyan *et al.* reported a longer diagnostic delay (10.9 *vs* 5.9 years, $P < 0.001$) when comparing patients with and without uveitis in a single US academic centre [21]. These results, together with our findings, suggest that a longer delay translates into a longer period with uncontrolled inflammation that might influence the appearance of uveitis. Cakar *et al.* found higher CRP levels in AS patients with a longer diagnostic delay, while a recent meta-analysis found higher burden of disease in those with delayed diagnosis including mobility and functional indices [22, 23]. Additionally, Varkas *et al.* found that longer disease duration in axSpA patients was associated with a higher risk of developing anterior uveitis and IBD. Also, higher mean levels of CRP in patients with uveitis and IBD suggest a cumulative exposure to inflammation, although no data on diagnostic delay were reported [24].

Our analysis did not find a significant association between longer diagnostic delay and EMMs in PsA. Small numbers and lower EMM incidence in PsA might be a possible explanation. However, a higher proportion of PsA patients are likely to have received DMARDs for peripheral joint involvement or for psoriasis treatment, which might influence the development of EMMs. Treating cutaneous psoriasis with biologic DMARDs may decrease the incidence of PsA, suggesting that a better control of inflammation may also impact the incidence of EMMs [25]. Unfortunately, treatment data were not available in our cohorts to explore this question. Larger, longitudinal studies with detailed treatment data are needed to confirm this hypothesis.

There were limitations to this study. Patients were enrolled in the study based on their primary clinician diagnosis rather than validated criteria such as the Classification Criteria for Psoriatic Arthritis (CASPAR) or modified New York (mNY) criteria [26, 27]. The characteristics of EMMs, including the time of onset, were either recalled by the participants or extracted from clinical notes, which may have introduced measurement bias. However, this limitation is common where investigators rely on patient recall or clinical notes; prospective designs also have limitations, e.g. attrition and cost. Another limitation is missing HLA-B27 data and lack of treatment data in our cohorts, both of which could potentially impact the incidence of EMMs. Moreover, CRP was not collected systematically in all cohorts, which prevented us from exploring the hypothesis that the effect of diagnostic delay on EMM events is explained by uncontrolled inflammation.

In conclusion, these data show that the prevalence of EMMs including uveitis, IBD and psoriasis is higher in AS than PsA, with a substantial proportion presenting before the onset of the articular disease. A longer diagnostic delay is associated with a greater probability of uveitis and IBD in AS, perhaps due to uncontrolled inflammation over time. These results highlight the need for multi-specialty collaboration to improve diagnostic strategies and referral pathways in order to reduce diagnostic delay in SpA.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data are available upon reasonable request to the corresponding author.

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Supplementary Material. Diagnostic delay is associated with Uveitis and Inflammatory Bowel Disease in AS: a study of extra-musculoskeletal manifestations in SpA.

Supplementary Table 1: Missing data proportions of demographic variables in AS divided by geographical location.

AS	***Iberian America***	***Barcelona***	***Leeds***
N	1169	472	456
Age	3/1169 (0.3%)	0/472 (0%)	1/456 (0.2%)
Sex	0/1169 (0%)	1/472 (0.2%)	11/456 (2.4%)
HLA-B27 positivity	1169/1169 (100%)	25/472 (5.30%)	149/456 (32.7%)
Age symptom onset	32/1169 (2.7%)	10/472 (2.1%)	100/456 (21.9%)
Disease duration	288/1169 (24.6%)	8/472 (1.7%)	50/456 (10.96%)
Diagnostic delay	299/1169 (25.6)	16/472 (3.4%)	111/456 (24.3%)
EMM onset date	145/290 (50%)	35/140 (25%)	93/168 (55.4%)

Supplementary Table 2: Missing data proportions of demographic variables in PsA divided by geographical location.

PsA	***Iberian America***	***Barcelona***	***Leeds***
N	392	442	622
Age	1/392 (0.3%)	1/442 (0.1%)	3/622 (0.5%)
Sex	0/392 (0%)	0/442 (0%)	33/622 (5.3%)
HLAB27	392/392 (100%)	51/442(11.5%)	318/622 (51.1%)
Age symptom onset	12/392 (3.1%)	10/442 (2.3%)	57/622 (9.2%)
Disease duration	67/392 (17.1%)	95/442 (21.5%)	159/622 (25.6%)
Diagnostic delay	70/392 (17.9%)	95/442 (21.5%)	180/622 (28.9%)
Psoriasis duration	155/392 (39.5%)	22/442 (5%)	189/622 (30.4%)

PsA after psoriasis	155/392 (39.5%)	26/442 (5.9%)	194/622 (31.2%)
Psoriasis-PsA delay	189/392 (48.2%)	76/442 (17.2%)	246/622 (39.6%)
EMM onset date	12/21 (57.1%)	5/15 (33.3%)	8/37 (21.6%)

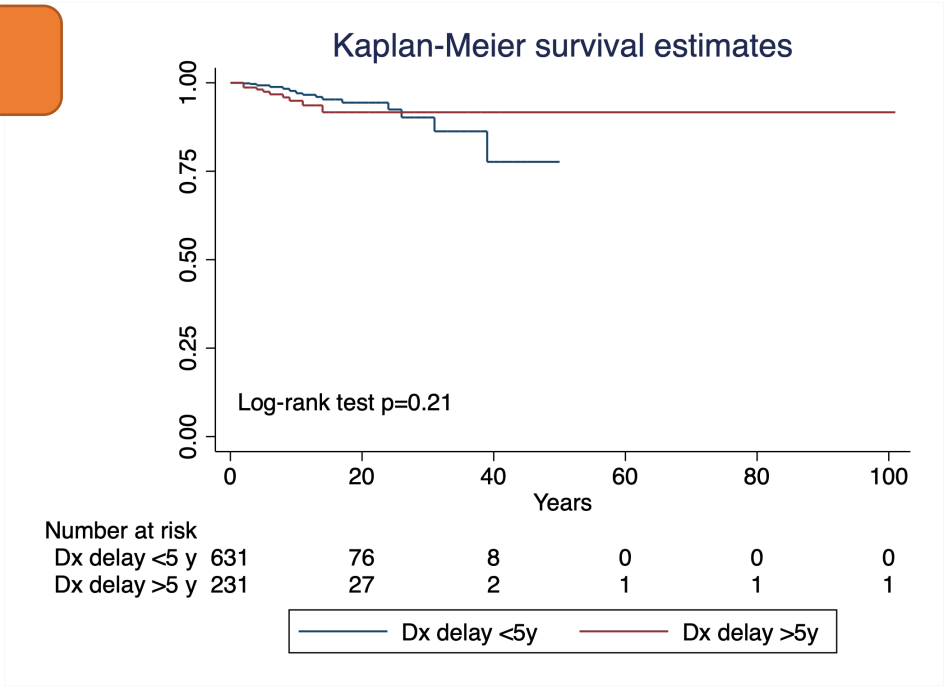
Supplementary Table 3 a and 3b: Incidence rate ratios of demographic characteristics divided by EMM (Uveitis/IBD) and Disease (AS/PSA).

Uveitis	***AS***		***PsA***	
Variables	Incidence Rate Ratio	95% CI	Incidence Rate Ratio	95% CI
Sex (F/M)	1.1	0.88-1.39	1.86	0.83-4.47
Age onset categories				
- 18-29 y	0.95	0.76-1.19	1.71	0.77-3.74
- 30-39 y	1.02	0.78-1.33	0.91	0.33-2.18
- 40-49 y	1.42	0.98-2.02	0.75	0.22-1.99
- 50-59 y	0.48	0.17-1.06	0.90	0.23-2.60
- >60 y	0.45	0.01-2.53	-	-
HLA-B27	**1.99**	**1.17-3.64***	**6.6**	**1.98-21.99***
Diagnostic delay	**1.55**	**1.27-1.92***	1.46	0.61-3.29

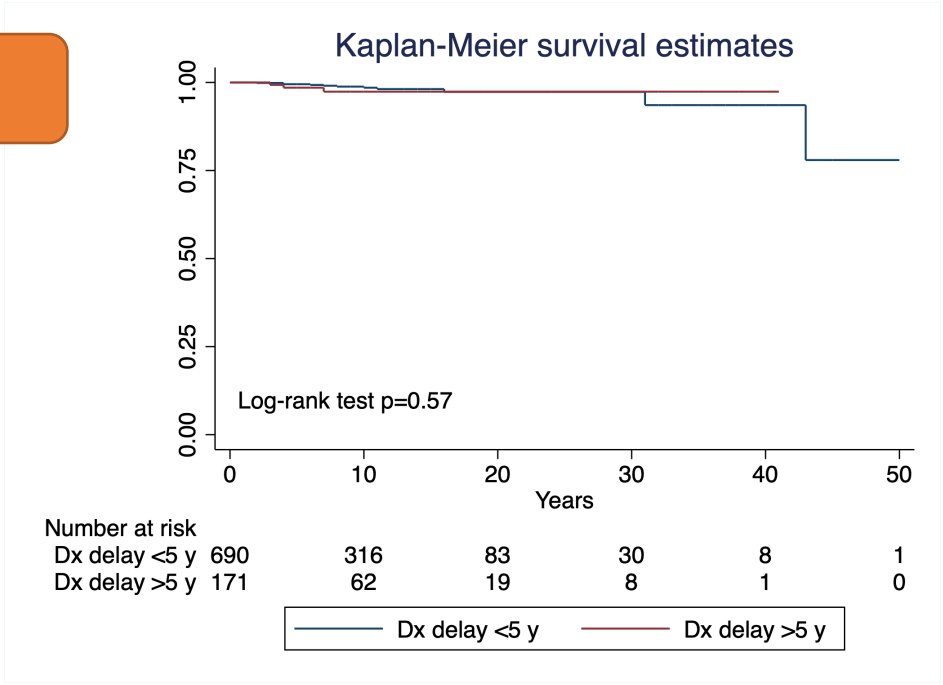
IBD	***AS***		***PsA***	
Variables	Incidence Rate Ratio	95% CI	Incidence Rate Ratio	95% CI
Sex (F/M)	**2.61**	**1.86-3.66***	2.28	0.66-9.97
Age onset categories				
- 18-29 y	**0.36**	**0.25-0.51***	0.32	0.03-1.44
- 30-39 y	1.68	1.13-2.46	0.49	0.05-2.20
- 40-49 y	**2.21**	**1.28-3.6***	2.76	0.79-9.06
- 50-59 y	**3.35**	**1.78-5.85***	1.06	0.12-4.78
- >60 y	2.47	0.29-9.11	2.86	0.32-12.9
HLA-B27	**0.21**	**0.14-0.34***	1.06	0.02-8.74
Diagnostic delay	0.70	0.49-1.01	0.84	0.15-3.17

Figure 4a and 4b: Kaplan Meier survival curves of EMMs in PsA divided by diagnostic delay (5 year cut-off)

Uveitis
PsA



IBD
PsA



In the multivariable Cox regression analysis, HRs for diagnostic delay divided by a 5 year cut-off were not significant for uveitis (HR 1.58, 95%CI 0.64-3.91) or IBD events (HR 2.73, 95%CI 0.65-11.52) in PsA.

Study 2. Similar biologic drug response regardless of radiographic status in axial spondyloarthritis: data from the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis registry.

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Concise report

Similar biologic drug response regardless of radiographic status in axial spondyloarthritis: data from the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis registry

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Abstract

Objective. To describe the baseline characteristics, biologic DMARD (bDMARD) response and drug survival of axial SpA (axSpA) patients in the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) according to radiographic status.

Methods. The BSRBR-AS is a national prospective cohort including axSpA participants classified according to the Assessment of SpondyloArthritis international Society criteria. In this analysis, baseline data of patients starting bDMARDs were compared. Ankylosing Spondylitis Disease Activity Scores (ASDASs) for low disease status, clinically important improvement (CII) and major improvement (MI) at 1 year were used to assess treatment response. Cox proportional hazards analysis was performed after adjusting for clinically relevant confounders.

Results. A total of 1145 axSpA patients were included. Higher male prevalence, older age and longer disease duration were seen in the radiographic axSpA (r-axSpA) subgroup. Based on a complete case analysis (290 patients), two-thirds of patients achieved an ASDAS low disease state at 1 year regardless of radiographic status [non-radiographic axSpA (nr-axSpA) 64.2% *vs* r-axSpA 66.1]. No statistically significant differences were seen between the subgroups in attaining ASDAS CII (nr-axSpA 50.7% *vs* r-axSpA 44.7%) or MI (nr-axSpA 20% *vs* r-axSpA 18.7%). Drug survival probability curves were similar for both subgroups and the hazard ratio for nr-axSpA/axSpA was 0.94 (95% CI 0.69, 1.28) when adjusted for sex, age, baseline ASDAS with CRP, smoking status, disease duration, HLA-B27 and prescribed biologic.

Conclusions. Although there appeared to be some differences in the baseline characteristics when exploring this cohort according to radiographic status, which are likely related to the natural history of the disease, the level of biologic response and drug survival was comparable between nr-axSpA and r-axSpA.

Key words: ankylosing spondylitis, axial spondyloarthritis, drug survival, biological therapy, epidemiology

CLINICAL SCIENCE

Rheumatology key messages

- This is the largest prospective study comparing nr-axSpA and r-axSpA showing similar baseline characteristics.
- Drug response evaluated by ASDAS and drug survival was comparable between nr-axSpA and r-axSpA.
- These results add evidence that similar treatment strategies should be followed in nr-axSpA and r-axSpA.

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Introduction

AS is the established phenotype of axial SpA (axSpA), an inflammatory condition affecting primarily the enthesis and axial skeleton, with a usually earlier, more heterogeneous phenotype classified as non-radiographic axSpA (nr-axSpA) [1]. Nr-axSpA has caused much controversy in recent years, with some arguing that it represents an

earlier disease stage that might progress to AS, called radiographic axSpA (r-axSpA), while others believe that it represents a separate entity that should be treated distinctively. Following the introduction of the Assessment of Spondyloarthritis international Society (ASAS) classification criteria [2], the rheumatology community has an increased awareness of the diagnostic issues in axSpA if such criteria are misused, particularly in the non-radiographic patient subgroup. Yet, despite growing evidence that nr-axSpA and r-axSpA show a comparable burden of disease [3], different treatment strategies are still suggested [4].

Biologic DMARDs (bDMARDs) have completely changed the outlook for patients with axSpA, with significant numbers achieving long-term remission or low disease activity over time. There are ample data on the efficacy of TNF inhibitors (TNFis) in nr-axSpA coming from phase III trials [5–8]. However, only a handful of trials (RAPID-axSpA and ESTHER trial) [5, 6] and a post-hoc analysis of the INFAST study looked at the whole axSpA spectrum [9], including patients with both non-radiographic and radiographic disease and showing comparable results across both subgroups. Real-life data are even more scarce, with only a couple of small studies [10, 11] and two larger cohorts, the DANBIO register and the Swiss Clinical Quality Management (SCQM) Cohort [12, 13] published to date.

The British Society for Rheumatology Biologics Registry for Ankylosing Spondylitis (BSRBR-AS) [14] holds a large volume of data comprising both patient subgroups (AS and nr-axSpA), with significant numbers exposed to biologic agents. Based on the hypothesis that both subgroups are part of the same disease continuum and hence have a comparable response to treatment, the aims of this study were to explore the baseline characteristics of the two populations in the BSRBR-AS cohort and to evaluate the level of disease control according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) and the drug survival of the first bDMARD at 1 year.

Methods

Longitudinal data from the prospective BSRBR-AS cohort study were used for this analysis. The BSRBR-AS cohort has been previously described [14]. Briefly, it includes axSpA patients meeting the ASAS criteria or the modified New York criteria for AS from 83 rheumatology centres across the UK recruited between December 2012 and December 2017. To enter the registry, patients with axSpA were required to be biologic naïve and were subsequently included in the 'biologic cohort' if starting a bDMARD (comprised only of TNFis at the time, mainly originator adalimumab, etanercept, infliximab or certolizumab pegol) or remained in the 'non-biologic cohort' otherwise. Clinical data and patient-reported questionnaires were retrieved at 3, 6 and 12 months and annually thereafter in the biologic cohort.

For this analysis, we included all axSpA patients starting a bDMARD who were categorized in the r-axSpA (participants with documented X-ray evidence of sacroiliitis as per the modified New York criteria in their medical notes) or the nr-axSpA subgroup (no such evidence). The primary outcome of our study was response to bDMARDs at 1 year follow-up defined as 12 months (S.D. 4) from the baseline visit and drug survival of the first initiated bDMARD. Treatment response was assessed with the ASDAS-CRP (calculated using collected CRP values and relevant patient-reported outcomes items). Where CRP was normal or <0.2 mg/dl, the value of 0.2 was used in the formula as recommended by Machado *et al.* [15]. Different scenarios were explored: patients achieving a low disease state (ASDAS <2.1), an ASDAS reduction of ≥ 2.0 [major improvement (MI)] or an ASDAS reduction of ≥ 1.1 [clinically important improvement (CII)]. Analysis was restricted to patients with an ASDAS available at baseline. We performed an additional analysis classifying patients as responders if they achieved an ASDAS low disease state or showed an ASDAS MI or CII. Where the 12 month assessment was missing but individuals remained on a drug, they were considered as responders if they demonstrated a response at 6 months.

Statistical analysis

Baseline characteristics were compared between both subgroups (nr- *vs* r-axSpA). Student's *t*- or Mann–Whitney U test for continuous variables and chi-squared test for categorical variables were used. The proportion of patients attaining an ASDAS low disease state, MI or CII were compared when the ASDAS was available for both the baseline and 1 year time point (complete case analysis).

Drug survival was defined as the time from initiation to the end of the first bDMARD (switches to biosimilars were not considered a treatment discontinuation) or to the last available follow-up date (censoring) and were explored using Kaplan–Meier plots and the log-rank test. Cox proportional hazards analysis was performed after adjusting for clinically relevant confounders (sex, age, baseline ASDAS, smoking status, disease duration, HLA-B27 and prescribed biologic) to assess the possible impact of radiographic status on response to bDMARD therapy. The proportional hazards assumption was not violated after analytical and graphical testing. All analysis was conducted using Stata version 16.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics were available in 1145 patients (Table 1), of whom 727 (63.5%) had radiographic sacroiliitis and were classified as r-axSpA. Regarding the nr-axSpA population, 90% ($n = 378$) had a positive SIJ MRI, as per the standardized ASAS definition, while only 40 patients were classified according to the clinical arm

TABLE 1 Baseline characteristics of patients of the BSRBR-AS cohort according to radiographic status

Variables	Level	nr-axSpA (*n* = 418)	r-axSpA (*n* = 727)	*P*-value
Age, mean (S.D.), years		39.7 (12.3)	46.1 (13.4)	<0.001
Sex, *n* (%)	Male	239 (57)	529 (73)	<0.001
Symptom duration, mean (S.D.), years		11.3 (10.9)	16.7 (12.9)	<0.001
Diagnostic delay, median (IQR), years		3.0 (1.0–10.0)	3.0 (0.0–11.0)	0.83
HLA-B27 (missing = 325)		227 (73)	387 (76)	0.40
Inflammatory back pain, *n* (%)		405 (97)	697 (97)	0.40
Uveitis, *n* (%)		92 (22)	205 (30)	0.003
Crohn's/colitis, *n* (%)		55 (13)	113 (17)	0.11
Psoriasis, *n* (%)		79 (19)	115 (17)	0.43
BMI, mean (S.D.)		27.5 (5.6)	28.2 (5.8)	0.10
Comorbidity count, mean (S.D.)		0.6 (0.9)	0.7 (1.0)	0.016
Smoking status, *n* (%)	Never smoked	148 (43)	218 (38)	0.040
	Ex-smoker	96 (28)	207 (36)	
	Current smoker	100 (29)	154 (27)	
CRP, median (IQR), mg/dL		0.5 (0.1–1.3)	0.9 (0.3–2.5)	<0.001
BASDAI, median (IQR)		6.7 (5.3–7.8)	6.5 (5.0–7.7)	0.12
BASFI, median (IQR)		5.9 (4.2–7.8)	6.5 (4.4–8.3)	0.043
BAS-G, mean (S.D.)		7.0 (2.0)	6.8 (2.0)	0.056
ASDAS-CRP, mean (S.D.)		2.8 (0.8)	2.8 (0.9)	0.32
ASQOL, median (IQR)		13.0 (9.0–16.0)	13.0 (9.0–15.5)	0.29
Concomitant NSAID use, *n* (%)		311 (75)	560 (77)	0.43
Biologic (to start), *n* (%)	Adalimumab	238 (57)	436 (60)	0.20
	Etanercept	131 (31)	220 (30)	
	Certolizumab	35 (8)	47 (6)	
	Golimumab	5 (1)	12 (2)	
	Secukinumab	7 (2)	10 (1)	
	Infliximab	2 (<1)	2 (<1)	

ASQOL: Ankylosing Spondylitis Quality of Life questionnaire.

[2]. Compared with nr-axSpA, those with r-axSpA were more likely to be male, older and had longer disease duration. Uveitis was more frequently reported in the r-axSpA population, who also were more likely to be ever-smokers. Baseline BASFI and CRP levels were higher in the r-axSpA subgroup. When exploring comorbidities, these were statistically more frequent in the r-axSpA subgroup, with the main difference seen in the prevalence of hypertension (see supplementary material 1, available at *Rheumatology* online).

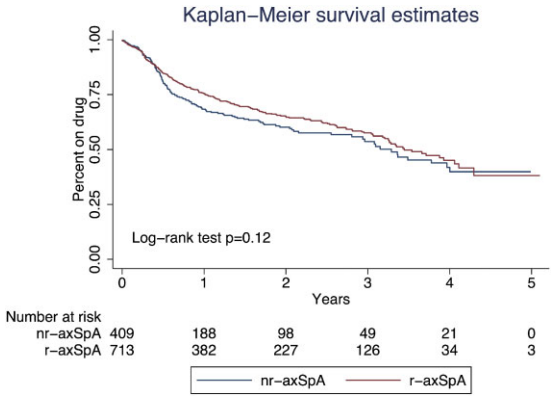
Disease activity and treatment response

Disease activity measures and functional index at baseline and the 1 year time point are presented in supplementary material 2, available at *Rheumatology* online. Follow-up ASDAS was available in only 290 patients, so we explored the baseline characteristics of patients with missing values and found no significant differences in baseline ASDAS-CRP, concomitant NSAID or TNF drug used (supplementary material 3, available at *Rheumatology* online). Of note, patients with missing values were significantly younger and had a shorter disease duration. Overall, two-thirds of the patients with available follow-up ASDAS data achieved a low disease state (ASDAS <2.1) at 1 year regardless of radiographic status [nr-axSpA 64.2% *vs* r-axSpA 66.1%; difference −1.9% (95% CI −13.7, 9.8)]. Further, no significant differences were seen between the subgroups in attaining ASDAS CII [nr-axSpA 50.7% *vs* r-axSpA 44.7%; difference 6.0% (95% CI −7.8, 19.8)] or MI [nr-axSpA 20% *vs* r-axSpA 18.7%; difference 1.3% (95% CI −9.7, 12.3)]. Additionally, no differences were seen between the r- and nr-axSpA subgroups when patients were classified as responders (ASDAS low disease state, CII or MI) or non-responders [nr-axSpA 76.2% *vs* r-axSpA 72.6 responders; difference 3.6% (95% CI −5.2, 12.3)].

Drug survival

The median follow-up was 24 months (IQR 12–39). The first bDMARD stop time was available for 1122 patients. A total of 387 patients (33.8%) stopped their first bDMARD due to adverse events (nr-axSpA 34%, r-axSpA 37%) and lack of efficacy (nr-axSpA 35%, r-axSpA 30%) as the most frequent reasons for discontinuation, with no statistically significant differences found between both subgroups. Kaplan–Meier curves were similar for both subgroups (log-rank test $P = 0.12$), with a median survival time of 39.5 months (95% CI 33.7, 48.1) in the nr-axSpA subgroup *vs* 41.4 months (95% CI 38.5, 49.4) in the r-axSpA subgroup (Fig. 1). In the multivariable analysis, the hazard ratio for nr-axSpA/axSpA was 0.94 (95% CI 0.69, 1.28) when adjusted for sex, age, baseline ASDAS-CRP, smoking status, disease duration, HLA-B27 status and prescribed biologic.

FIG. 1 Kaplan–Meier survival curves of nr-axSpA *vs* r-axSpA



Interaction terms with gender and HLA-B27 were added into the model and did not show significant differences. When subdividing the nr-axSpA population into those fulfilling the ASAS imaging or clinical criteria, survival curves were similar for the three subgroups (supplementary material 4, available at *Rheumatology* online).

Discussion

Publication of the ASAS classification criteria led to considerable debate over the last decade as to whether both nr-axSpA and r-axSpA should be considered the same entity. Incidentally, the ASAS criteria were never created to separate, but to encompass the whole axSpA continuum, facilitating the identification of homogeneous cohorts in clinical trials. In our analysis of real-world data from a prospective multicentre cohort, baseline demographic and clinical characteristics were broadly similar between nr-axSpA and r-axSpA (AS). Further, the level of bDMARD response according to the ASDAS was comparable at 1 year between subgroups, as was the survival time of the first bDMARD, even in the adjusted multivariable analysis. Baseline characteristics of our cohort were similar to previously published reports, although some particularities are worth mentioning. In our study, HLA-B27 prevalence was similar between nr- and r-axSpA, as shown in the SCQM cohort, while r-axSpA patients from the DANBIO study had a higher prevalence of positive HLA-B27 [12, 13]. There is a rationale to assuming that nr- and r-axSpA have the same genetic background as part of the whole axSpA continuum. The differences with the Danish registry might be explained by the heterogeneity of the included patients, as recruitment started in 2000, predating the publication of the ASAS criteria, which led to the cohort being classified retrospectively for the analysis. In the BSRBR-AS cohort, r-axSpA patients are more frequently male than nr-axSpA patients and this is in line with published literature [3]. In addition, CRP levels and smoking history were different between subgroups and might explain a higher likelihood of progressing to r-axSpA, as these have been postulated as radiographic progression factors [16]. The higher radiographic damage of r-axSpA might relate to higher BASMI and BASFI scores found in this subgroup as part of the natural history of axSpA. Moreover, comorbidity count was statistically higher in patients with r-axSpA, mainly because of the prevalence of hypertension. Older age and longer disease duration in the r-axSpA subgroup might explain these findings [17].

We centred our analysis on the ASDAS response, as this has been shown to have good discriminatory power in both AS (r-axSpA) and nr-axSpA [18]. Similar to our real-world data, a recent clinical trial including patients with nr-axSpA and r-axSpA treated with certolizumab achieved the same treatment response at week 48 measured by ASDAS [19]. When exploring the available evidence in observational cohorts, the 1 year treatment response as per the ASDAS was higher in the r-axSpA subgroup in the SCQM cohort, although this was not statistically significant [13]. In the DANBIO study, the ASDAS response was similar between both subgroups, although this was evaluated at the 3 and 6 month time points. Differences in drug survival have been explored in a few cohorts [10, 12, 20]. Overall, all reports show similar treatment adherence in nr-axSpA and r-axSpA as outlined in our study. Interestingly, a small retrospective study from Italy did show lower drug survival in nr-axSpA [20] and poorer adherence in patients with nr-axSpA was seen in the DANBIO cohort [12], although this was not confirmed in the multivariate analysis. Most patients were classified as nr-axSpA due to a positive SIJ MRI (ASAS imaging arm), so conclusions on drug survival similarities between the clinical and imaging arms should be interpreted with caution.

To our knowledge, this is the largest prospective cohort study comparing drug response and baseline characteristics between nr-axSpA and r-axSpA. Another strength is the fact that the study inclusion criteria were based on fulfilment of the ASAS classification criteria as opposed to being retrospectively adjudicated, ensuring the homogeneity of the study population. A limitation of our study is mainly the amount of missing data at the 1 year time point. This issue was addressed by analysing excluded patients and finding that there were no differences in baseline disease activity or treatment used. The excluded patients were younger and had a shorter disease duration, suggesting that they were doing well, which might justify why they did not attend follow-up. An additional analysis using a 6 month assessment if they stayed on a bDMARD increased the sample to 407, showing the same proportion of responders. Also, statistical power was adequate (0.89) with this sample size at $\alpha = 0.05$ to find a 20% difference between subgroups. In addition, we performed the drug survival analysis with most of the population (1122 patients), confirming the hypothesis that there are no differences between subgroups. Another limitation is the absence of regression analysis comparing the ASDAS response between

subgroups, as this overlapped with a similar study in this cohort looking at predictors of TNFi response in axSpA at the first follow-up (10 weeks–9 months) [21]. In that analysis, disease criteria were not associated with a lack of response, supporting our results. Moreover, it is well known that SIJ assessment has limited reliability, thus misclassification of nr/r-axSpA [22] may have occurred in some cases, although this cannot be confirmed in the absence of CT or MRI of all patients. However, this study reflects real-life practice whereby clinicians have to routinely consider this possibility.

In conclusion, nr-axSpA and r-axSpA present with similar baseline characteristics in a large multicentre cohort and achieve the same level of response to bDMARDs with analogous drug survival. These results support a unique treatment strategy for axSpA and encourage future clinical trial design to encompass the whole spectrum of axSpA rather than address nr-axSpA and r-axSpA as independent diseases.

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Data availability statement

The data underlying this article were provided by the BSRBR-AS register committee. Data will be shared on request to the corresponding author with permission of the above institution.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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Supplementary Materials for

Similar biologic drug response regardless of radiographic status in axial spondyloarthritis: data from the BSRBR-AS registry.

Xabier Michelena, Sizheng Steven Zhao, Sayam Dubash, Linda E Dean, Gareth T Jones, Helena Marzo-Ortega.

Supplementary material 1. Comparison of comorbidities prevalence between nr- and r-axSpA.

Variables	**nr-axSpA** (n=418)	**r-axSpA** (n=727)	**p-value**
Ischemic heart disease, n (%)	5 (1%)	22 (3%)	0.050
Chronic heart failure, n (%)	5 (1%)	6 (1%)	0.53
Cerebrovascular accident, n (%)	2 (<1%)	7 (1%)	0.37
Hypertension, n (%)	37 (9%)	131 (18%)	<0.001
Diabetes, n (%)	14 (3%)	32 (4%)	0.38
Asthma, n (%)	52 (13%)	77 (11%)	0.34
Chronic bronchitis/emphysema, n (%)	2 (<1%)	14 (2%)	0.045
Gastric ulcer, n (%)	10 (2%)	33 (5%)	0.066
Liver disease, n (%)	2 (<1%)	9 (1%)	0.21
Renal disease, n (%)	8 (2%)	10 (1%)	0.48
Depression, n (%)	88 (21%)	136 (19%)	0.33
Cancer, n (%)	7 (2%)	18 (3%)	0.37
Tuberculosis, n (%)	6 (1%)	18 (3%)	0.24
Demyelinating disease, n (%)	0 (0%)	1 (<1%)	0.45

Supplementary material 2. Disease activity measures in nr-axSpA and r-axSpA at baseline, 6 months and 1-year timepoint.

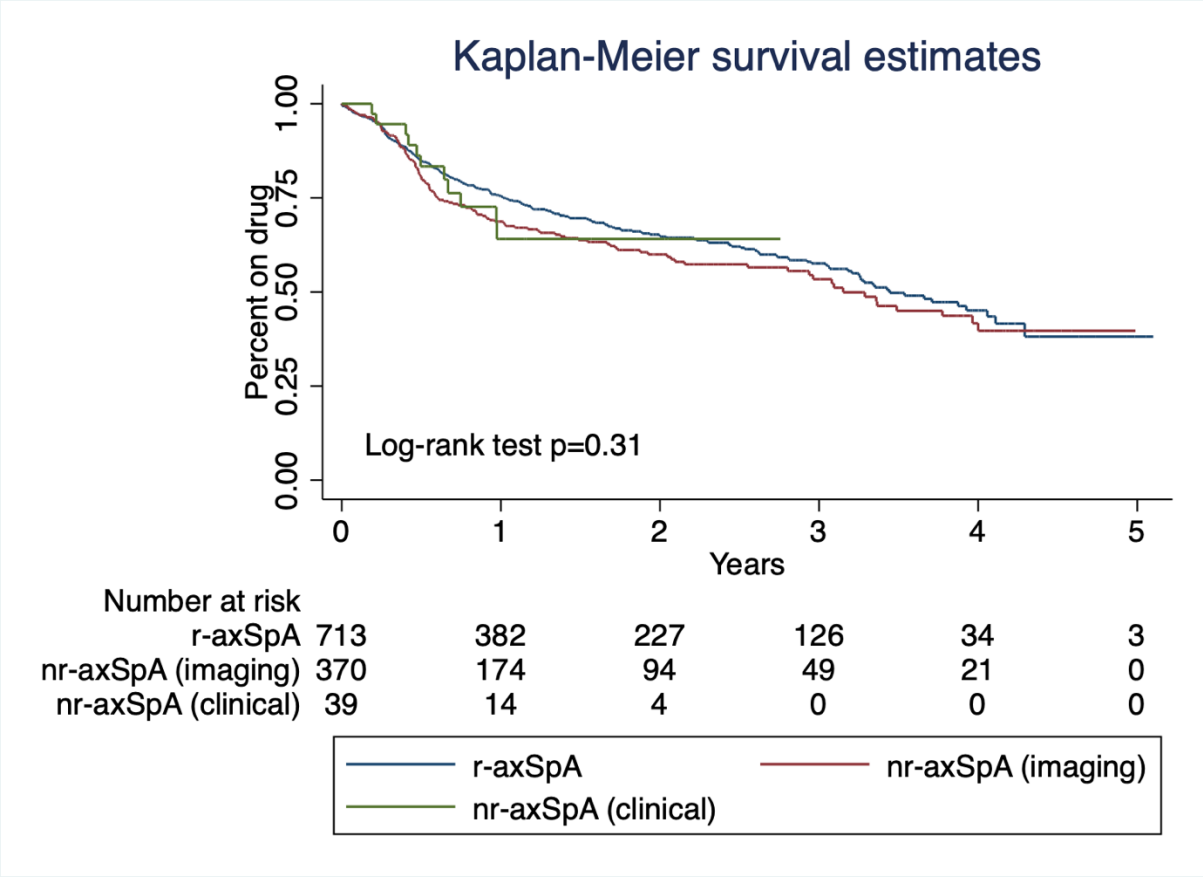
Variables	**Baseline***		**6 months**		**1 year*****	
	nr-axSpA	r-axSpA	nr-axSpA	r-axSpA	nr-axSpA	r-axSpA
BASDAI, median (IQR)	6.7 (5.3-7.8)	6.5 (5-7.7)	4.2 (2.5-6)	4.1 (2.3-6.3)	4.45 (2.8-6.6)	4.1 (1.9-6.25)
BASFI, median (IQR)	5.9 (4.2-7.8)	6.5 (4.4-8.3)	3.5 (2-5.8)	4.3 (1.9-7.3)	3.6 (1.9-6.2)	4.1 (1.9-6.7)
BAS-G, mean (SD)	7.0 (2.0)	6.8 (1.97)	4.6 (2.4)	4.8 (2.5)	4.47 (2.8)	4.2 (2.7)
ASDAS – CRP						
- **Total n**	286	473	117	180	95	195
- **Value, mean (SD)**	2.8 (0.8)	2.8 (0.9)	1.8 (0.9)	1.9 (1.0)	1.8 (0.9)	1.7 (1.0)
- **Inactive disease**	4.2%	5.3%	32.5%	32.2%	35.8%	42.6%
- **Low disease**	13.6%	15.9%	33.3%	26.7%	28.4%	23.6%
- **High disease**	67.1%	56.0%	31.6%	38.3%	32.6%	28.7%
- **Very high disease**	15.0%	22.8%	2.6%	2.8%	3.2%	5.1%

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BAS-G: Bath Ankylosing Spondylitis Global, ASDAS: Ankylosing Spondylitis Disease Activity Score, CRP: C-Reactive Protein *Patients with values: BASDAI=915 , BASFI=921, BAS-G=914, ASDAS-CRP=759 **Patients with values: BASDAI=377 , BASFI=378, BAS-G=377, ASDAS-CRP=297 ***Patients with values: BASDAI= 378, BASFI=381, BAS-G=379, ASDAS-CRP=290

Supplementary material 3. Comparison of baseline characteristics of patients with missing ASDAS follow-up values and those with available follow-up ASDAS.

Variables	**Level**	**Patients with follow-up ASDAS** (n=290)	**Patients without follow-up ASDAS** (n=855)	**p-value**
Age, mean (SD)		46.1 (13.6)	43.0 (13.2)	<0.001
Gender, n (%)	male	195 (67%)	573 (67%)	0.94
r-axSpA, n (%)		195 (67%)	532 (62%)	0.12
Symptom duration, mean (SD)		16.5 (13.1)	14.2 (12.2)	0.007
Diagnostic delay, median (IQR)		3.0 (1.0, 11.0)	3.0 (0.0, 11.0)	0.65
HLA-B27, n (%)		174 (79%)	440 (73%)	0.092
Smoking status, n (%)	Never smoked	110 (42%)	256 (39%)	0.16
	Ex-smoker	90 (35%)	212 (32%)	
	Current smoker	60 (23%)	194 (29%)	
CRP, median (IQR)		0.8 (0.2, 2.5)	0.6 (0.2, 2.0)	0.048
ESR, median (IQR)		13.5 (4.0, 30.0)	12.0 (5.0, 25.5)	0.85
BMI, mean (SD)		27.7 (5.5)	28.0 (5.8)	0.47
ASDAS-CRP, mean (SD)		2.8 (0.9)	2.8 (0.9)	0.88
NSAID concomitant use, n (%)		226 (79%)	645 (76%)	0.26
bDMARD, n (%)	Humira (ADA)	174 (60%)	500 (58%)	0.13
	Enbrel (ETA)	62 (21%)	193 (23%)	
	Simponi (GOL)	5 (2%)	12 (1%)	
	Cimzia (CZP)	30 (10%)	52 (6%)	
	Remicade (INF)	1 (<1%)	1 (<1%)	
	Inflectra (INF)	0 (0%)	1 (<1%)	
	Remsima (INF)	0 (0%)	1 (<1%)	
	Benepali (ETA)	17 (6%)	78 (9%)	
	Cosentyx (SEC)	1 (<1%)	16 (2%)	
	Erelzi (ETA)	0 (0%)	1 (<1%)	

Supplementary material 4: Kaplan-Meier survival curves of nr-axSpA (clinical arm), nr-axSpA (imaging arm) and r-axSpA.



Study 3. Characterising the axial phenotype of psoriatic arthritis: a study comparing axial psoriatic arthritis and ankylosing spondylitis with psoriasis from the REGISPONSER registry.

Michelena X, López-Medina C, Erra A, Juanola X, Font-Ugalde P, Collantes E, Marzo-Ortega H.

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Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Characterising the axial phenotype of psoriatic arthritis: a study comparing axial psoriatic arthritis and ankylosing spondylitis with psoriasis from the REGISPONSER registry

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ABSTRACT

Aims To explore the clinical and radiographical characteristics of axial psoriatic arthritis (PsA) and to compare it with ankylosing spondylitis (AS) with psoriasis.

Methods Cross-sectional study from the national multicentre registry REGISPONSER where participants fulfilled the European Spondyloarthropathy Study Group spondyloarthritis criteria at entry. Clinical, laboratory and radiographical characteristics between patients classified as axial PsA and AS with psoriasis by their rheumatologist are compared according to HLA-B27 status.

Results Of 2367 patients on REGISPONSER, n=405 had PsA, of whom 27% (n=109) had axial involvement as per the treating rheumatologist. 30% (n=26/86) of axial PsA were HLA-B27 positive. In the AS group, 9% (127/1422) had a history of psoriasis and were more frequently male, with longer diagnostic delay and more anterior uveitis than those with axial PsA who had more peripheral involvement and nail disease. Patients with HLA-B27-negative axial PsA reported less inflammatory pain and structural damage compared with AS with psoriasis. By contrast, HLA-B27-positive axial PsA shared clinical characteristics similar to AS and psoriasis although with a lower BASRI score. In the multivariable analysis, patients with AS and psoriasis were independently associated with HLA-B27 positivity (OR 3.34, 95% CI 1.42 to 7.85) and lumbar structural damage scored by BASRI (OR 2.14, 95% CI 1.4 to 3.19).

Conclusion The more prevalent axial PsA phenotype is predominantly HLA-B27 negative and presents different clinical and radiological manifestations when compared with AS with psoriasis. There is great heterogeneity in what rheumatologists consider axial PsA from a clinical and imaging perspective, highlighting the need for research into possible genetic drivers and a consensus definition.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is great heterogeneity in what is considered axial psoriatic arthritis (PsA) with a prevalence range varying between 11% and 78%.
⇒ Research in axial PsA is hampered by the lack of a definition of what is axial PsA.

WHAT THIS STUDY ADDS

⇒ Axial PsA has different clinical and radiographical characteristics when compared with ankylosing spondylitis (AS)/r-axSpA (radiographic-axSpA) with and without psoriasis.
⇒ Axial PsA is largely independent of HLA-B27 and presents different clinical and radiographical manifestations when compared with AS/r-axSpA with psoriasis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There is a need for identifying genetic drivers underpinning axial PsA to better understand its differential characteristics when compared with axial spondyloarthritis.

INTRODUCTION

Inflammatory disease of the axial skeleton is a hallmark of spondyloarthritis (SpA) and one of the clinical phenotypes of psoriatic arthritis (PsA).[1] Indeed, when Moll *et al* described the SpA concept in 1974, they included PsA within the overall SpA group based on the high prevalence of sacroiliac and spine involvement, which they estimated at 22.9% at that time.[2] Historically, research in PsA has focused on the more prevalent peripheral arthritis phenotype with efforts to characterise axial involvement in PsA being hampered by the lack of a definition of axial PsA leading to a great heterogeneity on prevalence (varying between 11% and 78%), clinical and radiographical findings being described in the literature.[3]

At the clinical level, the challenge remains as to whether axial PsA represents a distinct entity or the coexistence of psoriasis and axial spondyloarthritis (axSpA).[4] There are few studies comparing axial PsA with axSpA reporting significant differences in prevalence of sex, body mass index (BMI), HLA-B27 positivity, peripheral arthritis, nail involvement, dactylitis and extramusculoskeletal manifestations.[5–8] To our knowledge, only one study to date fully characterised and compared the radiographical findings including the spine with complete ankylosis of the sacroiliac joints (SIJs) and bridging syndesmophytes seen more likely in the radiographical form of axSpA (ankylosing spondylitis (AS)) when compared with axial PsA.[7] Further, a single study compared axial PsA with the AS subset with a history of psoriasis finding more back pain at presentation in the AS with psoriasis group as well as a higher grade of sacroiliitis, worse metrology and worse Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) compared with axial PsA.[9] No comparison dividing axial PsA according to HLA-B27 status was performed in these studies, and only one report by Queiro *et al* described the differences between HLA-B27-negative and HLA-B27-positive patients in an axial PsA cohort.[10] Taking into account that HLA-B27 prevalence is as low as ~20% in PsA compared with 80%–90% in axSpA,[11 12] the main question is whether HLA-B27-positive axial PsA is more similar to AS with psoriasis, suggesting that the axial PsA phenotype may be driven by other genetic factors different from HLA-B27. Thus, the aims of this study were to explore the axial phenotype of PsA regarding its clinical and radiographical characteristics and to compare it with AS with psoriasis with a further subanalysis according to HLA-B27 status.

METHODS

We performed a cross-sectional study from the national, multicentre (31 centres) Spanish REGISPONSER registry recruiting between March 2004 and March 2007. Eligibility for study entry was fulfilment of the European Spondyloarthropathy Study Group criteria. For the current analysis, we included patients who had a primary diagnosis of PsA or AS as confirmed by the treating rheumatologist. Specifics of the REGISPONSER registry have been previously published.[13]

Data collected

Clinical, laboratory and imaging data were systematically collected in all patients. Demographic characteristics included age, sex, time to diagnosis (defined as time from symptom onset to diagnosis), BMI and family history of spondyloarthritis (SpA). In addition, past or present (ever) history of cervical pain, inflammatory back pain (fulfilling the Calin criteria[14]), alternating buttock pain, anterior uveitis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis, skin psoriasis and psoriatic nail disease were collected. In patients with skin psoriasis, SpA onset before or after psoriasis was determined using PsA/AS and psoriasis time of diagnosis. Laboratory tests included HLA-B27, C reactive protein (CRP) and erythrocyte sedimentation rate. Rheumatoid factor and hand/foot plain X-rays were not systematically collected in this study, which predates the development and publication of the Classification for Psoriatic Arthritis (CASPAR) classification criteria for PsA.[15]

Radiographs of the cervical, lumbar and pelvic X-rays, including SIJs, were performed in all participants. Images were scored using the Bath Ankylosing Spondylitis Radiology Index (BASRI) by the local reader, who was in all cases a rheumatologist with an interest in SpA. Additionally, the following patient-reported outcomes (PROs) were gathered irrespective of diagnosis: BASDAI, Bath Ankylosing Spondylitis Functional Index, Ankylosing Spondylitis Disease Activity Score-CRP.

Group definition

The axial PsA group included patients with a primary diagnosis of PsA and axial involvement as defined by the treating rheumatologist who had access to the full set of clinical, laboratory and imaging data. The AS group included patients with a rheumatologist diagnosis of AS and current or history of psoriasis as recorded during the study visit. Modified New York Criteria (mNYc) for Ankylosing Spondylitis, ASAS (Assessment of Spondyloarthritis International Society) classification criteria for axSpA and CASPAR were retrospectively applied to the study population.

Analysis

Descriptive statistics are shown as proportions/percentages for categorical variables and mean/SD or median/IQR as appropriate. Demographic, clinical and radiological characteristics were compared between the two groups (axial PsA and AS with psoriasis). A further sensitivity analysis was performed including all patients with PsA with definite radiographical sacroiliitis according to the local reader. Student's t-test or Mann-Whitney U tests for continuous variables and χ^2 for categorical variables were used. Same statistics were used for further subgroup comparisons and sensitivity analysis. Associations between possible relevant demographic, clinical and radiological predictors, and disease groups (axial PsA vs AS with psoriasis) were explored with univariable and multivariable logistic regression. A non-automated model selection methodology was used including variables with a p value of <0.1 in the univariable analysis as well as plausible relevant variables considered by the investigators. Variable collinearity was assessed and the more clinically relevant variable was included in the model. All analyses were conducted using Stata V.16.1.

RESULTS

A total of 405 patients with a primary diagnosis of PsA and 1422 patients with a primary diagnosis of AS were analysed. Twenty-seven per cent (n=109) of the patients with PsA had axial involvement as per the treating

rheumatologist, and 9% (n=127) of patients with AS had current or a history of skin psoriasis (online supplemental figure 1). Ninety-six per cent (1369/1422) of patients with a primary diagnosis of AS and 100% of AS with psoriasis patients fulfilled the mNYc for AS and the ASAS classification criteria (imaging arm) for axSpA when applied retrospectively. 60% (244/405) patients with a primary diagnosis of PsA fulfilled the CASPAR criteria for PsA when applied retrospectively with variables other than rheumatoid factor and imaging data which were not collected systematically. CASPAR criteria were applied taking into account the following variables: inflammatory back pain, peripheral disease or enthesitis as entry criterion and current or history of psoriasis, family history of psoriasis, dactylitis and nail disease as major and minor criteria. A sensitivity analysis comparing relevant characteristics (excluding variables used for the classification criteria) did not show significant differences between patients with CASPAR-positive and CASPAR-negative PsA (online supplemental table 1).

Clinical and radiographical axial characteristics of the whole PsA cohort

Of the whole PsA cohort, 127/405 (31.5%) reported a history of inflammatory back pain or alternating buttock pain. Cervical pain was present in 20/405 (5%) of the whole PsA cohort. Pelvic X-rays were available in 395/405 (98%) of patients with PsA with 63% of patients (n=249) having normal SIJ as scored by the local reader (BASRI=0). A total of 91/395 (23%) had definite sacroiliitis (BASRI ≥2) with 8%, and 4% scored as BASRI grade III and IV, respectively. Complete sets of spine X-rays (ie, cervical and lumbar spine) were available in 385/405 (95%), of which 296 patients (76%) were scored as having a normal lumbar spine and 295 patients (76%) had a normal cervical spine. BASRI of ≥2 was reported in 12% of lumbar radiographs and in 11% of cervical radiographs. Cervical spine abnormalities were scored in 5/39 (13%) of subjects with definite sacroiliitis and no changes in the lumbar spine. In patients who reported a history of inflammatory back pain or alternating buttock pain (127/405), 59/127 (46.5%) had definite sacroiliitis (BASRI≥2) of whom 26/59 (44%) had associated spondylitic changes (BASRI ≥2). Isolated spondylitis was identified in 21 patients with PsA (6%). Six patients were classified as axial PsA in the absence of IBP, radiographical sacroiliitis or radiographical spondylitis. Of these, three had a history of cervical pain and the other three had low-grade sacroiliitis (grade 1).

Comparison of clinical and radiographical characteristics of axial PsA and AS with psoriasis

Of the 109 patients classified as axial PsA (27% of the whole PsA cohort), 86.2% (94/109) had a mixed (peripheral+axial) and 13.8% (15/109) a pure axial phenotype. Demographic, clinical and radiographical variables comparing axial PsA and AS with psoriasis are presented in table 1. Patients with axial PsA were more frequently women (37.6% vs 21.3%, p=0.006) and had a shorter disease duration (7 vs 9 years, p=0.04) and diagnostic delay (1.0 vs 3.5 years, p=0.005) when compared with patients with AS with psoriasis. Inflammatory back pain (93.7% vs 78.9%, p<0.001), alternating buttock pain (63.2% vs 38%, p<0.001) and uveitis (12.8% vs 2.8%, p=0.005) were more frequently reported in the AS with psoriasis group, while peripheral arthritis (78.0% vs 58.1%, p=0.001) and nail involvement (43.1% vs 25.8%, p=0.005) were more frequently found in the axial PsA population. BASRI scores in SIJs, lumbar and cervical spine were higher in the AS with psoriasis group when compared with the axial PsA group (p<0.001). A sensitivity analysis using a radiographical definition of axial PsA (PsA diagnosis and definite SIJ involvement in pelvic X-rays) showed the same results when compared with AS with psoriasis (online supplemental table 2).

Effect of psoriasis in patients with AS compared with axial PsA

Participants with a primary diagnosis of AS were then divided according to personal history of psoriasis. Clinical, demographic, laboratory and radiographical findings from patients with AS with psoriasis (n=127), AS with absent history of psoriasis (n=1289) and axial PsA (n=109) are presented in online supplemental table 3. Psoriasis in patients with AS conferred a higher BMI (27.8 vs 26.6, p=0.012) as well as higher likelihood of presenting with dactylitis (24.6% vs 3.3%, p<0.001), peripheral arthritis (58.1% vs 30.4%, p<0.001) and nail disease (25.8% vs 0.4%, p<0.001). HLA-B27 positivity was higher in the AS group with no psoriasis (84.7% vs 66.7%, p<0.001). Differences between axial PsA compared with AS with no psoriasis were consistent with previous comparison (axial PsA vs AS with psoriasis) and shown in online supplemental table 2,3.

Effect of HLA-B27 in axial PsA

Clinical, demographic, laboratory and radiographical findings from patients with axial PsA subdivided by HLA-B27 status are presented in table 2. The only significant differences between HLA-B27-positive and HLA-B27-negative axial PsA were the presence of family history of SpA (27% vs 9%, p=0.022) and a higher percentage of patients with a diagnosis of skin psoriasis made before the SpA diagnosis in the HLA-B27-negative subgroup (95% vs 63%, p=0.002). When comparing axial PsA divided by HLA-B27 with AS with psoriasis, patients with HLA-B27-negative axial PsA reported less inflammatory pain (78% vs 93.7%, p=0.002), were more likely to present with psoriasis before SpA onset (95% vs 77%, p=0.02) and had less structural damage compared with AS with psoriasis. By contrast, HLA-B27-positive axial PsA shared similar clinical characteristics with AS and psoriasis patients although a lower BASRI score when evaluating structural damage. Additional analysis were performed comparing HLA-B27-negative axial PsA versus HLA-B27-negative AS with psoriasis and HLA-B27-positive axial PsA versus HLA-B27-positive AS with psoriasis (online supplemental table 4), which showed less inflammatory back pain/

Table 1 Comparison of demographic, clinical and radiographical characteristics between axial PsA and AS with psoriasis

Variable	Axial PsA N=109	AS with psoriasis N=127	P value
Demographic characteristics			
Age (years), mean (SD)	50.1 (12.9)	49.9 (12.6)	0.89
Age at diagnosis (years), mean (SD)	42.2 (13.9)	37.9 (12.8)	0.016
Sex (female), n (%)	41 (37.6)	27 (21.3)	0.006
Disease duration (years), median (IQR), mean (SD)	7.0 (2.5–13.0)	9.0 (5.0–18.0)	0.040
Diagnostic delay (years),* median (IQR), mean (SD)	1.0 (0.0–5.0), 4.7 (8.0)	3.5 (0.0–11.0), 7.2 (8.4)	0.005
BMI, mean (SD)	27.8 (5.6)	27.8 (5.3)	0.99
Family history of SpA, n (%)	14/97 (14.4)	19/113 (16.8)	0.64
Clinical characteristics, n (%)			
Cervical pain	12/109 (11.0)	21/127 (16.5)	0.22
Inflammatory back pain	92/109 (84.4)	121/127 (95.3)	0.005
Alternating buttock pain	41/108 (38.0)	79/125 (63.2)	<0.001
Anterior uveitis	3/109 (2.8)	16/125 (12.8)	0.005
Inflammatory bowel disease	1/108 (0.9)	5/127 (3.9)	0.14
Dactylitis	37/109 (33.9)	31/126 (24.6)	0.12
Enthesitis	38/108 (35.2)	49/125 (39.2)	0.53
Peripheral arthritis	85/109 (78.0)	72/124 (58.1)	0.001
Nail disease	47/109 (43.1)	32/124 (25.8)	0.005
Psoriasis before SpA onset	60/68 (88)	64/83 (77)	0.076
Laboratory findings			
HLA-B27, n (%)	26/86 (30)	62/93 (67)	<0.001
CRP (mg/L), median (IQR)	9.3 (16.0)	9.3 (15.9)	0.99
ESR (mm/hour), median (IQR)	16.6 (17.3)	19.1 (16.4)	0.26
Radiographical findings			
Definite sacroiliitis (BASRI ≥2), n (%)	60/109 (55.0)	122/122 (100.0)	<0.001
Isolated spondylitis (no sacroiliitis), n (%)	11/104 (10.6)	0 (0)	<0.001
Any radiographical finding, n (%)	71/104 (68.3)	122/122 (100.0)	<0.001
BASRI sacroiliac joint, median (IQR)	2.0 (0.0–3.0)	3.0 (2.0–4.0)	<0.001
BASRI lumbar, median (IQR)	0.0 (0.0–2.0)	2.0 (1.0–3.0)	<0.001
BASRI cervical, median (IQR)	0.0 (0.0–1.0)	1.0 (0.0–3.0)	<0.001
PROs			
BASDAI, median (IQR)	4.2 (2.2–6.4)	4.1 (2.4–6.4)	0.77
BASFI, median (IQR)	3.2 (1.1–5.4)	3.8 (1.7–6.6)	0.12
ASDAS-CRP, median (IQR)	2.4 (1.6–3.3)	2.7 (1.9–3.5)	0.28

*Time from symptom onset to diagnosis.
AS, ankylosing spondylitis; 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; ESR, erythrocyte sedimentation rate; PRO, patient-reported outcome; PsA, psoriatic arthritis; SpA, spondyloarthritis.

alternating back pain and radiographical damage in axial PsA regardless of HLA-B27 status when compared with the axSpA population with psoriasis. HLA-B27-negative AS with patients with psoriasis had more cervical pain, dactylitis and presented more frequently with psoriasis before the axSpA diagnosis compared with HLA-B27-positive AS with psoriasis.

Demographic, clinical and radiographical factors associated with a clinician diagnosis of AS with psoriasis (rather than axial PsA)

Univariable associations are shown in online supplemental table 5. In the multivariable analysis, patients with AS and psoriasis were independently associated with HLA-B27 positivity (OR 3.34, 95% CI 1.42 to 7.85) and

Table 2 Comparison of demographic, clinical and radiographical characteristics between axial PsA subdivided by HLA-B27 status and AS with psoriasis

Variable	Axial PsA B27 positive N=26	Axial PsA B27 negative N=60	P value	AS with psoriasis N=127	Axial PsA B27 positive versus AS with psoriasis *P value*	Axial PsA B27 neg versus AS with psoriasis *P value*
Demographic characteristics						
Age, mean (SD)	45.1 (11.6)	49.7 (12.2)	0.11	49.9 (12.6)	0.075	0.92
Age at diagnosis, mean (SD)	35.6 (11.1)	42.6 (13.6)	0.024	37.9 (12.8)	0.40	0.025
Sex (female), n (%)	11/26 (42)	25 (43)	0.93	27 (21.3)	0.024	0.002
Disease duration, median (IQR)	7.0 (2.0–15.0)	7.0 (2.0–15.0)	0.66	9.0 (5.0–18.0)	0.36	0.025
Diagnostic delay, median (IQR)	1.0 (0.0, 4.0)	1.0 (0.0, 4.0)	0.91	3.5 (0.0, 11.0)	0.081	0.047
BMI, mean (SD)	28.6 (6.3)	26.5 (5.2)	0.17	27.8 (5.3)	0.27	0.44
Family history of SpA, n (%)	6/26 (27)	5/60 (9)	0.022	19/113 (16.8)	0.16	0.18
Clinical characteristics, n (%)						
Cervical pain	3/26 (12)	6/60 (10)	0.83	21/127 (16.5)	0.52	0.24
Inflammatory back pain	24/26 (92.3)	47/60 (78)	0.27	121/127 (95.3)	0.54	0.002
Alternating buttock pain	12/26 (46)	20/60 (33)	0.26	79/125 (63.2)	0.11	<0.001
Anterior uveitis	2/26 (8)	1/60 (2)	0.16	16/125 (12.8)	0.46	0.014
Inflammatory bowel disease	1/26 (4)	0/60 (0)	0.13	5/127 (3.9)	0.98	0.12
Dactylitis	5/26 (19)	22/60 (37)	0.11	31/126 (24.6)	0.56	0.088
Enthesitis	10/26 (38)	20/60 (33)	0.65	49/125 (39.2)	0.94	0.44
Peripheral arthritis	18/26 (69)	47/60 (78)	0.37	72/124 (58.1)	0.29	0.007
Nail disease	9/26 (35)	27/60 (45)	0.37	32/124 (25.8)	0.36	0.009
Psoriasis before SpA onset	10/16 (63)	36/38 (95)	0.002	64/83 (77)	0.16	0.020
Laboratory findings						
CRP (mg/L), median (IQR)	10.5 (17.5)	9.7 (17.5)	0.85	9.3 (15.9)	0.73	0.87
ESR (mm/hour), median (IQR)	19.4 (23.5)	16.5 (16.4)	0.53	19.1 (16.4)	0.95	0.33
Radiographical findings, n (%)						
Definite sacroiliitis (BASRI ≥2)	15/26 (58)	31/60 (52)	0.61	122/122 (100.0)	<0.001	<0.001
Isolated spondylitis (no sacroiliitis)	3/6 (50)	6/18 (33)	0.47	0 (0)	<0.001	<0.001
Any radiographical finding, n (%)	18/25 (72)	37/56 (66)	0.60	122/122 (100.0)	<0.001	<0.001
BASRI sacroiliac joint, median (IQR)	2.0 (1.0–3.0)	2.0 (0.0–3.0)	0.55	3.0 (2.0–4.0)	<0.001	<0.001

Continued

Table 2 Continued

Variable	Axial PsA B27 positive N=26	Axial PsA B27 negative N=60	P value	AS with psoriasis N=127	Axial PsA B27 positive versus AS with psoriasis *P value*	Axial PsA B27 neg versus AS with psoriasis *P value*
BASRI lumbar, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.55	2.0 (1.0–3.0)	<0.001	<0.001
BASRI cervical, median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.19	1.0 (0.0–3.0)	<0.001	<0.001
PROs						
BASDAI, median (IQR)	4.6 (2.2–6.4)	4.4 (2.3–6.4)	0.91	4.1 (2.4–6.4)	0.92	0.99
BASFI, median (IQR)	2.0 (1.0–4.8)	2.3 (1.1–5.4)	0.46	3.8 (1.7–6.6)	0.086	0.16
ASDAS-CRP, median (IQR)	2.6 (2.0–3.2)	2.3 (1.5–3.5)	0.60	2.7 (1.9–3.5)	0.77	0.27

AS, ankylosing spondylitis; 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; ESR, erythrocyte sedimentation rate; PRO, patient-reported outcome; PsA, psoriatic arthritis.

lumbar structural damage scored by BASRI (OR 2.14, 95% CI 1.4 to 3.19) (figure 1).

DISCUSSION

This study explored the axial phenotype of a historic multicentre SpA cohort including patients with AS/r–axSpA and PsA. Our results show that there is an heterogenous understanding of axial involvement in PsA with a combination of clinical and radiographical findings in the SIJs and lumbar/cervical spine found in what rheumatologists consider axial PsA, which underscores the need for a unifying definition. Rheumatologists have often wondered whether axial PsA is part of the axSpA spectrum, where 10% of the population is reported to have concomitant skin psoriasis, or whether it represents a distinct PsA subset. When comparing the axial PsA population with that of patients with AS who have concomitant psoriasis in this study, significant differences were seen in clinical presentation with more severe radiographical findings seen in the AS with psoriasis group. Further, when subdividing the axial PsA population according to HLA-B27 status, the clinical and imaging characteristics of HLA-B27-positive axial PsA appeared to be more similar to that of patients with AS with psoriasis although with significantly higher levels of structural damage seen in the latter. These findings suggest that axial PsA as understood by clinicians appears to be overall and regardless of HLA-B27 status associated with less radiographical progression than AS. Interestingly, no differences in PROs were seen in the respective group comparisons.

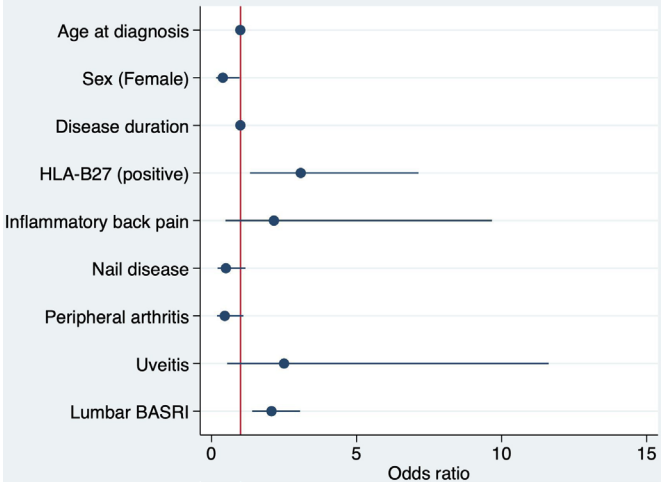

Figure 1 Final multivariable model with factors associated with ankylosing spondylitis with psoriasis versus axial psoriatic arthritis (ref). BASRI, Bath Ankylosing Spondylitis Radiology Index.

The main weakness of our study is the lack of a standardised definition of axial PsA. Yet, a number of studies have also compared cohorts of axial PsA with axSpA, using different definitions that must be taken into account when interpreting their results. In the Toronto study,[9] axial PsA was defined as all patients with PsA that had SIJ radiographical changes fulfilling the mNYc. Jadon *et al* used the same definition but also included spine syndesmophytes as criteria to classify patients as axial PsA[7]; however, they did not differentiate axial PsA from AS with psoriasis. Fragoulis *et al* used a combination of inflammatory axial symptoms and imaging findings (SIJ/lumbar spine X-ray or MRI).[6] A recent study by Benavent *et al*[5] used a similar approach to our study, basing the classification of axial PsA on the opinion of the treating rheumatologist. However, the main difference and a strength of our study is the complete characterisation of

our cohort with availability of clinical data together with pelvic, lumbar and cervical X-ray data for all patients, including those not classified as axial PsA. Interestingly, and despite a different axial PsA definition used in the Toronto study,[9] we found similar results when comparing axial PsA and AS with psoriasis in our study population. In both studies, male prevalence, younger age, positive HLA-B27, presence of inflammatory back pain, higher SIJ radiographical scores and uveitis were more frequently reported in the AS with psoriasis cohort, as expected in a primary AS/r-axSpA population. In addition, we report higher BASRI scores in the lumbar and cervical spine in those patients with AS and psoriasis. Although these data were not available in the Toronto study, the authors reported a higher BASMI in patients with AS with psoriasis, which is known to correlate well with radiographical damage.[16]

When looking at HLA-B27, a higher prevalence was found in the AS group (with and without psoriasis) when compared with the PsA group, as expected. Further subanalysis showed that HLA-B27 was found more often in patients with AS without psoriasis compared with those with a history of psoriasis contrary to findings reported in the Toronto cohort where a similar prevalence of HLA-B27 was seen between the groups, although we note that no pairwise comparison was reported in that study.[9] This difference between the two studies could be related to the different inclusion criteria used, or to possible misclassification in both studies. Additionally, we found that the subgroup of patients with AS and psoriasis resembled that of axial PsA with a higher BMI compared with AS without psoriasis (not reported in the Toronto study). Likewise, the presence of skin psoriasis in AS seems to modify the clinical phenotype with more peripheral disease, dactylitis and nail disease seen in this subgroup, likely driven by genetic factors other than HLA-B27 as shown by its lower prevalence when compared with AS with no skin psoriasis. Another interesting observation is that patients with HLA-B27-negative AS and axial PsA were more likely to present with skin psoriasis before the onset of articular symptoms, resembling the presentation of peripheral PsA as compared with AS/r-axSpA. Similarly, patients with HLA-B27-positive axial PsA reported an onset of articular symptoms before that of skin psoriasis as seen in axial SpA or AS. Further, patients with HLA-B27-negative AS presented with more dactylitis and cervical pain compared with patients with HLA-B27-positive AS suggesting a more similar phenotype to PsA.

From an imaging viewpoint, patients with axial PsA had less radiographical damage than AS with psoriasis regardless of HLA-B27 status, suggesting again the presence of other genetic drivers. Coates *et al* reported the association of HLA-B27 and radiographical expression of axSpA (including both AS and axial PsA) with more severe radiographical damage including higher grades of sacroiliitis and more marginal syndesmophytes and symmetry seen in HLA-B27-positive patients (regardless of clinical diagnosis of axSpA or PsA).[17] However, no difference was seen in the prevalence of SIJ symmetry and non-marginal syndesmophytes considered typical radiographical findings of axial PsA, suggesting the existence of factors other than HLA-B27 driving this latter phenotype.

To our knowledge, this is the largest study benefitting from a complete imaging data set comprising cervical, lumbar and pelvic X-rays for all patients of a PsA cohort independent from their clinical phenotype (peripheral or axial) and comparing it with AS with psoriasis. Also, we have further divided the axial PsA cohort by HLA-B27 status shown in previous reports to be relevant in the radiographical and clinical phenotype.[10 17] The main limitation of our study is its cross-sectional nature and, as mentioned before, the fact that the primary diagnoses were based on physician assessment as the study predates the publication of the ASAS[18] or CASPAR classification criteria.[15] In common with other studies, however, and reflecting the lack of validated definitions and criteria, axial involvement was defined by the rheumatologist. Another limitation is the fact that our study compares the 'full spectrum' of axial PsA with the axSpA radiographical population (AS). Ideally, a population comprising the full spectrum of axSpA, including non-radiographical disease, would have been desirable but this were not included in REGISPONSER, which predates the publication of the ASAS classification criteria.[18] In the absence of a clinical or imaging definition of axial PsA, we decided to use the rheumatologist definition rather than focus on the presence of radiographical sacroiliitis in order to also encompass those patients with axial PsA, which may have an isolated lumbar/cervical involvement without sacroiliitis.[7] Our approach was validated by a subsequent sensitivity analysis using radiographical sacroiliitis (BASRI ≥2) as defining criteria which did not show significant differences between the groups when compared with clinician definition. Another limitation is the lack of central reading of the radiographs with multiple readers involved. Yet, it is important to note that the local readers participating in the REGISPONSER registry are rheumatologists with an interest in SpA, members of the Spanish Spondyloarthropathies Study Group of the Spanish Society of Rheumatology, who underwent a 2 -day training in the study processes, well versed in the reading of spinal and SIJ radiographs both in clinical practice and in research settings, and as such represent a highly specialised group of clinicians.[13] This in itself could be considered a strength as it reflects clinical practice in a specialist setting and allows us to encompass the whole spectrum of clinical and radiographical findings described in axial PsA.[3] In this line, as X-rays were scored using BASRI, we do not have details on the morphology of syndesmophytes or posterior element involvement, which has been shown as a difference in radiological presentation between AS and axial PsA.[19]

Finally, HLA-B27 data were limited with 23 (21%) missing values in the axial PsA group, similar to the AS with psoriasis group (n=34, 27%) reflecting clinical practice where HLA-B27 testing is not universal in PsA

cohorts. Nevertheless, we found significant results when subdividing the cohort according to HLA-B27 despite reduced numbers suggesting that HLA-B27 modulates the clinical phenotype and imaging morphotype of axial PsA. This is in accordance with a previous MRI study where HLA-B27-positive axial PsA subjects with active inflammatory back pain had more bone marrow oedema findings than the HLA-B27-negative group, although less than axSpA.[20] Similarly, the presence of psoriasis appears to modulate an AS subgroup, more likely to be HLA-B27 negative and with clinical characteristics more akin to those of PsA. Whether these findings represent a misclassification of the study population or a true phenotypical difference will only be answered by a systematic evaluation of the genotype underpinning these cohorts. Currently available Genome-Wide Association studies in PsA lack fully detailed radiographical and clinical data that could bring light to a better definition of axial PsA, and future research efforts should be aimed to address this crucial question.[21 22]

In conclusion, axial PsA appears to be a distinct phenotype within the PsA disease spectrum with different clinical and radiographical characteristics when compared with AS/r-axSpA with and without psoriasis. Axial PsA is largely independent of HLA-B27 and presents different clinical and radiographical manifestations when compared with AS with psoriasis, highlighting the need for a better understanding of other genetic drivers to define specific classification criteria for this entity in order to allow for better management of these patients.

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Ethics approval All patients gave informed written consent to participate in the REGISPONSER registry, which was approved centrally by the ethics committee of the Reina Sofia University Hospital from Cordoba (Spain). There is no ID for this approval as at that time this commitee did not use numbers. Scan of the official document can be provided if needed. The participants gave informed consent to participate in the study before taking part.

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SUPPLEMENTARY FILES

Characterising the axial phenotype of psoriatic arthritis: a study comparing axial psoriatic arthritis and ankylosing spondylitis with psoriasis from the REGISPONSER registry.

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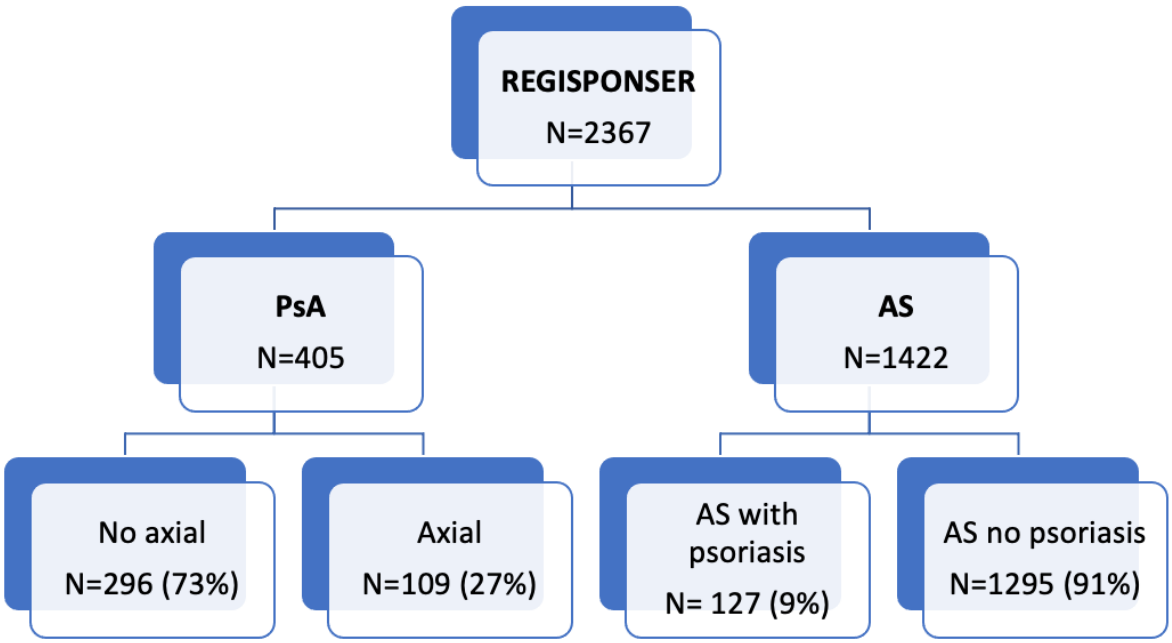
Figure 1. Patient Flow Chart.



Supplementary Table 1. Clinical characteristics off patients with a primary diagnosis of PsA regarding CASPAR criteria fulfillment (excluding variables used for classification criteria fulfillment).

Variable	CASPAR criteria negative N=162	CASPAR criteria positive N=244	p-value
Age (years), mean (SD)	52.3 (13.8)	50.8 (13.2)	0.29
Sex, female	70 (43.5%)	107 (43.9%)	0.94
Peripheral arthritis	139 (86.3%)	214 (87.7%)	0.69
Lower limb arthritis	99 (61.5%)	159 (65.2%)	0.45
Upper limb arthritis	88 (54.7%)	146 (59.8%)	0.30
Cervical pain	7 (4.3%)	13 (5.3%)	0.66
Inflammatory back pain	40 (24.8%)	70 (28.9%)	0.37
Psoriasis before SpA onset	79 (88.8%)	148 (89.7%)	0.82
HLA-B27	20 (21.7%)	29 (18.5%)	0.53
CRP (mg/L), median (IQR)	8.1 (14.7)	8.3 (9.8)	0.86
ESR (mm/h), median (IQR)	18.7 (18.5)	18.9 (13.9)	0.89

Supplementary Table 2. Demographic, clinical and radiographic characteristics comparison between axial PsA (defined by definite sacroiliitis, ie BASRI≥2) and AS with psoriasis.

Variable	Axial PsA (Rx defined) N=91	AS with psoriasis N=127	p-value
Demographic characteristics			
Age (years), mean (SD)	51.4 (13.0)	49.9 (12.6)	0.40
Age at diagnosis (years), mean (SD)	42.5 (14.2)	37.9 (12.8)	0.014
Sex, female	29/91 (31.9%)	27/127 (21.3%)	0.077
Disease duration (years), median (IQR)	7.0 (4.0, 13.0)	9.0 (5.0, 18.0)	0.19
Diagnostic delay (years)*, median (IQR)	2.0 (0.0, 9.0)	3.5 (0.0, 11.0)	0.16
BMI, mean (SD)	28.0 (5.2)	27.8 (5.3)	0.88
Family history of SpA	10/78 (12.8%)	19/113 (16.8%)	0.45
Clinical characteristics			
Cervical pain	7/91 (7.7%)	21/127 (16.5%)	0.054
Inflammatory back pain	61/90 (67.8%)	121/127 (95.3%)	<0.001
Alternating buttock pain	25/90 (27.8%)	79/125 (63.2%)	<0.001
Anterior uveitis	4/90 (4.4%)	16/125 (12.8%)	0.037
Inflammatory bowel disease	0/90 (0.0%)	5/127 (3.9%)	0.057
Dactylitis	31/91 (34.1%)	31/126 (24.6%)	0.13
Enthesitis	20/90 (22.2%)	49/125 (39.2%)	0.009
Peripheral arthritis	73/91 (80.2%)	72/124 (58.1%)	<0.001
Nail disease	41/91 (45.1%)	32/124 (25.8%)	0.003
Psoriasis before SpA onset	42/54 (78%)	64/83 (77%)	0.93
Laboratory findings			
HLA-B27	20/60 (33%)	62/93 (67%)	<0.001
CRP (mg/L), median (IQR)	9.0 (12.2)	9.3 (15.9)	0.88
ESR (mm/h), median (IQR)	16.7 (14.2)	19.1 (16.4)	0.26
Radiographic findings			
BASRI sacroiliac joint, median (IQR)	3.0 (2.0, 3.0)	3.0 (2.0, 4.0)	<0.001
BASRI lumbar, median (IQR)	1.0 (0.0, 2.0)	2.0 (1.0, 3.0)	<0.001
BASRI cervical, median (IQR)	0.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.003
Patient reported outcomes (PROs)			
BASDAI, median (IQR)	3.7 (2.2, 6.0)	4.1 (2.4, 6.4)	0.28
BASFI, median (IQR)	2.9 (1.3, 5.0)	3.8 (1.7, 6.6)	0.043
ASDAS-CRP, median (IQR)	2.5 (1.6, 3.2)	2.7 (1.9, 3.5)	0.28

*Time from symptom onset to diagnosis

Supplementary table 3. Demographic, clinical and radiographic characteristics comparison between axial PsA and AS with and without psoriasis.

Variable	Axial PsA N=109	AS with no psoriasis N=1289	AS with psoriasis N=127	axial PsA vs AS with no psoriasis p-value	AS with no psoriasis vs AS with psoriasis p-value
Demographic characteristics					
Age (years), mean (SD)	50.1 (12.9)	47.7 (12.7)	49.9 (12.6)	0.060	0.068
Age at diagnosis (years), mean (SD)	42.2 (13.9)	34.5 (11.6)	37.9 (12.8)	<0.001	0.002
Sex, female	41/109 (37.6%)	324/1,289 (25.1%)	27/127 (21.3%)	0.004	0.33
Disease duration (years), median (IQR)	7.0 (2.5, 13.0)	12.0 (5.0, 20.0)	9.0 (5.0, 18.0)	<0.001	0.068
Diagnostic delay (years)*, median (IQR)	1.0 (0.0, 5.0)	4.0 (1.0, 11.0)	3.5 (0.0, 11.0)	<0.001	0.38
BMI, mean (SD)	27.8 (5.6)	26.6 (4.4)	27.8 (5.3)	0.012	0.005
Family history of SpA	14/97 (14.4%)	245/1,200 (20.4%)	19/113 (16.8%)	0.16	0.36
Clinical characteristics					
Cervical pain	12/109 (11.0%)	139/1,289 (10.8%)	21/127 (16.5%)	0.94	0.051
Inflammatory back pain	92/109 (84.4%)	1,275/1,289 (98.9%)	121/127 (95.3%)	<0.001	<0.001
Alternating buttock pain	41/108 (38.0%)	842/1,273 (66.1%)	79/125 (63.2%)	<0.001	0.51
Anterior uveitis	3/109 (2.8%)	283/1,282 (22.1%)	16/125 (12.8%)	<0.001	0.016
Inflammatory bowel disease	1/108 (0.9%)	68/1,289 (5.3%)	5/127 (3.9%)	0.045	0.52
Dactylitis	37/109 (33.9%)	43/1,284 (3.3%)	31/126 (24.6%)	<0.001	<0.001
Enthesitis	38/108 (35.2%)	378/1,281 (29.5%)	49/125 (39.2%)	0.22	0.025
Peripheral arthritis	85/109 (78.0%)	391/1,288 (30.4%)	72/124 (58.1%)	<0.001	<0.001
Nail disease	47/109 (43.1%)	5/1,287 (0.4%)	32/124 (25.8%)	<0.001	<0.001
Laboratory findings					
HLA-B27	26/86 (30.2%)	993/1,173 (84.7%)	62/93 (66.7%)	<0.001	<0.001
CRP (mg/L), median (IQR)	9.3 (16.0)	9.1 (13.5)	9.3 (15.9)	0.92	0.90
ESR (mm/h), median (IQR)	16.6 (17.3)	18.3 (16.1)	19.1 (16.4)	0.32	0.57
Radiographic findings					
BASRI sacroiliac joint, median (IQR)	2.0 (0.0, 3.0)	3.0 (3.0, 4.0)	3.0 (2.0, 4.0)	<0.001	0.034

BASRI lumbar, median (IQR)	0.0 (0.0, 2.0)	2.0 (0.0, 3.0)	2.0 (1.0, 3.0)	<0.001	0.55
BASRI cervical, median (IQR)	0.0 (0.0, 1.0)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	<0.001	0.41
Patient reported outcomes (PROs)					
BASDAI, median (IQR)	4.2 (2.2, 6.4)	4.1 (2.2, 5.9)	4.1 (2.4, 6.4)	0.51	0.31
BASFI, median (IQR)	3.2 (1.1, 5.4)	3.6 (1.4, 6.0)	3.8 (1.7, 6.6)	0.37	0.23
ASDAS-CRP, median (IQR)	2.4 (1.6, 3.3)	2.6 (1.8, 3.4)	2.7 (1.9, 3.5)	0.59	0.35

*Time from symptom onset to diagnosis

Supplementary table 4. Demographic, clinical and radiographic characteristics of axial PsA and AS with psoriasis compared pairwise regarding B27 status.

Variable	Axial PsA B27 negative N=60	AS with psoriasis B27 negative N=31	p-value	Axial PsA B27 positive N=26	AS with psoriasis B27 positive N=62	p-value	AS with psoriasis B27 pos vs neg p-value
Demographic characteristics							
Age (years), mean (SD)	49.7 (12.2)	51.3 (11.2)	0.54	45.1 (11.6)	48.7 (13.3)	0.23	0.36
Age at diagnosis (years), mean (SD)	42.6 (13.6)	42.3 (12.2)	0.91	35.6 (11.1)	33.5 (11.1)	0.41	<0.001
Sex, female	26/60 (43%)	3/31 (10%)	0.001	11/26 (42%)	10/62 (16%)	0.009	0.40
Disease duration (years), median (IQR)	7.0 (4.0-11.0)	7.5 (3.0-15.0)	0.47	7.0 (2.0-15.0)	13.0 (7.0-22.0)	0.034	0.016
Diagnostic delay (years)*, median (IQR)	1.0 (0.0-9.0)	3.5 (1.0-13.0)	0.099	1.0 (0.0-4.0)	5.0 (1.0-10.0)	0.032	0.92
BMI, mean (SD)	28.6 (6.3)	27.3 (3.7)	0.34	26.5 (5.2)	28.0 (5.0)	0.23	0.52
Family history of SpA	5/55 (9%)	4/25 (16%)	0.36	7/24 (29%)	11/58 (19%)	0.31	0.75
Clinical characteristics							
Cervical pain	6/60 (10%)	9/31 (29%)	0.020	3/26 (12%)	6/62 (10%)	0.79	0.017
Inflammatory back pain	47/60 (78%)	29/31 (94%)	0.064	23/26 (88%)	61/62 (98%)	0.041	0.21
Alternating buttock pain	20/60 (33%)	18/31 (58%)	0.023	12/26 (46%)	42/62 (68%)	0.058	0.36
Anterior uveitis	1/60 (2%)	1/30 (3%)	0.61	2/26 (8%)	11/62 (18%)	0.23	0.054

Inflammatory bowel disease	0/60 (0%)	0/31 (0%)		1/26 (4%)	4/62 (6%)	0.63	0.15
Dactylitis	22/60 (37%)	11/30 (37%)	1.00	5/26 (19%)	7/62 (11%)	0.32	0.004
Enthesitis	20/60 (33%)	13/31 (42%)	0.42	10/26 (38%)	24/61 (39%)	0.94	0.81
Peripheral arthritis	47/60 (78%)	20/31 (65%)	0.16	18/26 (69%)	31/61 (51%)	0.11	0.21
Nail disease	27/60 (45%)	11/30 (37%)	0.45	9/26 (35%)	10/62 (16%)	0.054	0.028
Psoriasis before SpA onset	36/38 (95%)	24/26 (92%)	0.69	10/16 (62%)	20/37 (54%)	0.57	0.001
Laboratory findings							
CRP (mg/L), median (IQR)	9.7 (17.5)	11.8 (19.7)	0.62	10.5 (17.5)	7.1 (9.6)	0.26	0.14
ESR (mm/h), median (IQR)	16.5 (16.4)	23.2 (16.8)	0.082	19.4 (23.5)	16.9 (14.0)	0.55	0.068
Radiographic findings							
BASRI sacroiliac joint, median (IQR)	2.0 (0.0-3.0)	3.0 (2.0-4.0)	<0.001	2.0 (1.0-3.0)	3.0 (3.0-4.0)	<0.001	0.20
BASRI lumbar, median (IQR)	0.0 (0.0-1.0)	2.0 (1.0-3.0)	<0.001	0.0 (0.0-1.0)	2.0 (1.0-4.0)	<0.001	0.87
BASRI cervical, median (IQR)	0.0 (0.0-1.0)	2.0 (0.0-3.0)	<0.001	0.0 (0.0-0.0)	1.0 (0.0-3.0)	0.002	0.23
Patient reported outcomes (PROs)							
BASDAI, median (IQR)	4.4 (2.3-6.4)	4.3 (3.2-6.2)	0.70	4.6 (2.2-6.4)	4.0 (2.1-5.7)	0.66	0.33
BASFI, median (IQR)	2.3 (1.1-5.4)	4.8 (2.4-6.8)	0.035	2.0 (1.0-4.8)	3.3 (1.2-5.8)	0.29	0.13
ASDAS-CRP, median (IQR)	2.3 (1.5-3.5)	3.0 (2.0-3.6)	0.19	2.6 (2.0-3.2)	2.5 (1.7-3.1)	0.64	0.20

*Time from symptom onset to diagnosis

Supplementary Table 5. Univariable analysis of factors associated with AS with psoriasis vs axial PsA (ref).

Variable	OR (95% CI)	p-value
Age at diagnosis	0.96 (0.95-0.99)	0.018
Sex	0.45 (0.25-0.79)	0.006
Disease duration	1.03 (1.01-1.07)	0.015
BMI	0.99 (0.95-1.05)	0.992
HLA-B27	4.83 (0.35-0.82)	0.0001
Inflammatory back pain	3.97 (1.69-9.32)	0.001
Nail disease	0.45 (0.264-0.79)	0.006
Peripheral arthritis	0.39 (0.219-0.69)	0.001
Anterior Uveitis	5.18 (1.47-18.32)	0.011
Dactylitis	0.63 (0.36-1.12)	0.116
Lumbar BASRI	2.14 (1.66-2.76)	0.0001

Study 4. Exploring the unifying concept of Spondyloarthritis: a latent class analysis of the REGISPONSER registry.

Michelena X, Sepriano A, Zhao SS, López-Medina C, Collantes E, Font-Ugalde P, Juanola X, Marzo-Ortega H.

Submitted

Exploring the unifying concept of Spondyloarthritis: a latent class analysis of the REGISPONSER registry.

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KEY WORDS

Spondyloarthritis, Axial Spondyloarthritis, Peripheral spondyloarthritis, unsupervised methods.

ABSTRACT

Objectives: The aim of our study is to identify the potential distinct phenotypes within a broad Spondyloarthritis (SpA) population.

Methods: We conducted a cross-sectional study using the REGISPONSER registry with data from 31 specialist centres in Spain including patients with SpA who fulfilled the European Spondyloarthropathy Study Group (ESSG) criteria. A latent class analysis (LCA) was performed to identify the latent classes underlying SpA according to a set of predefined clinical and radiographic features, independently of expert opinion.

Results: In a population of 2319 SpA patients, a 5 classes LCA model yielded the best fit. Classes named 'axial with spinal damage' and 'axial with SIJ damage" show a primarily axial SpA phenotype defined by inflammatory back pain and high HLA-B27 prevalence. Patients in class 'axial + peripheral' show similar distribution of manifest variables to previous classes but also have a higher likelihood of peripheral involvement (peripheral arthritis/dactylitis) and enthesitis, therefore representing a mixed (axial and peripheral) subtype. Classes 'Peripheral + psoriasis' and 'Axial + peripheral + psoriasis' are indicative of peripheral SpA (and/or PsA) with high likelihood of psoriasis, peripheral involvement, dactylitis, nail disease, and low HLA-B27 prevalence, while class 'Axial + peripheral + psoriasis' also exhibits increased probability of axial involvement both clinically and radiologically.

Conclusion: The identification of 5 latent classes in the REGISPONSER registry with significant overlap between axial and peripheral phenotypes is concordant with a unifying concept of SpA. Psoriasis and related features (nail disease and dactylitis) influence the phenotype of both axial and peripheral manifestations.

KEY MESSAGES

What is already known about this subject?

- Spondyloarthritis (SpA) is a term used to describe a heterogeneous group of diseases with overlapping clinical features.
- The absence of biomarkers has forced clinical research to be based on clinical characteristics and expert judgement leading to a long-standing debate on whether to “lump” or “split” these conditions to facilitate their understanding.

What does this study add?

- Unsupervised latent class analysis identifies five distinct clinical SpA entities defined by a combination of both axial and peripheral manifestations, and the presence of psoriasis.
- The significant overlap between the axial and peripheral phenotypes challenges the simple dichotomous differentiation between “axial SpA” and “peripheral SpA” and is concordant with the concept of SpA as whole.
- A latent class model that exclusively includes patients with history of psoriasis and/or nail disease suggests features such as dactylitis, nail disease and low HLA-B27 being more common in phenotypes compatible with the concept of axial PsA than with the concept of axial SpA with psoriasis.

How might this impact on clinical practice or future developments?

- The identification of these classes provides a better understanding of the broad SpA spectrum. Psoriasis and related features such as nail disease and dactylitis influence the phenotype of both axial and peripheral manifestations.
- Future work including precise immune-pathology and genetic signature studies is needed to forward our understanding of SpA.

INTRODUCTION

The concept of Spondyloarthritis (SpA), including both axial spondyloarthritis (axSpA) and several predominantly peripheral arthritis such as psoriatic arthritis (PsA), reactive arthritis (ReA), and arthritis associated with inflammatory bowel disease (IBD), was first described by Moll and Wright in Leeds, in 1974 (1). Subsequently, the Amor and the European Spondyloarthropathy Study Group (ESSG) classification criteria were developed as the first attempts to classify patients within the whole spectrum of SpA (2,3). In 2009, the Assessment of Spondyloarthritis international Society (ASAS), taking advantage of significant advances in the detection of early axial disease with magnetic resonance imaging (MRI), proposed a new set of classification criteria aimed to facilitate research in this area. These criteria introduced the terms "axSpA" to cover the spectrum of axial phenotypes and "peripheral spondyloarthritis" (pSpA) to describe the full range of SpA diseases that primarily affect the peripheral skeleton (4,5). This terminology inevitably brought forward the "splitting" of SpA into two clinical entities (axial and peripheral) which has been further consolidated by the concurrent growth in PsA research due in part to the relative ease with which PsA can be diagnosed in the presence of skin or nail disease (6). At the intersection however, lies the more recently advanced concept of axial PsA with ongoing debate on whether this represents a unique PsA phenotype or the coexistence of psoriasis and axSpA (7,8). Clinical research, to date, has failed to confirm whether these diseases can be distinguished from each other since clinical diagnosis and phenotypic classification are irretrievably linked to clinicians or experts' judgement.

Data-driven clustering methods enable identification of meaningful patterns within complex datasets, providing valuable insights into the inherent structure of diverse populations and could facilitate the understanding of SpA populations. Latent class analysis (LCA) offers several advantages compared to other clustering methods, as it is a model-based approach that can reveal the existence of unobserved, or latent, classes responsible for the observed relationships among variables. One key benefit is that LCA provides statistical rigor, generating probabilities of class membership and allowing for hypothesis testing and model comparisons. This helps researchers evaluate the fit of their model and select the most

appropriate number of latent classes independent of clinician or "expert" judgement (9). Recently, a LCA of data from the SpondyloArthritis Caught Early (SPACE) and DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohorts identified three latent classes of axSpA coinciding with three clinical entities named as pure axial SpA, axial SpA with peripheral signs, and axial SpA at risk (10). In the current study, we aimed to utilise LCA to identify potentially distinct classes within a broader SpA population, such as the REGISPONSER cohort, which encompasses the full spectrum of SpA.

METHODS

This was a cross-sectional study utilising baseline data from the multi-centre REGISPONSER registry. The REGISPONSER registry has been previously described (11). Briefly, adults (≥18 years) with a clinical diagnosis of SpA and meeting the European Spondyloarthropathy Study Group (ESSG) classification criteria including both axial and peripheral SpA were recruited in 31 specialist centres in Spain, between March 2004 and March 2007 (3). Clinical, laboratory and imaging parameters (conventional radiographs of pelvis, cervical and lumbar spine) were systematically collected in all patients regardless of their primary diagnosis and clinical symptoms. Radiographs were graded using the Bath Ankylosing Spondylitis Radiology Index (BASRI) by the local investigator (12). All patients gave informed written consent to participate in the REGISPONSER registry, which was approved centrally by the ethics committee of the Reina Sofia University Hospital from Cordoba (Spain).

A latent class analysis was performed with pre-selected features (manifest variables) which were then converted to categorical (binary) data as necessary in order to inform the model. Manifest variables included: family history of SpA (first degree relative with a diagnosis of SpA -Ankylosing Spondylitis, PsA, Reactive Arthritis, IBD-related arthritis and undifferentiated SpA); inflammatory back pain (fulfilling Calin Criteria)(13); peripheral arthritis, enthesitis, dactylitis as confirmed on physical examination by a rheumatologist; anterior uveitis, inflammatory bowel disease, nail disease, skin psoriasis (confirmed diagnosis); HLA-B27 positivity; elevated CRP (>5 mg/L); high grade sacroiliitis (BASRI ≥ 2), radiographic cervical involvement (BASRI ≥ 2), radiographic lumbar spine involvement (BASRI ≥ 2); axial manifestations (cervical, lower back or alternating buttock pain) as first or presenting

symptoms, peripheral manifestations as first symptom (peripheral arthritis or dactylitis) and/or enthesitis as first symptom. Manifest variables were recorded if “ever” present (i.e. any time in the past or at study visit).

The optimal number of classes for the model was determined by selecting the model that had the best fit, as assessed by statistical criteria (Akaike's information criterion (AIC), Bayesian information criterion (BIC), sample-size adjusted BIC entropy and likelihood ratio test) and by the presence of clinically recognizable patterns within each class. The model utilised all available data through the Full Information Maximum Likelihood (FIML) method, which imputed missing data under the assumption of Missing at Random (MAR). MAR was checked by visualising missingness distribution (Supplementary Material 1). As a sensitivity analysis, the final model was run again using only individuals with complete data available for all variables. Finally, the same model construction procedure was followed only including patients with a history (past or present) of psoriasis and/or nail disease.

Maximum likelihood estimates were used to assign each individual to the latent class that had the highest probability of being their true class, based on the manifest variables. Descriptive statistics were used to characterise demographic, clinical and radiographic characteristics of each class. Latent class analysis was performed utilising MPlus V8(12). Data manipulation and visualization were performed with Python 3.9 using the pandas, matplotlib and seaborn packages.

RESULTS

The baseline characteristics of the source REGISPONSER population (n=2319) are shown in Table 1. As seen in previous REGISPONSER reports (15), there is a notable incidence of axial-related variables, including a high prevalence of high grade sacroiliitis, HLA-B27 positivity and inflammatory back pain. A latent class model with 5 classes was determined to provide the best fit. The supplementary material contains all models ranging from 2 to 8 classes, along with their corresponding model fit statistics and clinical interpretation. The sensitivity analysis with 5 classes performed only in patients with complete data yielded similar results (Supplementary Table 13).

Figure 1 illustrates the distribution of conditional probabilities for each variable, as well as the probability of each class. To ensure clarity, we determined the order of classes by considering the percentage of each class (from highest to lowest) and then labelled them with a clinical description for further reference. 'Axial with spine damage' and 'axial with SIJ damage' classes demonstrate similar distributions, with a significant likelihood of inflammatory back pain (0.99 and 0.95) and axial as first symptom (both 0.97). As noted in the labels, the difference is in the likelihood of radiographic involvement of the lumbar (0.93 vs 0.03) and cervical spine (0.70 vs 0.02) as defined by a BASRI≥ 2 at each region. The rest of classes display a greater probability of presenting with peripheral arthritis as well as this being the presenting symptom. The 'axial+peripheral' class shares similar characteristics with 'axial with spine/SIJ damage' classes, including a comparable probability of HLA-B27 positivity (≈0.8) but more peripheral involvement (0.9 vs ≈0.2). By contrast, 'peripheral + psoriasis' and 'peripheral+axial+psoriasis' are more likely to present with psoriasis (≈0.9), dactylitis (0.35 and 0.46 respectively) and nail disease (0.35 and 0.6 respectively), while exhibiting a lower probability of HLA-B27 positivity (0.15 and 0.32 respectively). The main difference between these two classes is the probability of presenting with IBP and radiographic involvement of the sacroiliac joints and spine, which is mainly observed in the 'peripheral+axial+psoriasis' class.

Demographic, clinical and radiographic characteristics of the REGISPONSER registry stratified by latent class (class assigned to each subject) are shown in Table 2. The observed characteristics aligned with the model-based estimates. Notably, when examining additional variables that were not considered as manifest variables in the model, patients in classes 'peripheral + psoriasis' and 'axial + peripheral + psoriasis' were diagnosed at an older age, and class 'peripheral + psoriasis' demonstrated a female predominance (47.6% vs 30.1%). Median CRP (mg/L) was higher in 'axial with spine damage' (5.0) as were BASRI scores at the sacroiliac (4.0), lumbar (3.0) and cervical (2.0) spine level. Patient Reported Outcomes (PROs) did not exhibit any significant differences, except for higher BASFI scores in classes 'axial with spine damage' and 'axial + peripheral + psoriasis' and a higher score in BASDAI item 3 (peripheral involvement) in 'peripheral + psoriasis'.

The sub-analysis conducted on the subset of the population comprising patients with a history of psoriasis and/or nail disease (n=551), yielded an optimal model with 3 classes (Figure 2 and Supplementary Material 10). The main class is 'peripheral + psoriasis' marked by a peripheral phenotype (0.98), with a low probability of HLA-B27 positivity (0.13). The classes "Axial + peripheral + psoriasis' and 'axial + psoriasis' exhibit similar probability distributions, with a high likelihood of IBP and radiographic sacroiliitis. Some differences are however, noted between the two classes with the first being characterized by a higher probability of peripheral disease (0.89 vs 0.37), dactylitis (0.51 vs 0.03), and nail disease (0.49 vs 0.23) and the latter being associated with a higher likelihood of HLA-B27 positivity (0.68 vs 0.38) and axial symptoms first (0.94 vs 0.66). When assigning each subject to the class with the highest probability and analysing their characteristics, we found that the main variables aligned with those in the model as shown in Table 3.

DISCUSSION

The ongoing effort to characterise the SpA, has led to decades of debate on whether to "lump" or "split" these diseases. This debate has been further fuelled by the recent surge in research interest in axial PsA at the cross-roads between axial and peripheral SpA (16). In the current study and using an analytical unsupervised approach, we were able to identify five distinct classes or "splits", which were primarily distinguished by the presence of either peripheral or axial joint involvement and a history of skin psoriasis, although with significant overlap.

Our findings align with, to the best of our knowledge, the only previous latent class analysis conducted in a SpA setting performed by Sepriano et al (10). Analysing cohorts focusing on early axSpA (SPACE and DESIR), 4 classes were described that could be labelled as 'no SpA' (only seen in SPACE), 'pure axial', 'IBP with peripheral involvement' and 'at risk of SpA'(10). In our analysis, and upon examining the details of our various models (see Supplementary Material), we noted that the initial split was also seen between axial and peripheral involvement. When we added a third class, we observed a mixed axial and peripheral phenotype that aligns with the findings from the previous LCA. Interestingly, Sepriano et al did not identify an additional class that could account for differences between non-

radiographic and radiographic axSpA. Despite the absence of MRI data in our registry, which is relevant to the classification of nr-axSpA, we too did not identify any additional class that could explain differences within the axial phenotype subgroup which supports the view that this "division" between nr- and r-axSpA is an artificial construct (17–19). The additional class described in the axial phenotype model appears linked to a longer disease duration and, consequently, the higher likelihood of radiographic damage seen in the cervical and lumbar spine, in addition to the SIJs, consistent with previous reports in longitudinal cohorts (20). Similarly, a clustering analysis done in the ASAS-PerSpA Study (21), although using different methodology (k-means), clearly distinguished a predominantly axial and predominantly peripheral phenotype with a significant overlap of axial and peripheral manifestations, consistent with both our analysis and that of the SPACE and DESIR cohorts. These results suggest that the overarching SpA group shares more similarities than differences as supported by the consistent overlap of axial and peripheral clinical phenotypes seen in ours and other analyses. Interestingly, this mixed phenotype would only be classified as axSpA according to existing criteria if IBP is considered a "current" feature (4). Yet, the fluctuating nature of clinical manifestations in the different phenotypes adds to the understanding of the concept or "gestalt" of SpA, whereby if an specific clinical feature has "ever" been present, should be considered as defining.

In order to avoid any contamination of reasoning, we deliberately avoided matching the emerging classes with the primary clinical diagnosis. Instead, we aimed to characterise the classes as comprehensively as possible, to provide the readership with a better understanding of the implications of sub-grouping a broad SpA cohort. Yet, a degree of ascertainment bias cannot be ignored, since patients were included in the registry based on a clinical diagnosis made by the treating rheumatologist. Nevertheless, this cohort represents real world clinical settings. As conceived by Prof Bernard Amor and colleagues when the Amor criteria were originally proposed, the reader could interpret this analysis as being consistent with the unified concept of SpA with nuances that determine the different sub-classes or phenotypes (2). The classes we have hereby named 'Axial with spine damage', 'Axial with SIJ damage', and 'Axial + peripheral + psoriasis' exhibit characteristics consistent with SpA with a predominantly axial phenotype (i.e. axSpA), with psoriasis and its genetic background acting as a modifier in 'Axial + peripheral + psoriasis' as compared with the others. This "modifier"

ultimately determines other manifestations such as dactylitis and nail disease, with a lower prevalence of uveitis and IBD. With this same reasoning, ‘Axial + peripheral’ and ‘Peripheral + psoriasis’ may be interpreted as SpA with a predominantly peripheral phenotype (i.e. pSpA), with psoriasis once again likely driving the higher prevalence of dactylitis and nail disease, older age at presentation and lower prevalence of HLA-B27 positivity. From the perspective of an expert rheumatologist, classes could potentially be assigned a primary diagnosis. However, it is important to note that the assigned primary diagnosis will largely depend on the rheumatologist's education and background in the field. For instance, patients from the ‘Axial with spine/SIJ damage’ classes may receive a diagnosis of axial SpA, and classified as r-axSpA/AS, with ‘Axial with spine damage’ corresponding to longstanding disease as reflected by the higher proportion of spinal radiographic damage in addition to sacroiliitis. ‘Axial + peripheral’ class could be diagnosed as axial SpA or pure peripheral SpA, while ‘Peripheral + psoriasis’ class would likely be diagnosed as PsA and/or peripheral SpA. ‘Axial + peripheral + psoriasis’ could be named "axial PsA" or "axial SpA with psoriasis", a topic that has recently been explored in the literature with several studies comparing these entities (7, 8, 18). It is worth noting however, that when exploring the patients with psoriasis and/or nail disease in a dedicated sub-analysis and even recognizing the limitations of pre-selecting a population in these unsupervised methods, it could be argued that class ‘axial + peripheral + psoriasis’ may correspond to "axial PsA" with more dactylitis, nail disease, and peripheral involvement, in comparison to class ‘Axial + psoriasis’, which could be named "axial SpA with psoriasis”. Interestingly, a higher likelihood of nail disease was seen in those with axial disease and psoriasis, even more so than in those with peripheral disease and psoriasis, a fact that was brought forward as an independent predictor of response to treatment in the MAXIMISE study recruiting patients with a rheumatologist diagnosis of axial PsA (23).

This study has several limitations that need to be acknowledged. First, the cross-sectional nature of the study did not allow the evaluation of the stability and consistency of the classes over time, which would be desirable having in mind the changing and evolving nature of the clinical SpA phenotype. Secondly, the unavailability of MRI data precluded us from characterising early spinal disease more effectively. Additionally, while the source population comprises the entire SpA spectrum, there was an over-representation of axial SpA. Nevertheless, we identified distinct classes that align with the various clinical phenotypes.

The study also has several strengths. It was conducted on a large multicentre cohort recruited by expert rheumatologists with an interest in SpA being representative of the broad disease spectrum. In addition, the full availability of clinical and radiographic data independent of clinical characteristics and symptomatology, with little contamination by the primary diagnosis, make this a unique dataset to conduct this type of unsupervised analysis. Furthermore, the selection of manifest variables and the LCA methodology were aimed at avoiding the intrinsic circularity associated to clinician or expert input in diagnosis and case ascertainment definitions, which is a critical issue in such analyses.

In conclusion, we identified 5 latent classes providing a data-driven perspective on the concept of SpA that can be subdivided into predominant axial and peripheral forms in accordance with current understanding. Psoriasis appears to have a key role in phenotype definition in both forms with dactylitis and nail disease being more common in the axial psoriatic phenotype. The significant overlap between axial and peripheral phenotypes however highlights the commonalities within the SpA disease spectrum. While the clinical utility of these latent classes remains to be determined, they provide a starting point for precision medicine developments. Going forwards, precise immune-biology and genetic signature studies are needed to validate these disease classifications, in order to enhance our understanding of SpA, and ultimately, improve the lives of affected individuals.

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CONTRIBUTIONS

XM, AS and HMO designed the study. XM performed the statistical analyses and wrote the first draft of the manuscript. All authors critically interpreted the results, reviewed the draft version and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research project.

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Table 1. Selected features of the REGISPONSER registry.

Feature	Values
Total, n	2319
Family history of SpA, n (%)	1495/2319 (64.5)
Inflammatory back pain (IBP), n (%)	1841/2313 (79.6)
Peripheral arthritis, n (%)	1137/2319 (49.0)
Enthesitis, n (%)	911/2319 (39.3)
Dactylitis, n (%)	289/2319 (12.5)
Nail disease, n (%)	208/2304 (9.0)
Axial first symptom, n (%)	1672/2319(72.1)
Peripheral first symptom, n (%)	860/2319 (37.1)
Enthesitis first symptom, n (%)	221/2319 (9.5)
Psoriasis, n (%)	542/2306 (23.5)
Anterior Uveitis, n (%)	363/2298 (15.8)
IBD, n (%)	112/2305 (4.9)
HLA-B27 positive, n (%)	1382/1902 (72.7)
Elevated CRP (>5 mg/dL), n (%)	902/2085 (43.3)
High grade sacroiliitis (BASRI ≥ 2) , n (%)	1664/2209 (75.3)
Lumbar spine radiographic involvement (BASRI ≥ 2), n (%)	830/2179 (38.1)
Cervical spine radiographic involvement (BASRI ≥ 2), n (%)	622/2132 (29.2)

SpA: Spondyloarthritis, IBD: Inflammatory Bowel Disease, CRP: C-Reactive Protein, BASRI: Bath Ankylosing Spondylitis Radiology Index.

Table 2. Demographic, clinical and radiographic characteristics across latent classes in REGISPONSER.

	'Axial with spine damage'	'Axial with SIJ damage'	'Axial + peripheral'	'Peripheral + psoriasis'	'Axial + peripheral + psoriasis'
Variable	N=725	N=708	N=409	N=334	N=143
Demographic characteristics					
Age, mean (SD)	52.5 (11.6)	41.0 (11.8)	44.3 (12.8)	50.9 (14.0)	50.4 (12.2)
Age at diagnosis, mean (SD)	36.3 (12.0)	33.1 (10.9)	33.3 (13.1)	43.2 (13.7)	41.5 (13.0)
Sex, female	110/725 (15.2%)	275/708 (38.8%)	150/409 (36.7%)	159/334 (47.6%)	36/143 (25.2%)
Disease duration, median *(IQR)*	15.0 (7.0-24.0)	6.0 (3.0-12.0)	8.5 (3.0-17.0)	6.0 (3.0-12.0)	7.0 (3.0-13.5)
*Diagnostic delay, me*dian *(*IQR*)*	6.0 (2.0-14.0)	3.0 (1.0-8.0)	1.0 (0.0-6.0)	1.0 (0.0-3.0)	2.0 (0.0-10.0)
BMI, mean (SD)	27.5 (4.5)	25.6 (4.2)	26.0 (4.3)	27.0 (4.4)	27.9 (5.7)
Family history of SpA	140/669 (20.9%)	147/660 (22.3%)	58/363 (16.0%)	25/301 (8.3%)	12/118 (10.2%)
Clinical characteristics					
Inflammatory back pain	724/725 (99.9%)	704/708 (99.4%)	323/408 (79.2%)	27/333 (8.1%)	136/142 (95.8%)
Alternating buttock pain	493/718 (68.7%)	427/700 (61.0%)	184/401 (45.9%)	16/333 (4.8%)	74/139 (53.2%)
Anterior uveitis	142/720 (19.7%)	124/700 (17.7%)	91/405 (22.5%)	1/333 (0.3%)	5/140 (3.6%)
Inflammatory bowel disease	25/724 (3.5%)	54/701 (7.7%)	22/406 (5.4%)	10/332 (3.0%)	1/142 (0.7%)
Psoriasis	39/723 (5.4%)	42/701 (6.0%)	23/408 (5.6%)	298/332 (89.8%)	140/142 (98.6%)
Dactylitis	17/721 (2.4%)	13/703 (1.8%)	67/405 (16.5%)	108/333 (32.4%)	63/142 (44.4%)
Enthesitis	225/719 (31.3%)	157/700 (22.4%)	201/405 (49.6%)	43/333 (12.9%)	61/141 (43.3%)
Peripheral arthritis	185/723 (25.6%)	100/700 (14.3%)	362/409 (88.5%)	329/334 (98.5%)	109/142 (76.8%)
Nail disease	4/723 (0.6%)	0/700 (0.0%)	0/407 (0.0%)	117/333 (35.1%)	87/141 (61.7%)
Laboratory findings					

HLA-B27 positive, n (%)	545/646 (84.4%)	504/623 (80.9%)	278/342 (81.3%)	27/196 (13.8%)	30/99 (30.3%)
CRP (mg/L), median (IQR)	5.0 (2.0-12.4)	3.5 (1.6-8.9)	3.7 (1.3-8.0)	4.8 (2.0-10.0)	3.9 (2.0-10.0)
ESR (mm/h), median (IQR)	15.0 (8.0-25.0)	12.0 (7.0-21.0)	13.0 (8.0-22.0)	17.0 (9.0-25.0)	13.0 (7.0-21.0)
Radiographic findings					
Radiographic sacroiliitis	713/715 (99.7%)	552/654 (84.4%)	262/376 (69.7%)	33/326 (10.1%)	104/138 (75.4%)
BASRI sacroiliac joint, median (IQR)	4.0 (3.0-4.0)	2.0 (2.0-3.0)	2.0 (1.0-3.0)	0.0 (0.0-0.0)	2.0 (2.0-3.0)
BASRI lumbar spine, median (IQR)	3.0 (2.0-4.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	1.0 (0.0-2.0)
BASRI cervical spine, median (IQR)	2.0 (1.0-4.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	1.0 (0.0-2.0)
Patient Reported Outcomes					
BASDAI, median (IQR)	4.2 (2.4-6.0)	3.8 (2.0-5.8)	3.4 (1.6-5.6)	3.9 (2.0-6.1)	4.0 (2.4-5.8)
Item 2 BASDAI, median (IQR)	6.0 (3.0-8.0)	5.0 (3.0-7.0)	4.0 (1.0-7.0)	3.0 (0.0-7.0)	5.0 (2.0-7.0)
Item 3 BASDAI, median (IQR)	2.0 (0.0-5.0)	2.0 (0.0-5.0)	3.0 (1.0-6.0)	5.0 (2.0-7.0)	3.0 (1.0-6.0)
Item 6 BASDAI, median (IQR)	3.0 (2.0-5.0)	3.0 (1.0-5.0)	2.0 (0.0-5.0)	2.0 (1.0-5.0)	3.0 (1.0-5.0)
BASFI, median (IQR)	4.6 (2.2-6.6)	2.3 (0.8-4.8)	2.3 (0.8-4.7)	2.2 (0.6-4.8)	3.7 (1.6-5.6)
VAS Global, median (IQR)	5.0 (3.0-7.0)	5.0 (2.0-7.0)	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (2.0-6.0)
ASDAS-CRP, median (IQR)	2.7 (1.9-3.5)	2.4 (1.6-3.3)	2.2 (1.5-3.1)	2.4 (1.6-3.3)	2.6 (1.6-3.3)

BMI: Body Mass Index, SpA: Spondyloarthritis, CRP: C-Reactive protein, ESR: Erythrocyte Sedimentation Rate, BASRI: Bath Ankylosing Spondylitis Radiology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index VAS: Visual Analogue scale, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score.

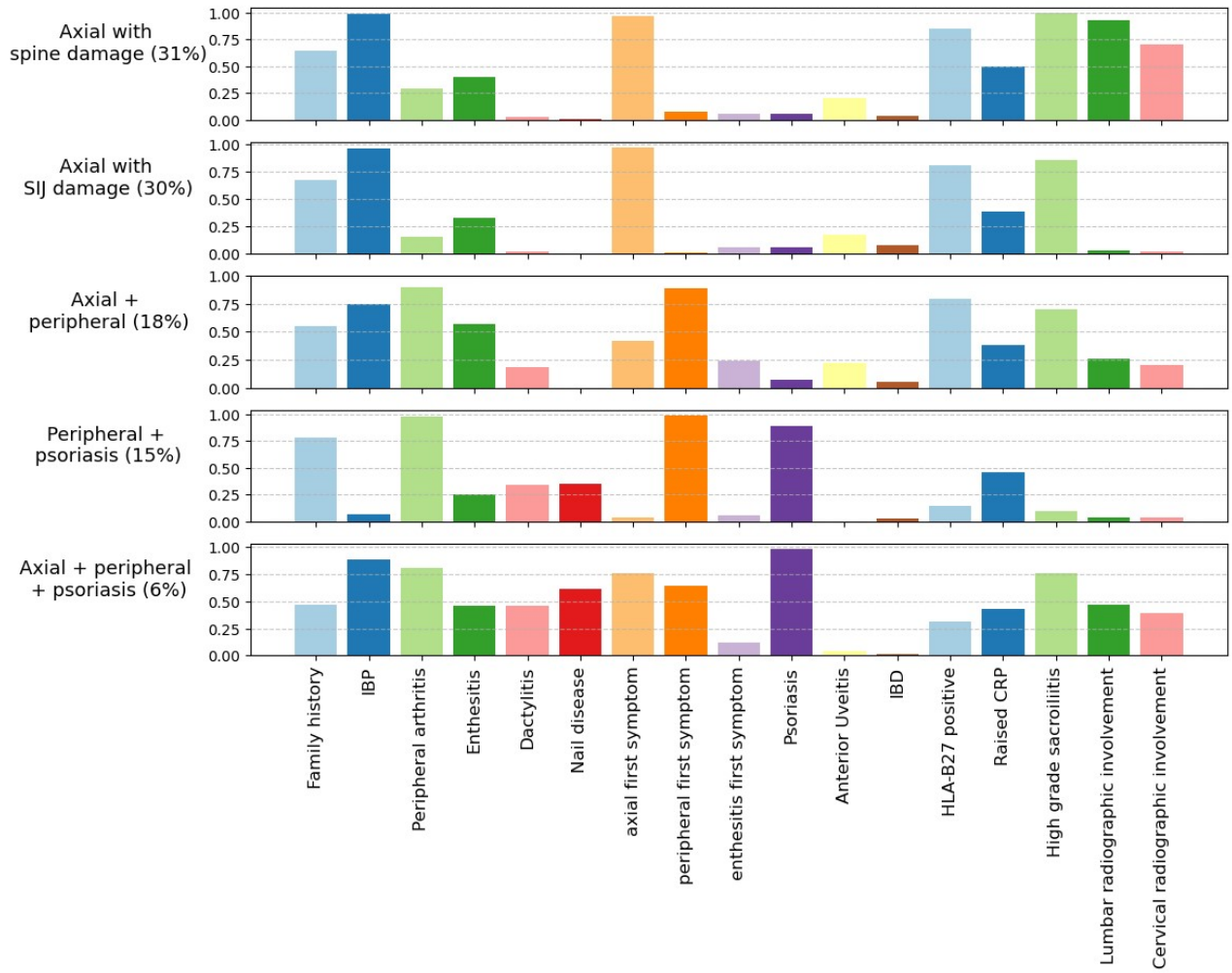
Table 3. Demographic, clinical and radiographic characteristics divided by latent classes in the REGISPONSER population with a history of psoriasis and/or nail disease.

	'Peripheral + psoriasis'	'Axial + peripheral + psoriasis'	'Axial + psoriasis'
Variable	N=304	N=133	N=114
Demographic characteristics			
Age, mean (SD)	51.9 (13.7)	50.0 (12.5)	48.4 (12.6)
Age at diagnosis, mean (SD)	43.9 (14.0)	39.9 (12.8)	38.6 (13.4)
Sex, female	141/304 (46.4%)	40/133 (30.1%)	27/114 (23.7%)
Disease duration, median (IQR)	7.0 (3.0-13.0)	7.0 (3.0-15.0)	7.0 (3.0-16.0)
Diagnostic delay, median (IQR)	1.0 (0.0-3.0)	2.0 (0.0-10.0)	4.0 (1.0-10.0)
BMI, mean (SD)	27.1 (4.4)	27.5 (5.9)	27.7 (4.4)
Family history of SpA	24/271 (8.9%)	13/112 (11.6%)	19/105 (18.1%)
Clinical characteristics			
Inflammatory back pain	29/303 (9.6%)	126/132 (95.5%)	114/114 (100.0%)
Alternating buttock pain	13/303 (4.3%)	65/129 (50.4%)	66/114 (57.9%)
Anterior uveitis	1/303 (0.3%)	11/130 (8.5%)	13/114 (11.4%)
Inflammatory bowel disease	0/302 (0.0%)	3/133 (2.3%)	7/113 (6.2%)
Psoriasis	302/303 (99.7%)	130/133 (97.7%)	110/113 (97.3%)
Dactylitis	102/303 (33.7%)	63/132 (47.7%)	2/114 (1.8%)
Enthesitis	39/303 (12.9%)	64/132 (48.5%)	28/112 (25.0%)
Peripheral arthritis	299/304 (98.4%)	112/132 (84.8%)	40/112 (35.7%)
Nail disease	119/303 (39.3%)	63/131 (48.1%)	26/112 (23.2%)
Laboratory findings			
HLA-B27 positive, n (%)	24/173 (13.9%)	32/87 (36.8%)	65/96 (67.7%)
CRP (mg/L), median (IQR)	5.0 (2.0-10.0)	4.0 (2.5-8.3)	4.0 (1.9-10.0)
ESR (mm/h), median (IQR)	17.0 (9.0-26.0)	13.0 (7.0-21.0)	12.0 (7.0-22.0)
Radiographic findings			
Radiographic sacroiliitis (fulfiling mNYC criteria)	30/296 (10.1%)	102/129 (79.1%)	92/111 (82.9%)
BASRI sacroiliac joint, median (IQR)	0.0 (0.0-0.0)	2.0 (2.0-3.0)	3.0 (2.0-4.0)
BASRI lumbar spine, median (IQR)	0.0 (0.0-0.0)	1.0 (0.0-2.0)	1.0 (0.0-3.0)
BASRI cervical spine, median (IQR)	0.0 (0.0-0.0)	1.0 (0.0-3.0)	0.0 (0.0-2.0)
Patient Reported Outcomes			
BASDAI, median (IQR)	4.1 (2.1-6.2)	4.0 (2.1-5.8)	4.1 (2.4-6.2)

Item 2 BASDAI, median (IQR)	4.0 (0.0-7.0)	5.0 (2.0-7.0)	6.0 (3.0-8.0)
Item 3 BASDAI, median (IQR)	5.0 (2.0-7.0)	3.0 (1.0-6.0)	3.0 (0.0-6.0)
Item 6 BASDAI, median (IQR)	3.0 (1.0-5.0)	2.0 (1.0-5.0)	4.0 (2.0-5.0)
BASFI, median (IQR)	2.3 (0.7-5.1)	3.6 (1.4-5.4)	3.8 (1.4-6.4)
VAS Global, median (IQR)	4.0 (2.0-7.0)	4.0 (2.0-6.0)	5.0 (3.0-7.0)
ASDAS-CRP, median (IQR)	2.5 (1.6-3.4)	2.4 (1.5-3.3)	2.7 (2.0-3.3)

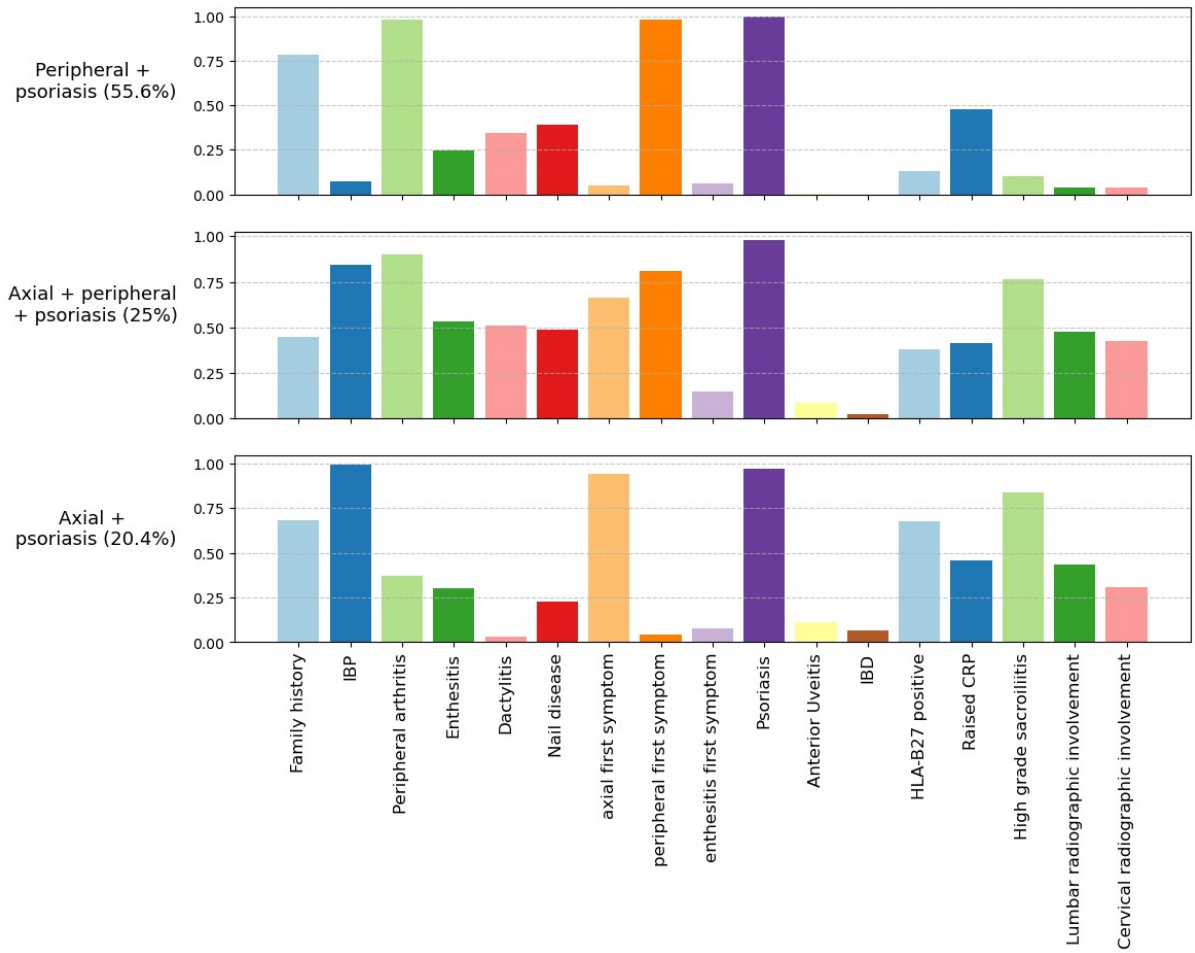
BMI: Body Mass Index, SpA: Spondyloarthritis, CRP: C-Reactive protein, ESR: Erythrocyte Sedimentation Rate, BASRI: Bath Ankylosing Spondylitis Radiology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index VAS: Visual Analogue scale, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score.

Figure 1. Bar chart of the distribution of the conditional probabilities of each feature according to the final LCA model in REGISPONSER.



Y axis shows the probability of each feature within each class. Labels are constructed based on clinical interpretation and for further reference. Classes are ordered by the percentage of each class (from highest to lowest). IBP: Inflammatory Back Pain, IBD: Inflammatory Bowel Disease, CRP: C-Reactive Protein, High grade sacroiliitis: sacroiliac joint BASRI score ≥ 2*, Lumbar radiographic involvement: lumbar BASRI*≥ 2*, Cervical radiographic involvement: cervical BASRI*≥ 2*.*

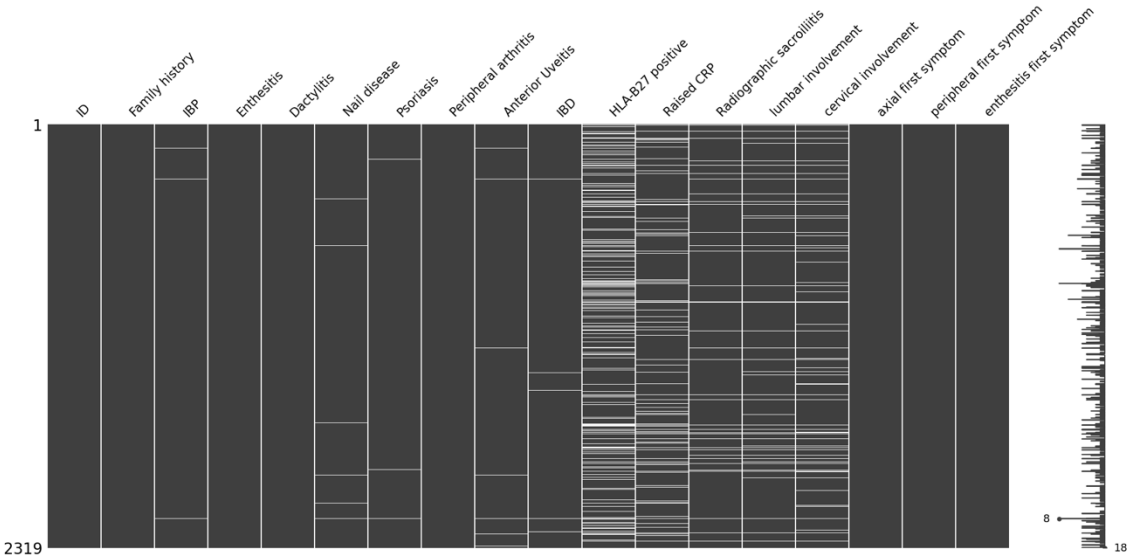
Figure 2. Bar chart of the distribution of the conditional probabilities of each feature according to the final LCA model in the REGISPONSER population with a history of psoriasis or nail disease.



Y axis shows the probability of each feature within each class. Labels are constructed based on clinical interpretation and for further reference. Classes are ordered by the percentage of each class (from highest to lowest). IBP: Inflammatory Back Pain, IBD: Inflammatory Bowel Disease, CRP: C-Reactive Protein, High grade sacroiliitis: sacroiliac joint BASRI score ≥ 2*, Lumbar radiographic involvement: lumbar BASRI*≥ 2*, Cervical radiographic involvement: cervical BASRI*≥ 2.

Supplementary Material. Exploring the unifying concept of Spondyloarthritis: a latent class analysis of the REGISPONSER registry.

Supplementary Figure 1. Matrix showing in white missing values of all manifest variables



Supplementary Table 1-8. Latent Class Models from 2 classes to 8 classes

Conditional probability of each manifest variable for each model with pre-specified number of classes is shown in the following tables. A comment with a clinical interpretation of the model is added. Likelihood ratio test comparing the model with the previous model with -1 class are also presented. Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-adjusted BIC and entropy for each model are presented in a line plot.

Supplementary Table 1. Latent class model with 2 classes

p=Probability of the latent class.

	class 1 p=71%	class 2 p=29%
Family history	0.637	0.664
IBP	0.971	0.366
Peripheral arthritis	0.302	0.951
Enthesitis	0.395	0.389
Dactylitis	0.040	0.331
Nail disease	0.019	0.265
axial first symptom	0.935	0.197
peripheral first symptom	0.133	0.953
enthesitis first symptom	0.078	0.139

Psoriasis	0.079	0.616
Anterior Uveitis	0.198	0.060
IBD	0.053	0.037
HLA-B27 positive	0.825	0.413
Raised CRP	0.438	0.420
Radiographic sacroiliitis	0.925	0.333
lumbar involvement	0.488	0.117
cervical involvement	0.374	0.093

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Comment: This divides the cohort into axial and peripheral.

Supplementary Table 2. Latent class model with 3 classes

	class 1 p=28%	class 2 p=17%	class 3 p=55%
Family history	0.541	0.764	0.660
IBP	0.857	0.113	0.976
Peripheral arthritis	0.826	0.971	0.175
Enthesitis	0.574	0.274	0.339
Dactylitis	0.214	0.350	0.010
Nail disease	0.094	0.347	0.009
axial first symptom	0.579	0.070	0.993
peripheral first symptom	0.724	0.986	0.005
enthesitis first symptom	0.233	0.069	0.035
Psoriasis	0.227	0.818	0.059
Anterior Uveitis	0.207	0.005	0.181
IBD	0.040	0.034	0.058
HLA-B27 positive	0.751	0.200	0.827
Raised CRP	0.407	0.443	0.442
Radiographic sacroiliitis	0.777	0.138	0.933
lumbar involvement	0.394	0.053	0.477
cervical involvement	0.320	0.047	0.356

Comment: The added class (class 1) is a mixed phenotype with axial and peripheral involvement. Class 2 is a mainly peripheral disease with high probability of psoriasis and Class 3 is mainly axial disease.

Supplementary Table 3. Latent class model with 4 classes

class 1 p=24%	class 2 p=16%	class 3 p=31%	Class 4 p=29%

Family history	0.522	0.771	0.649	0.671
IBP	0.823	0.099	0.993	0.955
Peripheral arthritis	0.882	0.969	0.259	0.145
Enthesitis	0.580	0.259	0.388	0.319
Dactylitis	0.243	0.348	0.018	0.015
Nail disease	0.109	0.354	0.012	0.010
axial first symptom	0.530	0.061	0.982	0.971
peripheral first symptom	0.802	0.988	0.052	0.008
enthesitis first symptom	0.231	0.061	0.045	0.056
Psoriasis	0.246	0.835	0.068	0.067
Anterior Uveitis	0.202	0.004	0.194	0.170
IBD	0.041	0.032	0.036	0.076
HLA-B27 positive	0.736	0.181	0.841	0.807
Raised CRP	0.408	0.445	0.498	0.376
Radiographic sacroiliitis	0.753	0.127	0.995	0.852
lumbar involvement	0.347	0.050	0.925	0.010
cervical involvement	0.277	0.046	0.693	0.017

Comment: Adding a new class, divides the previous class 3 (mainly axial disease) into two, with main differences seen in the amount of lumbar and cervical radiographic involvement in class 3 (Longstanding axial SpA).

Supplementary Table 4. Latent class model with 5 classes

	class 1 p=31%	class 2 p=30%	class 3 p=18%	class 4 p=15%	class 5 p=6%
Family history	0.648	0.669	0.550	0.779	0.468
IBP	0.993	0.956	0.747	0.068	0.887
Peripheral arthritis	0.287	0.153	0.899	0.979	0.812
Enthesitis	0.404	0.329	0.573	0.250	0.458
Dactylitis	0.023	0.018	0.187	0.346	0.463
Nail disease	0.008	0.001	0.000	0.351	0.615
axial first symptom	0.971	0.969	0.415	0.041	0.758
peripheral first symptom	0.077	0.007	0.891	0.988	0.640
enthesitis first symptom	0.055	0.061	0.238	0.060	0.124
Psoriasis	0.056	0.058	0.070	0.886	0.979
Anterior Uveitis	0.199	0.173	0.224	0.003	0.042

IBD	0.036	0.076	0.054	0.028	0.011
HLA-B27 positive	0.848	0.808	0.796	0.148	0.317
Raised CRP	0.497	0.382	0.383	0.460	0.429
Radiographic sacroiliitis	0.995	0.852	0.701	0.101	0.756
lumbar involvement	0.931	0.027	0.257	0.034	0.469
cervical involvement	0.705	0.024	0.198	0.036	0.391

Comment: Adding a new class, divides the previous class 1 (mixed axial and peripheral) in two classes: one with a very high probability of psoriasis, dactylitis and nail disease but less probability of HLA-B27 compared to the other.

Supplementary Table 5. Latent class model with 6 classes

	class 1 p=29%	class 2 p=27%	class 3 p=15%	class 4 p=5%	class 5 p=13%	class 6 p=11%
Family history	0.672	0.645	0.558	0.463	0.785	0.618
IBP	0.958	0.991	0.615	0.883	0.056	0.954
Peripheral arthritis	0.155	0.198	0.871	0.820	0.983	0.831
Enthesitis	0.325	0.364	0.535	0.430	0.227	0.624
Dactylitis	0.018	0.009	0.197	0.461	0.362	0.145
Nail disease	0.002	0.005	0.000	0.650	0.397	0.021
axial first symptom	0.976	1.000	0.361	0.761	0.033	0.636
peripheral first symptom	0.009	0.000	0.886	0.640	0.995	0.673
enthesitis first symptom	0.055	0.032	0.263	0.094	0.050	0.185
Psoriasis	0.059	0.052	0.106	1.000	0.977	0.081
Anterior Uveitis	0.176	0.186	0.139	0.020	0.003	0.317
IBD	0.076	0.039	0.082	0.017	0.000	0.026
HLA-B27 positive	0.812	0.841	0.699	0.292	0.111	0.877
Raised CRP	0.382	0.497	0.351	0.435	0.479	0.454
Radiographic sacroiliitis	0.855	0.991	0.492	0.755	0.106	0.999
lumbar involvement	0.000	0.913	0.049	0.462	0.043	0.803
cervical involvement	0.015	0.668	0.017	0.385	0.044	0.668

Comment: Axial disease is subdivided in 2 classes (class 3 and 6) encompassing the mixed axial-peripheral phenotype but with little differences. The main difference is the more severe radiographic disease in class 6.

Supplementary Table 6. Latent class model with 7 classes

class 1 p=10%	class 2 p=6%	class 3 p=27%	class 4 p=13%	class 5 p=28%	class 6 p=10%	class 7 p=6%

Family history	0.563	0.472	0.647	0.787	0.670	0.608	0.577
IBP	0.587	0.848	0.994	0.051	0.950	0.960	0.762
Peripheral arthritis	0.873	0.836	0.201	0.984	0.156	0.830	0.801
Enthesitis	0.285	0.395	0.367	0.231	0.303	0.642	1.000
Dactylitis	0.077	0.454	0.010	0.361	0.015	0.150	0.380
Nail disease	0.000	0.661	0.005	0.389	0.002	0.026	0.000
axial first symptom	0.303	0.737	1.000	0.028	0.979	0.640	0.524
peripheral first symptom	0.991	0.656	0.000	1.000	0.007	0.672	0.634
enthesitis first symptom	0.042	0.068	0.033	0.044	0.035	0.180	0.709
Psoriasis	0.067	1.000	0.052	0.966	0.060	0.094	0.168
Anterior Uveitis	0.144	0.016	0.188	0.003	0.172	0.308	0.184
IBD	0.117	0.016	0.040	0.000	0.078	0.022	0.014
HLA-B27 positive	0.760	0.263	0.841	0.113	0.814	0.881	0.643
Raised CRP	0.338	0.419	0.498	0.477	0.380	0.448	0.419
Radiographic sacroiliitis	0.594	0.732	0.991	0.100	0.862	1.000	0.435
lumbar involvement	0.089	0.453	0.913	0.037	0.000	0.845	0.039
cervical involvement	0.026	0.380	0.665	0.037	0.017	0.730	0.015

Comment: More subdivisions which are difficult to interpret, rather than a new class with high probability of presenting enthesitis as first symptom (class 7).

Supplementary Table 7. Latent class model with 8 classes

	class 1	class 2	class 3	class 4	class 5	class 6	class 7	class 8
Family history	0.584	0.788	0.550	0.473	0.652	0.559	0.667	0.673
IBP	0.957	0.052	0.585	0.863	0.995	0.650	1.000	0.950
Peripheral arthritis	0.878	0.984	0.853	0.826	0.211	0.962	0.200	0.162
Enthesitis	0.622	0.219	0.227	0.399	0.367	1.000	0.928	0.290
Dactylitis	0.161	0.358	0.055	0.456	0.012	0.464	0.026	0.017
Nail disease	0.016	0.397	0.000	0.672	0.005	0.000	0.030	0.002
axial first symptom	0.637	0.030	0.311	0.752	0.999	0.462	0.598	0.986
peripheral first symptom	0.752	0.998	0.980	0.648	0.002	0.848	0.015	0.008
enthesitis first symptom	0.143	0.040	0.045	0.075	0.023	0.567	0.993	0.000
Psoriasis	0.089	0.972	0.065	1.000	0.053	0.199	0.090	0.060
Anterior Uveitis	0.310	0.003	0.139	0.017	0.188	0.155	0.267	0.171

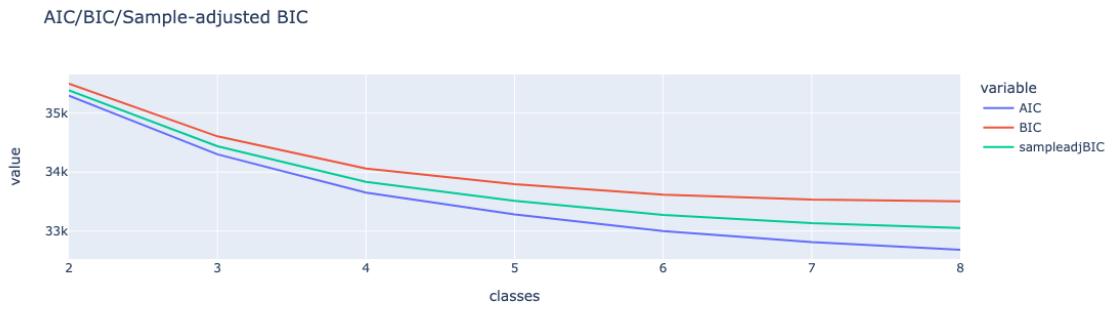
IBD	0.023	0.000	0.131	0.017	0.039	0.002	0.071	0.075
HLA-B27 positive	0.898	0.111	0.750	0.270	0.844	0.636	0.757	0.809
Raised CRP	0.460	0.475	0.315	0.423	0.500	0.471	0.262	0.384
Radiographic sacroiliitis	0.994	0.104	0.607	0.749	0.991	0.387	0.735	0.864
lumbar involvement	0.824	0.040	0.092	0.469	0.922	0.021	0.252	0.000
cervical involvement	0.744	0.041	0.023	0.393	0.670	0.015	0.088	0.021

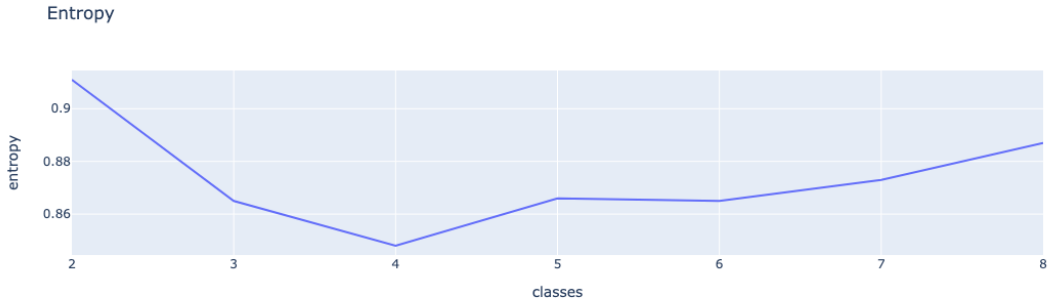
Comment: Difficult to interpret*

Supplementary Table 8. Likelihood Ratio Tests, AIC, BIC, Sample-adjusted BIC and Entropy of all models

Classes	**VUONG-LO-MENDELL-RUBIN LRT**		**LO-MENDELL-RUBIN ADJUSTED LRT**	
	H0 Loglikelihood Value	P-Value	Value	P-Value
2	-20.261.339	0.0000	5.259.913	0.0000
3	-17.612.527	0.0000	1.023.475	0.0000
4	-16.044.337	0.0000	697.178	0.0000
5	-16.755.740	0.0021	401.631	0.0022
6	-16.553.485	0.0004	317.936	0.0004
7	-16.393.378	0.0189	220.988	0.0193
8	-16.282.092	0.0659	164.907	0.0678

Classes	**AIC**	**BIC**	**Sample-adjusted BIC**	**Entropy**
2	35295.054	35496.265	35385.063	0.911
3	34300.241	34604.932	34436.541	0.865
4	33653.481	34061.652	33836.072	0.848
5	33284.971	33796.622	33513.852	0.866
6	33000.755	33615.886	33275.927	0.865
7	32814.183	33532.794	33135.646	0.873
8	32684.094	33506.185	33051.847	0.887





Comment: From a statistical perspective, a model featuring seven classes outperforms a six-class model, as evidenced by decreasing values for AIC, BIC, and sample-adjusted BIC when adding classes. However, entropy begins to increase with the inclusion of five classes, and more importantly, the addition of a sixth class offers minimal benefit when interpreted from a clinical perspective. Therefore, a five-class model was ultimately chosen as the optimal model.

Supplementary Table 9-12. Latent Class Models from 2 classes to 4 classes in the population with history of psoriasis and/or nail disease.

Conditional probability of each manifest variable for each model with pre-specified number of classes is shown in the following tables. A comment with a clinical interpretation of the model is added. Likelihood ratio test comparing the model with the previous model with -1 class are also presented. Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-adjusted BIC and entropy for each model are presented in a line plot.

Supplementary Table 9. Latent class model with 2 classes

p=Probability of the latent class.

	class 1 p=60.2%	class 2 p=39.8%
Family history	0.766	0.551
IBP	0.112	0.969
Peripheral arthritis	0.981	0.614
Enthesitis	0.255	0.440
Dactylitis	0.376	0.242
Nail disease	0.405	0.344
axial first symptom	0.068	0.860
peripheral first symptom	0.983	0.392
enthesitis first symptom	0.067	0.118
Psoriasis	0.997	0.972
Anterior Uveitis	0.003	0.110

IBD	0.000	0.046
HLA-B27 positive	0.130	0.576
Raised CRP	0.465	0.442
Radiographic sacroiliitis	0.154	0.821
lumbar involvement	0.073	0.464
cervical involvement	0.064	0.378

Comment: Division in peripheral and axial.

Supplementary Table 10. Latent class model with 3 classes

	class 1 p=55.6%	class 2 p=25%	class 3 p=20.4%
Family history	0.787	0.448	0.681
IBP	0.072	0.846	0.993
Peripheral arthritis	0.980	0.898	0.371
Enthesitis	0.244	0.534	0.303
Dactylitis	0.347	0.510	0.030
Nail disease	0.390	0.487	0.225
axial first symptom	0.047	0.660	0.942
peripheral first symptom	0.982	0.810	0.045
enthesitis first symptom	0.064	0.145	0.078
Psoriasis	0.998	0.977	0.971
Anterior Uveitis	0.003	0.083	0.114
IBD	0.000	0.022	0.063
HLA-B27 positive	0.128	0.382	0.677
Raised CRP	0.475	0.412	0.457
Radiographic sacroiliitis	0.104	0.767	0.835
lumbar involvement	0.037	0.478	0.436
cervical involvement	0.038	0.425	0.307

Comment: Axial phenotype is divided in two classes with one with higher positivity of HLAB27, more radiographic involvement and the other with more concomitant peripheral disease, nail disease and dactylitis.

Supplementary Table 11. Latent class model with 4 classes

	class 1 p=16.8%	class 2 p=13.8%	class 3 p=53%	class 4 p=16.4%
Family history	0.557	0.446	0.785	0.666
IBP	0.835	0.851	0.061	1.000
Peripheral arthritis	0.854	0.846	0.984	0.324
Enthesitis	0.573	0.544	0.220	0.249
Dactylitis	0.370	0.534	0.353	0.000
Nail disease	0.348	0.528	0.403	0.217
axial first symptom	0.674	0.669	0.030	0.987
peripheral first symptom	0.664	0.751	0.996	0.028
enthesitis first symptom	0.213	0.163	0.047	0.025
Psoriasis	1.000	0.947	0.997	0.978
Anterior Uveitis	0.065	0.110	0.003	0.110
IBD	0.048	0.014	0.000	0.051
HLA-B27 positive	0.434	0.405	0.117	0.694
Raised CRP	0.359	0.416	0.482	0.499
Radiographic sacroiliitis	0.480	0.952	0.114	0.892
lumbar involvement	0.000	0.890	0.051	0.483
cervical involvement	0.054	0.719	0.048	0.334

Comment: Axial phenotype is further subdivided with a new class with a more severe radiographic lumbar and cervical involvement.

Supplementary Table 12. Likelihood Ratio Tests, AIC, BIC, Sample-adjusted BIC and Entropy of all models

Classes	**VUONG-LO-MENDELL-RUBIN LRT**		**LO-MENDELL-RUBIN ADJUSTED LRT**	
	H0 Loglikelihood Value	P-Value	Value	P-Value
2	-4.525.251	0.0000	1.237.254	0.0000
3	-3.901.179	0.0071	157.303	0.0075
4	-3.821.835	0.1138	91.190	0.1159

Classes	**AIC**	**BIC**	**Sample-adjusted BIC**	**Entropy**
2	35295.054	35496.265	35385.063	0.911
3	34300.241	34604.932	34436.541	0.865
4	33653.481	34061.652	33836.072	0.848

Comment: From a statistical standpoint, both BIC metric and entropy experience an increase when transitioning from a three-class to a four-class model. Additionally, the three-class model is easier to interpret from a clinical perspective, leading to the conclusion that a model with three classes yields the best result.

Supplementary Table 13. Sensitivity Analysis with an LCA model with 5 classes only considering subjects with complete data.

	class 1 p=33.2%	**class 2 p=29.8%**	**class 3 p=14.3%**	**class 4 p=12.4%**	**class 5 p=10.3%**
Family history	0.715	0.731	0.603	0.755	0.620
IBP	1.000	1.000	0.631	0.194	0.967
Peripheral arthritis	0.224	0.164	0.981	0.992	0.796
Enthesitis	0.364	0.333	0.552	0.235	0.647
Dactylitis	0.009	0.018	0.218	0.421	0.197
Nail disease	0.010	0.013	0.000	0.497	0.073
axial first symptom	1.000	0.970	0.354	0.157	0.680
peripheral first symptom	0.007	0.015	0.910	0.968	0.692
enthesitis first symptom	0.024	0.065	0.246	0.045	0.203
Psoriasis	0.049	0.075	0.076	0.968	0.217
Anterior Uveitis	0.195	0.187	0.169	0.000	0.260
IBD	0.042	0.071	0.067	0.013	0.027

HLA-B27 positive	0.854	0.821	0.741	0.114	0.819
Raised CRP	0.502	0.378	0.337	0.449	0.434
Radiographic sacroiliitis	0.988	0.861	0.520	0.172	0.986
lumbar involvement	0.931	0.000	0.049	0.051	0.793
cervical involvement	0.657	0.018	0.009	0.065	0.695

DISCUSSION

The spectrum of spondyloarthritis (SpA) encompasses a group of chronic inflammatory conditions sharing common clinical findings, natural history, pathophysiology, and epidemiology (1). Over the years, efforts to characterize SpA have sparked a longstanding debate regarding the optimal approach—whether to categorize these diseases as a unified entity ("lump") or as distinct entities ("split") (115). This debate has been further fuelled by the recent surge in research interest, particularly in axial Psoriatic Arthritis (PsA), which lies at the intersection of axial and peripheral SpA (87).

Since the publication of the ASAS classification in 2009, a misinterpretation has arisen, leading to an artificial division of axial spondyloarthritis (axSpA) into non-radiographic and radiographic subtypes. This division has resulted in separate treatment guidelines for each subgroup, despite compelling evidence indicating that they actually represent the same disease (44). On the other hand, the presence of extra-musculoskeletal manifestations (EMM) such as uveitis, skin psoriasis, and inflammatory bowel disease (IBD) serves as a unifying feature in SpA, although their prevalence and implications vary across the spectrum of diseases (38,78). These differences have sparked discussions regarding whether these features merely act as modifiers of a global disease or indicate the presence of distinct entities.

The objective of this doctoral thesis is to seek evidence that could contribute to the ongoing debate by addressing the above mentioned aims by an in-depth exploration of clinical and imaging characteristics of the main axial and peripheral phenotypes and more significant unmet needs in SpA, namely diagnostic delay. Firstly, I was keen to investigate the prevalence of EMMs in large cohorts of axSpA and PsA, in order to understand their association with one of the key challenges in SpA diagnosis, namely diagnostic delay. Secondly, by exploring the potential similarities or differences in treatment response between non-radiographic axSpA (nr-axSpA) and radiographic

axSpA (r-axSpA), this thesis addresses an aspect that has raised questions in several treatment guidelines. Thirdly, the thesis seeks to examine the clinical and radiological distinctions between patients diagnosed primarily with r-axSpA accompanied by psoriasis and those diagnosed primarily with axial PsA, shedding light on their potential dissimilarities. Lastly, an unsupervised analysis was performed to identify if these aforementioned differences correspond to clearly differentiated phenotypes within the broader spectrum of SpA. By addressing these research gaps, this thesis aims to provide valuable insights into the ongoing debate surrounding the classification and management of SpA.

The first study demonstrated that in a large cohort including cohorts from different geographic locations, despite demographic variances, the frequency of uveitis and IBD is elevated in AS compared to PsA. Fascinatingly, in examining the attributes of SpA patients with EMMs, we noticed that a considerable number had uveitis or IBD before the SpA diagnosis was made. In addition, a longer diagnostic delay was linked with a higher risk of uveitis and IBD in AS, indicating that prolonged uncontrolled inflammation could affect the incidence of EMMs.

Despite the differences in occurrence rates, the natural history of both PsA and AS in relation to EMMs appears to be strikingly similar. As mentioned, EMMs (uveitis and IBD) often present before the SpA diagnosis in both axSpA and PsA cases, which is known in clinical practice. Yet, and as far as we are aware, this has only been previously investigated in a Swedish cohort, which showed that patients were diagnosed with SpA either before or after their IBD diagnosis (116). This link was most notable during the two years before and after the IBD diagnosis. However, the overall incidence of SpA continued to rise for the first 10 years after the IBD diagnosis, especially in patients with Crohn's disease. Consistent with our results, the strongest correlation in IBD was observed with newly diagnosed PsA (HR 12.0, CI 10.8-13.4), suggesting that most PsA diagnoses occur post-IBD diagnosis. Similarly, our data indicates that uveitis preceded the SpA diagnosis in about 40% of patients. These insights underscore the role of

gastroenterology and ophthalmology clinics as potential early detection points for PsA and axSpA.

Considering the aspect of diagnostic delay, there was not a connection found between a longer diagnostic delay and EMMs in PsA as compared to axSpA. The smaller sample size and a lower incidence of EMMs in PsA could be plausible reasons for this. Furthermore, the diagnostic delay in PsA is typically less than in axSpA, attributed to a more distinct clinical presentation (82). However, it is likely that a larger percentage of PsA patients have been administered disease modifying anti-rheumatic drugs (DMARDs) for peripheral joint symptoms or for psoriasis management, which could potentially affect the onset of EMMs (117). The application of biologic DMARDs to treat skin psoriasis could reduce the incidence of PsA, suggesting that enhanced inflammation control could likewise influence the incidence of EMMs. Regrettably, treatment data was not accessible in our cohorts to investigate this further. Future larger scale, longitudinal studies with comprehensive treatment data are required to validate this theory.

The primary drawbacks of this first study were that patients were included based on their clinician's diagnosis rather than validated criteria such as CASPAR or mNY criteria. The characteristics of EMMs, including the time it started, were either remembered by the participants or obtained from clinical records, which might have introduced measurement bias. However, relying on patient recall or clinical notes is a common limitation faced by investigators, and prospective designs also have their own limitations, such as attrition and cost. Another limitation was the absence of HLA-B27 data and treatment information in our groups, both of which could potentially influence the occurrence of EMMs. Furthermore, systematic collection of CRP lab data was not done in all cohorts, which prevented us from investigating the hypothesis that the impact of delayed diagnosis on EMM events is explained by uncontrolled inflammation.

As seen in the first study, diagnostic delay is prominent in SpA, particularly in axSpA. The ASAS classification criteria were introduced to facilitate the diagnosis of axSpA at an

earlier stage. However, a study examining the impact of these criteria comparing diagnostic delay before and after 2009 (when the ASAS criteria were published) found no significant reduction in diagnostic delay (118). This finding raises questions about whether nr- and r-axSpA are distinct diseases, especially considering that some patients with early axSpA or nr-axSpA may never progress to AS (119). From a practical standpoint, the focus shifts to investigating whether both subgroups respond similarly to bDMARDs, which was the subject of the second study in this thesis.

Utilising real-world data from a large prospective multi-center cohort, the BSRBR-AS, I showed that baseline demographic and clinical characteristics were similar between nr-axSpA and r-axSpA (AS). Additionally, bDMARD response measured by ASDAS was comparable at 1 year between subgroups, as was the survival time of the first bDMARD, even in the adjusted multivariable analysis.

When examining the baseline characteristics, we found that they were generally similar to previous observations. In our study, the prevalence of HLA-B27 was comparable between nr- and r- axSpA, as observed in the Swiss Clinical Quality Management (SCQM) cohort (36). However, r-axSpA patients from the DANBIO study had a higher prevalence of positive HLA-B27 (53). This suggests that nr-axSpA and r-axSpA may share a common genetic background as part of the broader axSpA spectrum. The disparities seen in the Danish registry data could be attributed to the heterogeneity of the included patients. It is important to note that recruitment for the study began in 2000, predating the publication of the ASAS criteria. Consequently, the cohort was retrospectively classified for analysis purposes. In the BSRBR-AS cohort, r-axSpA patients were more frequently male compared to nr-axSpA patients, aligning with findings in existing literature (30). The increased radiographic damage observed in r-axSpA could be linked to higher BASMI and BASFI scores found in this subgroup, reflecting the natural progression of axSpA.

My analysis shows similar ASDAS response at 1 year in both sub-groups to those seen in the C-OPTIMISE certolizumab trial (week 48) as well as in the SCQM cohort (36,120). This

was also explored in the DANBIO study although this was evaluated at the 3 and 6 month time points but still showing similar ASDAS response (53). The novelty of our study however, is exploring drug survival in a large prospective cohort showing no significant differences between the subgroups. Only a small retrospective study from Italy showed lower drug survival in nr-axSpA and poorer adherence was seen in the DANBIO cohort (53,121). It is relevant to note that in this studies majority of patients were categorised as nr-axSpA based on a positive SIJ MRI assessment using the ASAS imaging arm criteria. Therefore, it is important to exercise caution when drawing conclusions about similarities in drug survival between the clinical and imaging arms.

Interestingly, after the publication of the second study of this thesis, an analysis of the SCQM Cohort was published whereby patients with axSpA were categorized into three groups: nr-axSpA, those presenting with bilateral grade 2 sacroiliitis (r22axSpA), and those with unilateral/bilateral grade 3-4 sacroiliitis (r3+axSpA) (122). An exploration of TNFi retention rate amongst these groups revealed no observable differences between nr-axSpA and r22axSpA (previously classified as r-axSpA). However, a decreased risk of discontinuation was identified in r3+axSpA patients. The spinal radiographic progression, quantified by the modified stoke ankylosing spondylitis spinal score (mSASSS), was found to be alike in r22axSpA and nr-axSpA patients but significantly elevated in those with r3+axSpA. This investigation suggests that the current distinction between nr-axSpA and r-axSpA may not provide substantial value in predicting treatment outcomes and monitoring radiographic progression.

The third study of this thesis aimed to compare the clinical and radiographic characteristics of r-axSpA with psoriasis and primary axial PsA. There were significant differences in clinical presentation and r-axSpA patients with psoriasis demonstrated more severe radiographic findings. When the axial PsA population was further divided based on HLA-B27 status, HLA-B27 positive axial PsA's clinical and imaging characteristics resembled those of AS patients with psoriasis, although the latter group exhibited significantly higher levels of structural damage in both the SIJ and spine. These insights suggest that, regardless of HLA-B27 status, clinicians generally understand axial PsA to

be associated with less radiographic progression compared to AS. Interestingly, there were no observable differences in patient-reported outcomes (PROs) across the respective group comparisons.

The understanding of axial involvement in PsA among rheumatologists is varied, combining both clinical symptoms and radiographic findings observed in the sacroiliac joints as well as the lumbar/cervical spine. This heterogeneity in understanding what constitutes axial PsA underscores the urgent need for a unified definition. This is also the main limitation of axial PsA studies where different definitions are used. The analysis of the Toronto cohort, used a radiographic definition of axial PsA including those who had SIJ radiographic changes fulfilling the modified New York criteria (mNYc) (123). A study by Jadon et al, used a similar definition but also included spine syndesmophytes but in this case, they did not differentiate axial PsA form AS with psoriasis (96). Other authors classified patients based on the opinion of the treating rheumatologist as it was done in our study (124).

The main strength of this study is the complete characterization of our cohort with availability of clinical data together with pelvic, lumbar and cervical x-rays data for all patients, including those not classified as axial PsA. Despite utilizing a distinct definition for axial PsA in the Toronto study, our analysis yielded comparable findings when we contrasted axial PsA with AS accompanied by psoriasis in our study cohort (123). As anticipated in a primary AS/r-axSpA population, both studies documented higher instances of male prevalence, younger age at onset, positive HLA-B27 status, the occurrence of inflammatory back pain, higher SIJ radiographic scores, and uveitis in the AS with psoriasis cohort. Furthermore, we observed higher BASRI scores in the lumbar and cervical spine for those patients diagnosed with AS and psoriasis. While this specific data wasn't available in the Toronto study, the authors did note a higher BASMI in AS patients with psoriasis, a score known to show a strong correlation with radiographic damage (125).

The distinctive feature of this third study is the subdivision of the cohort according to the HLA-B27 status. AS patients without psoriasis were found to have a higher prevalence of HLA-B27 compared to those with a history of this condition. Additionally, the existence of skin psoriasis in AS patients seemed to alter the clinical phenotype, leading to an increase in peripheral disease, dactylitis, and nail disease in this subgroup. This shift is likely influenced by genetic factors other than HLA-B27, as indicated by its lower prevalence in AS patients without skin psoriasis.

One notable observation is that HLA-B27 negative AS and axial PsA patients were more prone to exhibit skin psoriasis prior to the emergence of joint symptoms, a pattern that mirrors the presentation of peripheral PsA rather than AS/r-axSpA. On the contrary, HLA-B27 positive axial PsA patients reported an onset of joint symptoms preceding the skin psoriasis, a characteristic similar to axial SpA or AS. Moreover, HLA-B27 negative AS patients displayed more dactylitis and cervical pain compared to their HLA-B27 positive counterparts, suggesting a phenotype more akin to PsA.

Regardless of HLA-B27 status, axial PsA patients exhibited less radiographic damage compared to those with AS accompanied by psoriasis, once more implying the influence of other genetic determinants. Coates et al. documented an association between HLA-B27 and radiographic manifestations of SpA (inclusive of both AS and axial PsA), observing more severe radiographic damage such as higher degrees of sacroiliitis and a greater prevalence of marginal syndesmophytes and symmetry in HLA-B27 positive patients, irrespective of their clinical diagnosis of axSpA or PsA (126). However, the prevalence of SIJ symmetry and non-marginal syndesmophytes, considered typical radiographic markers of axial PsA, showed no discernible difference. This suggests again the contribution of factors other than HLA-B27 in shaping this particular phenotype.

Ultimately, distinguishing whether the observed differences between axSpA with psoriasis and axial PsA arise from them being distinct, unrelated diseases or from the degree to which psoriasis modifies axSpA and PsA proves to be challenging. This question can only be addressed through genetic signature studies involving large SpA populations

and a comparison to the detailed clinical phenotypes (127,128). Motivated by the findings from the axSpA with psoriasis versus axial PsA research, the fourth study in this thesis undertook a novel statistical approach to uncover the hidden phenotypes within a SpA population.

The fourth study implemented an unsupervised analytical method, specifically latent class analysis, which identified five separate and distinct categories, or "splits". These were primarily differentiated by the occurrence of either peripheral or axial joint involvement and a history of skin psoriasis, although there was substantial overlap observed.

In order to fully comprehend these findings, it is particularly enlightening to understand how the population was progressively divided in the various models presented in the results. The initial division occurred based on the type of involvement, either axial or peripheral. This pattern aligns with previous latent class analysis work conducted by Sepriano et al., as well as a cluster analysis performed on the PerSpA cohort, with both underscoring that the principal differentiation within SpA lies between peripheral and axial manifestations (129,130). Interestingly, these studies highlighted a significant overlap between axial and peripheral categories, a fact that was also effectively captured within the classes that emerged in our research. Our findings, along with those of other analyses, suggest that the broader SpA group exhibits more similarities than disparities, as evidenced by the continuous overlap of axial and peripheral clinical phenotypes. Intriguingly, a “mixed phenotype” would only be categorized as axSpA based on existing classification criteria if IBP is deemed to be a "current" feature (13), whereas in real world clinical practice, the “ever” presence of a feature such as IBP could aid the clinical diagnosis being made. The findings of our study ratify that classification criteria should be used with caution, particularly within the clinical setting. Of note, we did not identify an additional class that could account for differences between nr- and r-axSpA, in accordance with the previous analysis by Sepriano et al, which is in line with the findings and discussion of the second study of this thesis, supporting the notion that both nr and r-axSpA are indeed part of one disease spectrum.

Moving forward, the interpretation of these mentioned “mixed” phenotypes can be challenging. This analysis can be viewed as aligning with the unified concept of SpA, with specific nuances defining the different subclasses or phenotypes. The classes we've termed 'Axial with spine damage', 'Axial with SIJ damage', and 'Axial + peripheral + psoriasis' demonstrate traits in line with SpA displaying a primarily axial phenotype or axSpA. Here, psoriasis and its genetic underpinnings act as modifiers in the 'Axial + peripheral + psoriasis' class, compared to the others, ultimately influencing other manifestations such as dactylitis, nail disease, and a lower prevalence of uveitis and IBD. An interpretation that can be applied also to the third study of this thesis. By the same logic, the 'Axial + peripheral' and 'Peripheral + psoriasis' classes can be interpreted as SpA with a predominantly peripheral phenotype or pSpA, with psoriasis potentially driving the higher prevalence of dactylitis, nail disease, older age at presentation, and lower prevalence of HLA-B27 positivity. From the viewpoint of expert clinicians, these classes could conceivably be assigned a primary diagnosis, although this largely depends on the rheumatologist's training and experience in the field. For instance, patients from the 'Axial with spine/SIJ damage' classes might be diagnosed with axial SpA, and categorized as r-axSpA/AS, with 'Axial with spine damage' signifying long-standing disease marked by a higher proportion of spinal radiographic damage alongside sacroiliitis. The 'Axial + peripheral' class could receive a diagnosis of either axial SpA or pure peripheral SpA, while the 'Peripheral + psoriasis' class would likely be diagnosed as PsA and/or peripheral SpA. The 'Axial + peripheral + psoriasis' class could be termed "axial PsA" or "axial SpA with psoriasis”, a hypothesis that has further been investigated in the dedicated sub-analysis only including those with an history of psoriasis and/or nail disease. In this sub-analysis, it can be argued that the 'axial + peripheral + psoriasis' class may correspond to "axial PsA" with more dactylitis, nail disease, and peripheral involvement compared to the 'Axial + psoriasis' class, which could be termed "axial SpA with psoriasis".

The last two studies in this thesis, derived from the same cohort, REGISPONSER, from which a number of limitations need to be acknowledged. First and foremost, both

studies rely on cross-sectional analyses, which precludes the evaluation of class stability in the unsupervised analysis and consistency of the observed differences in the axial PsA versus AS with psoriasis analysis. Further, the lack of MRI data presents a limitation, as this diagnostic technique is increasingly essential in characterizing SpA and could have provided additional insights into our cohort. Moreover, the REGISPONSER cohort has an overrepresentation of the axial phenotype. While this skewed representation benefited the third study by providing a larger sample of axial PsA patients, it didn't compromise the identification of distinct classes in the final study, as these classes aligned with various clinical phenotypes. The final point to note is that the REGISPONSER cohort was established using the ESSG criteria as inclusion criteria, while also retrieving the primary diagnosis from the treating rheumatologists. While this might be perceived as a limitation in the third analysis due to the lack of a validated definition for axial PsA, I believe it represents a strength in the final analysis, as it encompasses the entire spectrum of SpA.

The findings of this thesis underscore the shared characteristics across the spectrum of SpA diseases while also shedding light on their distinct nuances. The primary motivation behind distinguishing these diseases is to design more specific studies, paving the way for the development of novel therapeutic strategies to ultimately enhance the quality of life of individuals affected by SpA (131). The findings from this thesis highlight the need for a deep understanding of SpA's heterogeneity. It asserts that meaningful divisions can only emerge if we thoroughly characterize SpA's diversity and establish sub-groups based on these characteristics, rather than solely relying on patients' primary diagnoses.

Future research endeavours should be aimed at reducing the diagnostic delay associated with SpA diseases, with particular emphasis on EMMs. It is essential to design large, longitudinal cohort studies in collaboration with our colleagues in Gastroenterology and Ophthalmology to gain a deeper understanding of the interplay between uveitis/IBD and SpA. This could potentially open up opportunities for improved and earlier diagnosis. Initiatives like the SENTINEL study, which revealed a significant percentage of patients with anterior uveitis also having undiagnosed SpA, lay the groundwork for further

registries (132). Ideally, these registries should also characterize the immunogenotypic signature through blood and stool samples permitting more advanced microbiota, genetic, cellular and molecular analyses (133,134).

There is ample evidence suggesting the need to eliminate the artificial distinction between non-radiographic and radiographic axSpA, despite the continued requirement for separate approvals for new treatments (36,44,53,122,135,136). Rather than maintaining this division, research should focus on identifying the factors that affect the treatment response and the natural progression of the disease. As discussed earlier, radiographic damage at the time of treatment prescription presents a potential biomarker of disease progression, as do preliminary investigations into the impact of BMI or cytokine signatures (122,137,138).

Focused research is necessary to understand both the phenotypic and genotypic aspects of Axial PsA. The AXIS study, which is a joint initiative between GRAPPA and ASAS, promises to bring more clarity to this subject (139). Crucially, the findings from this thesis emphasize the subtle differences between axial PsA and axSpA with psoriasis, hypothesizing that psoriasis, with its unique genetic factors and hallmark clinical signs such as dactylitis and nail disease, alters the course of SpA. However, this needs to be confirmed through specialized genetic and cellular studies.

A better understanding of the SpA spectrum is crucial to an improved management and treatment of the patients with these diseases. One pressing question, directly related to the objectives of this thesis, is the potential effectiveness of IL-23 inhibition in treating axial involvement in PsA, considering its lack of success in axSpA (109,110). Although dedicated randomized controlled trials may shed light on this matter, the ultimate interpretation falls on the clinician making the diagnosis and considering the patient's unique characteristics (111). Gaining insight into the transition from psoriasis to psoriatic arthritis, the impact of EMMs on SpA diseases, and the influence of psoriasis (and its genetic contributors) on axial SpA, to list a few, could substantially enhance patient care

(140,141). The findings presented in this thesis, along with future research as previously outlined, will only prove beneficial if implemented across the entire SpA spectrum. This is because the shared features and differences can only truly be appreciated if we approach these conditions in joined clinics and in a multidisciplinary manner.

CONCLUSIONS

1. The prevalence of uveitis and inflammatory bowel disease (IBD) is higher in ankylosing spondylitis (AS) when compared to psoriatic arthritis (PsA) but shows similar natural history largely presenting before the onset of the spondyloarthritis (SpA) diagnosis.
2. Increased diagnostic delay is associated with a higher likelihood of uveitis and IBD in cases of AS.
3. Demographic, clinical, and radiographic traits, as well as drug response assessed by ASDAS and drug persistence, show remarkable similarity between non-radiographic and radiographic axial spondyloarthritis (axSpA).
4. Axial PsA differs in terms of clinical and radiographic features from AS/r-axSpA, both with and without psoriasis.
5. Axial PsA appears to be mostly HLA-B27 independent and exhibits distinct clinical and radiographic characteristics when compared to AS/r-axSpA with psoriasis.
6. An unsupervised latent class analysis uncovers five unique SpA clinical entities, defined by a blend of axial and peripheral manifestations, further nuanced by the presence of psoriasis.
7. A considerable overlap is observed between axial and peripheral phenotypes in SpA.
8. A latent class model that only includes patients with a history of psoriasis and/or nail disease indicates that traits such as dactylitis, nail disease, and a low HLA-B27 prevalence are more common in phenotypes aligned with the idea of axial PsA than axial SpA with psoriasis.
9. Ultimately, the SpA spectrum demonstrates significant heterogeneity, a complexity that must be fully appreciated to enhance the diagnosis, management, and treatment of patients affected by these conditions.

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