Clinical and imaging outcomes of different phenotypes of axial spondyloarthritis: 5-year analysis of the DESIR cohort

Sepriano, A.; Ramiro, S.; Heijde, D. van der; Moltó, A.; Gaujoux-Viala, C.; Dougados, M.; Landewé, R.

Seminars in Arthritis and Rheumatism 66 (2024) 152424

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Clinical and imaging outcomes of different phenotypes of axial spondyloarthritis: 5-year analysis of the DESIR cohort

Alexandre Sepriano [a,*], Sofia Ramiro [b], Désirée van der Heijde [c], Anna Moltó [d], Cécile Gaujoux-Viala [e], Maxime Dougados [f], Robert Landewé [g]

[a] NOVA Medical School, Universidade Nova de Lisboa, Portugal, and Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
[b] Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; and Zuyderland Medical Center, Heerlen, the Netherlands
[c] Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
[d] Department of Rheumatology, Hôpital Cochin. Assistance Publique - Hôpitaux de Paris ; Université de Paris, INSERM (U1153): CRESS, Paris, France
[e] IDESP Univ Montpellier, INSERM, Rheumatology Department, CHU Nîmes, Montpellier, France
[f] Paris Descartes University, Department of Rheumatology, Hôpital Cochin. Assistance Publique - Hôpitaux de Paris; INSERM (U1153): Clinical epidemiology and biostatistics, PRES Sorbonne Paris-Cité. PARIS 14, France
[g] Amsterdam University Medical Center (ARC), Amsterdam; and Zuyderland Medical Center, Heerlen, the Netherlands

ARTICLE INFO

Keywords:
Axial spondyloarthritis
Phenotypes
Prognosis

ABSTRACT

Objectives: To compare the long-term outcomes of three phenotypes of axial SpA (axSpA).
Methods: Patients with a clinical diagnosis of axSpA from the DESIR cohort were grouped into three phenotypes at baseline: 'Pure axSpA' ('Axial'), 'axSpA with peripheral signs' ('IBP+Peripheral') and 'axSpA at risk' ('At risk') by latent class analysis. Clinical and imaging data were collected up to 5 years. Clinical outcomes, measured in each visit, included disability (BASFI) and quality of life (QoL; SF36). Imaging outcomes included inflammatory and structural lesions on MRI and radiographs of spine and SIJ. The association between phenotype membership at baseline and each outcome was tested in multivariable GEE models.
Results: In total, 576 patients with axSpA were included. 'At risk' patients had worse disability and QoL than 'Axial' patients over time. For instance, 'At risk' patients had on average 0.4 more points in BASFI over time than 'Axial' patients [β (95 % CI): 0.4 (0.2; 0.7)]. This difference was mostly noted in female patients who were HLA-B27 positive. In addition, the difference between the 'At risk' and 'Axial' phenotypes was higher in patients receiving bDMARDs than in those not (β=0.6 vs 0.5), since BASFI improved more in 'Axial' (ΔBASFI: -1.3) than in 'At risk' (ΔBASFI: -0.9) treated patients. There were no differences in disability and QoL between 'Axial' and 'IBP+Peripheral' patients. Imaging outcomes were worse in the 'Axial' phenotype than in the others over time.
Conclusion: Patients with 'axSpA at risk' show worse self-reported outcomes over time and are less likely to benefit from anti-inflammatory treatment than those with a classical axSpA phenotype.

Key messages

- There are prognostic dissimilarities across distinct phenotypes of axial spondyloarthritis (axSpA).
- Patients with objective signs of axSpA show better patient reported outcomes than those without these markers.
- Rheumatologists might need to tailor treatment strategies according to the phenotype of axSpA.

Introduction

Patients with axial spondyloarthritis (axSpA) typically have chronic back pain (CBP) starting before the fourth decade of life [1]. In addition, patients with axSpA can also have involvement of the peripheral skeleton (e.g., peripheral arthritis and dactylitis), laboratory findings (e.g., elevated C reactive protein (CRP) and the presence of HLA-B27) and imaging abnormalities (e.g., bone marrow edema (BME) on magnetic

* Corresponding author at: NOVA Medical School, Universidade Nova de Lisboa, Campo dos, Mártires da Pátria, 130, 1169-056 Lisbon, Portugal.
E-mail address: alexsepriano@gmail.com (A. Sepriano).

https://doi.org/10.1016/j.semarthrit.2024.152424

Available online 2 March 2024

resonance imaging (MRI)). Patients with unequivocal damage on pelvic radiographs, according to the modified New York (mNY) criteria [2], are referred to as radiographic axSpA (r-axSpA) and those without as non-radiographic axSpA (nr-axSpA). However, this distinction is more important for classification than for diagnosing axSpA in clinical practice, in which setting the term axSpA (as a whole) is preferred [1].

There is no unique diagnostic test for axSpA. Instead, the diagnosis relies on pattern recognition. In clinical practice, the axSpA pattern (or *Gestalt*) can vary substantially across patients resulting in different degrees of diagnostic uncertainty [3]. Recognizing axSpA early in the disease course may improve outcomes [4], but is more challenging because the number of SpA features is usually lower at disease onset than in more established disease. The Assessment of SpondyloArthritis international Society (ASAS) axSpA classification criteria were developed to capture the *Gestalt* of axSpA, including the early phases of the disease, but they were never meant to be used for diagnosing axSpA in clinical practice [5]. The correct diagnosis of axSpA implies that clinicians are able to recognize the different phenotypes of the disease and can differentiate these from other, more common, look-a-like conditions (e.g., degenerative spine disease or widespread pain syndromes).

Using data from two axSpA inception cohorts, the SPondyloArthritis Caught Early (SPACE) and the DEvenir des Spondylarthopathies Indifférenciées Récentes (DESIR), we have previously identified three distinct phenotypes of the disease by latent class analysis [6]. One phenotype, that we labelled as 'Axial', was characterized by HLA-B27 positivity plus typical abnormalities on axial imaging. The second phenotype included patients with inflammatory back pain (IBP) and peripheral features (which we labelled 'IBP+Peripheral') and the third had patients with risk factors for axSpA (HLA-B27 and family history) but with a low likelihood of other SpA features (which we labelled 'At risk'). Patients with an 'Axial' and 'IBP+Peripheral' phenotype at baseline did not transition to another over time, while those in the 'At risk' class at baseline had an 11 % probability to switch to the 'IBP+Peripehral' phenotype over 5 years.

Prognostic information can help clinicians in managing axSpA. Patients with phenotypes which have worse prognosis at baseline may benefit from different treatment strategies than those who have a better prognosis. However, whether there are prognostic dissimilarities across the different above-mentioned phenotypes of axSpA is yet unclear. With this study we aimed at comparing the long-term clinical and imaging outcomes of the three previously identified phenotypes of axSpA.

Methods

Patients

Patients with axSpA from the DESIR inception cohort (clinicaltrials.gov ID: NCT01648907) were analysed. The DESIR cohort has been previously described in detail [7]. Briefly, in DESIR consecutive patients aged 18–50 with IBP (>3 months but <3 years), considered by the treating rheumatologist as having axSpA (level of confidence (LoC) ≥5, scale 0–10), were included. Only patients included in the previous analysis in which the phenotypes of axSpA were identified, were considered [6]. The database used for the current analysis was locked on 20th of June 2016. The study was approved by the appropriate local medical ethical committees. All patients signed the informed consent upon participation.

Clinical outcomes

Clinical data was collected at baseline, every 6 months up to 2 years and then yearly up to 5 years. The following outcomes were assessed in each visit: functional disability, quantified by the Bath Ankylosing Spondylitis Functional Index (BASFI; range: 0–10) [8], quality of life (QoL) quantified by the short form 36 physical (SF36 PCS) and mental (SF36 MCS) component scores (range: 0–100, higher scores are better) [9], mobility according to the Bath Ankylosing Spondylitis Metrology Index (BASMI; range: 0–10) [10]; employment status (employed vs unemployed); sick leave (i.e., temporary absence from work due to illness; yes vs no) and work disability (permanent absence from work due to illness; yes vs no). A detailed description of the definition of sick leave and work disability used in DESIR has been previously published [11,12].

Imaging outcomes

Radiographs of the spine and sacroiliac joints (X-spine and X-SIJ) and MRIs of the spine and SIJ (MRI-Spine and MRI-SIJ) were obtained at baseline, 2 and 5 years. Each image was independently scored by three trained central readers, blinded to chronology, clinical data and to the results of other imaging modality. By protocol, radiographs were performed in all 25 participating centers at each visit, but MRIs were only performed in all centers at baseline, while MRIs at 2 and 5 years were only obtained in 9 centers from Paris.

Spine inflammation was assessed on MRI-spine using the total Spondyloarthritis Research Consortium of Canada (SPARCC) score (range: 0–414) [13]. Spine structural damage was assessed on X-Spine according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS; range: 0–72) [14], and on MRI-spine as the total number of fatty lesions (range: 0–92) [15]. On the SIJ, inflammation was assessed on MRI-SIJ according to the total SPARCC score (range: 0–72) [16], structural damage was assessed on X-SIJ according to the modified New York (mNY) system as continuous score (range: 0–8) [2], and on MRI-SIJ as the number of fatty lesions (range: 0–40) [17]. Each imaging outcome was defined as the mean of the three readers.

Phenotypes of axSpA

Using latent class analysis, an analytical technique that circumvents potentially biased expert opinion, we have previously identified three latent (i.e., unobserved) phenotypes (or classes) of axSpA with the baseline data of DESIR [6]. These phenotypes were labelled by us as 'Pure axial SpA' ('Axial'), 'Axial SpA with peripheral signs' ('IBP+Peripheral') and 'Axial SpA at risk' ('At Risk') Patients with the 'Axial' phenotype had the highest likelihood of abnormal imaging (e.g., sacroiliitis on MRI-SIJ) and HLA-B27-positivity and were most consistent with the typical clinical picture of axSpA. The 'IBP+Peripheral' phenotype was characterized by 100 % likelihood of IBP (but without imaging abnormalities) in conjunction with peripheral features (arthritis, dactylitis or heel enthesitis). The 'At risk' phenotype was characterized by the presence of IBP (without imaging abnormalities) and risk factors for axSpA (HLA-B27 or family history) but without objective clinical signs.

Other variables

The following variables were also collected at the baseline visit: age (years), symptom duration (years), sex (male vs female), HLA-B27 status (positive vs negative), educational status (university vs not university). In addition, the following variables were collected at baseline and in each follow-up visit: elevated CRP (CRP >5 mg/L), axial spondyloarthritis disease activity score with CRP (ASDAS) [18], acute anterior uveitis (AAU; ever present vs absent), psoriasis (ever present vs absent), inflammatory bowel disease (IBD; ever present vs absent); job type (blue collar vs white collar); number of comorbidities (cardiovascular, endocrinal and respiratory diseases, malignancies and serious infections); treatment with non-steroidal anti-inflammatory drugs (NSAIDs; yes vs no); conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; yes vs no), and biological DMARDs (bDMARDs; yes vs no).

Data analysis

The latent class membership at baseline was operationalized as a categorical variable with the 'Axial' class as the reference, against which the other two classes were compared. The association between class membership at baseline and each outcome over time was tested in generalized estimating equations (GEE)-models with an exchangeable working correlation structure to account for the correlation between repeated observations over time from the same patient.

The final model for each clinical and imaging outcome was identified by following a series of steps. First, an interaction was tested between class-membership and three possible effect modifiers: age, sex and HLA-B27 status (each tested in a separate model). If a statistically significant interaction ($p < 0.15$) was found, provided it was also clinically meaningful, the subsequent steps were performed stratified for the levels of the effect modifier. Otherwise, the full model with no stratification was used.

Second, we tested whether the rate of change of each outcome followed a linear (constant over time) or a higher order (e.g., quadratic) distribution, by testing which of the different transformations of time yielded the best model goodness of fit (assessed as the lowest quasi-likelihood under the independence model criterion: QIC). A non-linear model was chosen when the non-linear factor (e.g., quadratic term) added significantly to the model ($p < 0.05$).

The final model for each outcome was adjusted for covariates selected on clinical grounds. Baseline covariates were age, sex, HLA-B27 status (if proven not to be effect modifiers) and educational status (university vs not university). In addition, the following time-varying covariates were also added: job type (blue collar vs white collar), ASDAS, extra musculoskeletal manifestations (EMM: AAU, psoriasis or IBD), number of comorbidities and treatment with NSAIDs, csDMARDs and bDMARDs.

Finally, we evaluated whether the association between class-membership at baseline and each outcome over time was modified by the treatment status (NSAIDS, csDMARDs and bDMARDs) at the first-year visit. That is: we tested whether there was a significant ($p < 0.15$) class-treatment interaction. If there was an interaction, the effect of class on the outcome was tested separately in patients treated and not treated at the one-year visit.

All analyses were performed with Stata V15.1.

Results

Baseline characteristics

In total, 576 patients with a clinical diagnosis of axSpA were included. Patients from the 'Axial' class, were more often male (80 %) than those from the 'IBP+Peripheral' (43 %) and 'At risk' (40 %) classes. Elevated CRP and inflammatory and structural lesions on axial imaging were more common in the 'Axial' than in the other classes (Table 1). Nonetheless, disability was lower in the 'Axial' class (BASFI: 2.7) than in 'IBP+Peripheral' (BASFI: 3.4) and 'At risk' class (BASFI: 2.9). The ASDAS at baseline was highest for the 'IBP+Peripheral' phenotype. Quality of life was similarly impaired across classes at baseline (SF36 PCS range: 37–41; SF36 MCS: 39–43).

Impairment in spinal mobility was limited in all classes, but

Table 1
Baseline characteristics across the phenotypes of axial spondyloarthritis.

	All ($N = 576$)	Axial ($N = 110$)	IBP+Peripheral ($N = 137$)	At Risk ($N = 329$)
Age (years), mean (SD)	33 (8)	31 (8)	33 (9)	34 (8)
Symptom duration (years), mean (SD)	1.5 (0.8)	1.6 (0.8)	1.3 (0.8)	1.6 (0.8)
Male sex, n (%)	269 (47)	80 (73)	59 (43)	130 (40)
HLA-B27, n (%)	345 (60)	102 (93)	71 (52)	172 (52)
Elevated CRP, n (%)	169 (29)	61 (56)	54 (39)	54 (16)
Peripheral arthritis, n (%) ($n = 574$)	145 (25)	15 (14)	118 (86)	12 (4)
SPARCC MRI-spine, mean (SD) ($n = 569$)	2.1 (6.7)	7.6 (13.6)	0.7 (1.9)	0.9 (2.3)
mSASSS on X-spine, mean (SD) ($n = 569$)	0.4 (1.5)	0.9 (2.8)	0.3 (1.0)	0.3 (1.0)
N fatty lesions on MRI-spine, mean (SD) ($n = 533$)	0.2 (0.8)	0.7 (1.4)	0.2 (0.7)	0.1 (0.3)
SPARCC MRI-SIJ, mean (SD) ($n = 574$)	3.1 (6.6)	11.7 (9.9)	1.8 (4.4)	0.7 (2.3)
mNY grade on X-SIJ, mean (SD) ($n = 575$)	1.3 (1.7)	3.5 (1.9)	0.9 (1.3)	0.7 (1.0)
N fatty lesions on MRI-SIJ, mean (SD) ($n = 568$)	1.1 (3.1)	3.8 (5.5)	0.6 (2.1)	0.4 (1.3)
ASDAS, mean (SD) ($n = 570$)	2.6 (0.9)	2.7 (0.9)	3.0 (1.0)	2.5 (0.9)
BASFI (0–10), mean (SD) ($n = 572$)	3.0 (2.2)	2.7 (2.1)	3.4 (2.2)	2.9 (2.2)
BASMI (0–10), mean (SD) ($n = 503$)	2.4 (0.9)	2.6 (1.1)	2.6 (1.1)	2.3 (0.8)
SF36 PCS (0–100), mean (SD)	39 (10)	41 (9)	37 (10)	40 (9)
SF36 MCS (0–100), mean (SD)	41 (11)	43 (11)	39 (11)	41 (11)
Current smoker, n (%) ($n = 571$)	213 (37)	59 (54)	42 (31)	112 (35)
High education (university) ($n = 574$)	350 (61)	59 (54)	87 (64)	204 (62)
Employed, n (%) ($n = 574$)	453 (79)	78 (71)	109 (80)	266 (81)
Type of job, n (%) ($n = 570$)				
White collar	377 (66)	54 (50)	94 (70)	229 (70)
Blue collar	73 (13)	24 (22)	14 (10)	35 (11)
Unemployed	120 (21)	31 (28)	27 (20)	62 (19)
Sick leave, n (%) ($n = 453$ employed)	24 (5)	4 (5)	6 (6)	14 (5)
Work disability, n (%)	5 (0.9)	1 (0.9)	2 (1.5)	2 (0.6)
Treatment, n (%)				
NSAIDs	535 (93)	108 (98)	124 (91)	303 (92)
Glucorticoids	70 (12)	10 (9)	24 (18)	36 (11)
csDMARDs ($n = 574$)	72 (13)	6 (6)	38 (28)	28 (9)
bDMARDs	0 (0)	0 (0)	0 (0)	0 (0)

CRP, c reactive protein; SPARCC, Spondyloarthritis Research Consortium of Canada; MRI-spine, magnetic resonance imaging of the spine; MRI-SIJ, MRI of the sacroiliac joints; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; X-spine, radiograph of the spine; N, number; mNY, modified New York; ASDAS, axial spondyloarthritis disease activity score; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; SF36 PCS, short form 36 physical component score; SF36 MCS, SF36 mental component score; NSAIDs, non-steroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biological DMARDs; SD, standard deviation.

somewhat more in the 'Axial' and the 'IBP+Peripheral' classes (mean BASMI of 2.6 in both) than in the 'At risk' class (BASMI: 2.3). 'Axial' patients were less often employed (71 %) than those from the 'IBP+Peripheral' (80 %) and 'At risk' (81 %) classes. 'Axial' patients were also more often smokers, had lower education and had more often blue-collar jobs than the other classes. Sick leave and work disability were uncommon in all patients at baseline (Table 1).

Change in outcomes and treatment over time

Out of the 576 patients, 502 (87 %) completed the 5-year follow-up. The percentage of completers in the 'Axial' (90 %) and 'IBP+Peripheral' (90 %) classes was higher than in the 'At risk' (85 %) class.

On average, BASFI decreased (improved) between the baseline and the 5-year visit in all classes, but the improvement in disability was more pronounced in the 'Axial' (ΔBASFI: −0.9) and 'IBP+Peripheral' (ΔBASFI: −1.3) than in the 'At risk' (ΔBASFI: −0.4) class. At the last visit the BASFI was lower in 'Axial' and 'IBP+Peripheral' (mean BASFI 1.8 and 2.1) than in the 'At risk' (mean BASFI 2.5) class (Fig. 1).

The SF36 PCS also improved (i.e., increased) less in the 'At risk' class (ΔSF36 PCS: +2) than in the other classes (+4 to +6), while the SF36 MCS improved most in patients of the 'IBP+Peripheral' class (Fig. 1). Similar to baseline, the mean SF36 PCS (range: 42–45) and SF36 MCS (44–46) was low in all classes at the final visit. BASMI remained low and essentially unchanged over time in all classes (ΔBASMI range: −0.3 to +0.1).

More patients in the 'Axial' class regained employment after 5 years (15 % increase) than in the other two classes (5–10 %). At the last visit, employment rate was similarly high in all classes (range: 86–90 %). Sick leave and work disability remained uncommon during follow-up in all patients (Supplementary Fig. S1).

The change over time in imaging outcomes is shown in Supplementary Fig. S2. Inflammatory lesions decreased and structural lesions increased over time in the 'Axial' class and remained almost absent and unchanged over time in the other two classes.

At the 1-year visit, treatment with bDMARDs was more common in the 'Axial' and 'IBP+Peripheral' (32 % each) than in the 'At risk' (20 %) classes. At this visit, treatment with csDMARDs was more frequent in the 'IBP+Peripheral' class (30 %) than in the other two classes (3–8 %), while the use of NSAIDs was frequent in all classes (71–80 %) at 1 year.

In total, 47 (43 %) of the 'Axial' patients received a bDMARD in at least one visit. This figure was similar for the 'IBP+Peripheral' (45 %) but lower for the 'At risk' (29 %) class. csDMARDs were used by 59 (43 %) of the 'IBP+Peripheral' patients in at least one visit and much less in the other classes (10–15 %). Almost all patients across classes used NSAIDs in at least one visit (95–99 %).

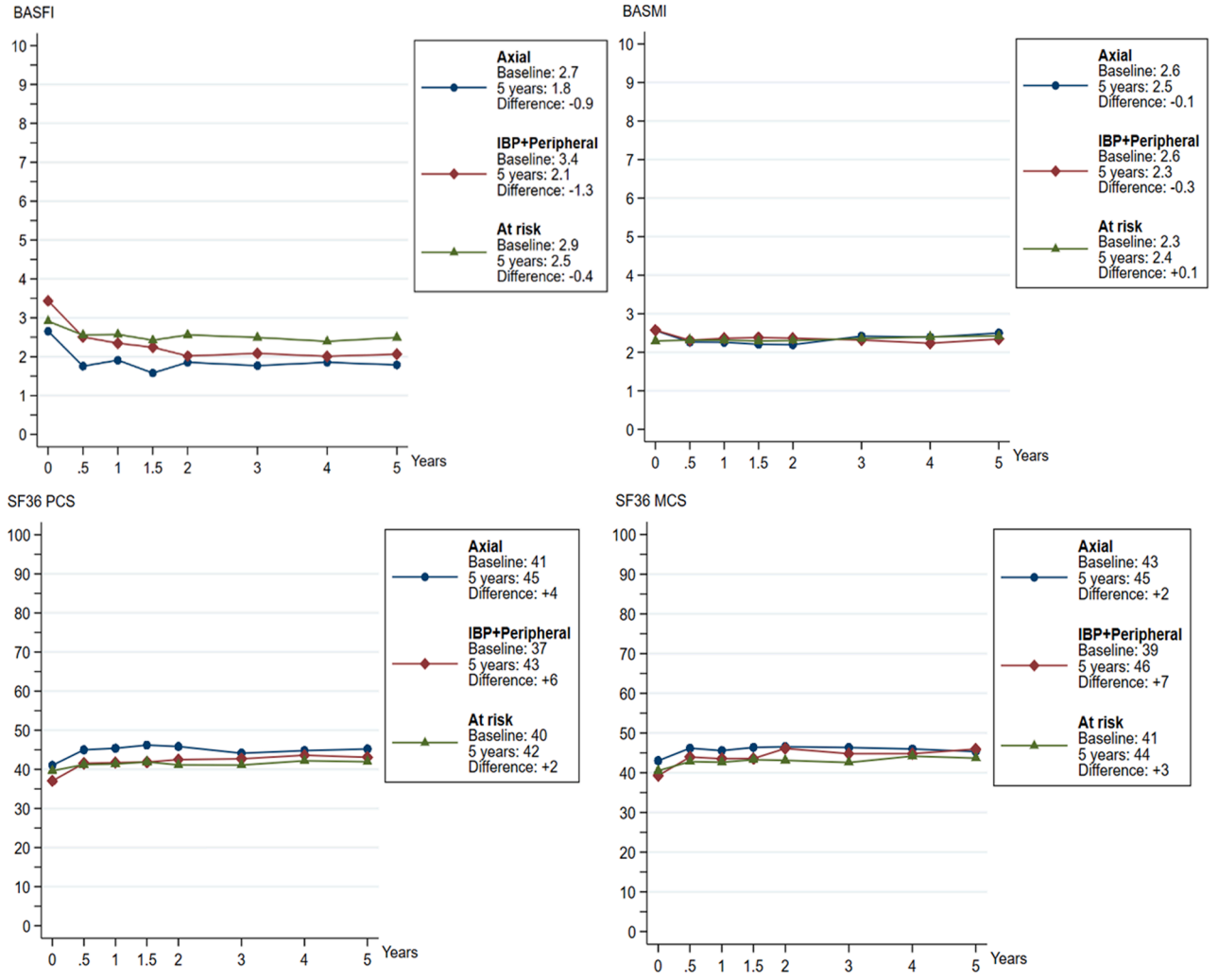

Fig. 1. Change in BASFI, BASMI, SF36 PCS and SF36 MCS over time, stratified on the latent class at baseline.
BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; SF36 PCS, short form 36 physical component score; SF36 MCS, SF36 mental component score.

Table 2
Effect of the baseline latent class on BASFI (0–10) over time stratified on sex and HLA-B27 status (multivariable models).

	Marginal model	Model with double interaction between latent class and sex and HLA-B27			
	All patients ($N = 574$) β (95 % CI)	Female & HLA-B27- ($N = 140$) β (95 % CI)	Female & HLA-B27+ ($N = 166$) β (95 % CI)	Male & HLA-B27- ($N = 89$) β (95 % CI)	Male & HLA-B27+ ($N = 179$) β (95 % CI)
Axial	REF	REF	REF	REF	REF
IBP+Peripheral	0.2 (−0.1; 0.5)	0.3 (−0.8; 1.4)	0.6 (0.0; 1.2)	−0.8 (−1.6; 0.1)	0.0 (−0.4; 0.3)
At risk	**0.4 (0.2; 0.7)**	0.5 (−0.6; 1.5)	**0.9 (0.4; 1.5)**	**−0.8 (−1.5; −0.1)**	0.2 (−0.1; 0.6)

Interaction between class and sex ($p = 0.04$) and between class and HLA-B27 ($p = 0.01$). The model including all patients is adjusted for age, sex, HLA-B27 status, educational status (university vs not university), job type (blue collar vs white collar), ASDAS, EMM (AAU, psoriasis or IBD), treatment with NSAIDs, csDMARDs and bDMARDs, and number of comorbidities. The model with a double interaction for sex and HLA-B27 is adjusted for age, educational status (university vs not university), job type (blue collar vs white collar), ASDAS, EMM (AAU, psoriasis or IBD), treatment with NSAIDs, csDMARDs and bDMARDs, and number of comorbidities. BASFI, Bath Ankylosing Spondylitis Functional Index; ASDAS, axial spondyloarthritis disease activity score; EMM; extra musculoskeletal manifestations; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biological DMARDs; REF, reference; CI, confidence interval; Bold values indicate statistically significant ($p < 0.05$) results. Both the marginal model and the model with the interaction are polynomials (4th order).

Association between latent classes at baseline and outcomes over time

In the multivariable models, the 'At risk' class had consistently higher BASFI over time than patients from the 'Axial' class (Table 2). Further analyses revealed however, that this difference was entirely explained by female patients who were HLA-B27 positive (interaction p-values: 0.04 and 0.01). In this subgroup, 'At risk' patients had, on average, 0.9 points higher BASFI than 'Axial' patients over time [adjusted (adj) β (95 % confidence interval; CI): 0.9 (0.4; 1.5). The opposite association was found in male patients who were HLA-B27-negative [adj β (95 % CI): −0.8 (−1.5; −0.1)]. There was no difference in disability between 'Axial' and 'IBP+Peripheral' patients (Table 2).

After adjusting for potential confounders, there were lower (worse) values for SF36 PCS in the 'At risk' (but not in the 'IBP+Peripheral') class, as compared with the 'Axial' class, but the effect size was small [adj β (95 % CI): −2.4 (−3.6; −1.2)]. Similar results were found for SF36 MCS. There were no meaningful differences in BASMI and work outcomes across classes over time (Table 3a).

The results of the multivariable models for the imaging outcomes are shown in Table 3b. The 'IBP+Peripheral' and 'At risk' classes had consistently better outcomes for all inflammatory and structural axial lesions over time, as compared with the 'Axial' class.

There was an interaction between class and treatment with TNFi at 1 year on BASFI ($p = 0.076$) and on SF-36 PCS ($p = 0.071$). The higher (worse) BASFI of the 'At risk' class compared with the 'Axial' class was more pronounced in patients treated with TNFi than those not treated (Table 4). Among patients treated with TNFi, however, there was more improvement in BASFI over time in the 'Axial' (ΔBASFI: −1.3) and 'IBP+Peripheral'(ΔBASFI: −2.4) than in the 'At risk' (ΔBASFI: −0.9) class. BASFI remained low across all classes in patients not treated with TNFi (Fig. 2). Similar findings, but to a lower extent, were observed for SF36 PCS (Table 4 and Fig. 2), but not for the other outcomes.

Discussion

In this study we have found prognostic dissimilarities across distinct phenotypes of patients who have a clinical diagnosis of axSpA. Despite a higher inflammatory burden and more structural damage on axial imaging, patients with a phenotype that is most consistent with the typical clinical picture of axSpA (the 'Axial' class) had better physical function and quality of life over 5 years than patients with only risk factors for axSpA but no objective clinical signs of the disease ('At risk'). These differences in prognosis were more pronounced in the subgroup receiving bDMARDs. Treated patients with the typical 'inflammatory axSpA' improve more over time than 'At risk' patients. Of note, except for better imaging outcomes, patients with IBP in conjunction with peripheral manifestations ('IBP+Peripheral') had a similar prognosis as those with an 'Axial' phenotype. These data demonstrate that rheumatologists might need to tailor treatment strategies according to the phenotype of axSpA and should be particularly vigilant in their indication of targeted DMARDs in patients without objective signs of inflammation.

Most of the patients with an 'Axial' phenotype were male, HLA-B27 positive and had objective markers of inflammation, that is, elevated CRP and high MRI SPARCC scores, especially in the SIJ. This phenotype will usually be recognized by rheumatologists as the typical clinical picture of axSpA. Although radiographic damage in the spine and SIJ was generally low in DESIR at baseline, it was more prominent in the 'Axial' than in the other phenotypes. The fact that 'Axial' patients were more often smokers, had lower levels of education and worked more often in blue-collar jobs is consistent with previous studies, one in DESIR [19], and another in an independent cohort [20], showing that, in addition to systemic inflammatory markers (e.g., ASDAS),

Table 3a
Effect of the baseline latent class on BASMI, SF36 PCS, SF36 MCS and work outcomes over time (multivariable models).

	BASMI (0–10) ($N = 537$) β (95 % CI)	SF36 PCS (0–100) ($N = 574$) β (95 % CI)	SF36 MCS (0–100) ($N = 574$) β (95 % CI)	Employment ($N = 574$) OR (95 % CI)	Sick leave ($N = 533$) OR (95 % CI)	Work disability ($N = 574$) OR (95 % CI)
Axial	REF	REF	REF	REF	REF	REF
IBP+Peripheral	−0.1 (−0.3; 0.1)	−1.5 (−2.9; 0.0)	−1.0 (−3.1; 1.1)	1.4 (0.8; 2.4)	0.4 (0.1; 1.2)	1.0 (0.3; 3.1)
At risk	**−0.2 (−0.4; −0.1)**	**−2.4 (−3.6; −1.2)**	**−2.2 (−4.1; −0.4)**	1.3 (0.8; 2.0)	0.8 (0.3; 2.1)	1.4 (0.4; 4.2)

Each model adjusted for age, sex, HLA-B27 status, educational status (university vs not university), job type (blue collar vs white collar), ASDAS, EMM (AAU, psoriasis or IBD), treatment with NSAIDs, csDMARDs and bDMARDs, and number of comorbidities. BASMI, Bath Ankylosing Spondylitis Metrology Index; SF36 PCS, short form 36 physical component score; SF36 MCS, SF36 mental component score; ASDAS, axial spondyloarthritis disease activity score; EMM; extra musculoskeletal manifestations; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biological DMARDs; REF, reference; OR, odds ratio; CI, confidence interval; Bold values indicate statistically significant ($p < 0.05$) results. Polynomial models are used for BASMI (4th order), SF36 PCS (4th order), SF36 MCS (4th order), sick leave (cubic) and work disability (quadratic).

Table 3b
Effect of baseline latent class on imaging outcomes over time (multivariable models).

	Spine			Sacroiliac joints		
	SPARCC MRI-spine (0–414) ($N = 562$) β (95 % CI)	mSASSS X-spine (0–72) ($N = 569$) β (95 % CI)	N fatty lesions MRI-spine (0–92) ($N = 526$) β (95 % CI)	SPARCC MRI-SIJ (0–72) ($N = 565$) β (95 % CI)	mNY grade X-SIJ (0–8) ($N = 571$) β (95 % CI)	N fatty lesions MRI-SIJ (0–40) ($N = 558$) β (95 % CI)
Axial	REF	REF	REF	REF	REF	REF
IBP+Peripheral	**−5.6 (7.7; −3.5)**	**−0.7 (−1.4; −0.1)**	**−0.4 (−0.6; −0.2)**	**−8.5 (−10.1; −7.0)**	**−2.6 (−3.0; −2.1)**	**−3.5 (−4.7; −2.3)**
At risk	**−5.4 (−7.5; −3.3)**	**−0.8 (−1.5; −0.1)**	**−0.5 (−0.7; −0.3)**	**−9.1 (−10.6; −7.6)**	**−2.7 (−3.1; −2.3)**	**−3.8 (−5.0; −2.6)**

Each model adjusted for age, sex, HLA-B27 status, educational status (university vs not university), job type (blue collar vs white collar), ASDAS, EMM (AAU, psoriasis or IBD), treatment with NSAIDs, csDMARDs and number of comorbidities. SPARCC, Spondyloarthritis Research Consortium of Canada; MRI-spine, magnetic resonance imaging of the spine; MRI-SIJ, MRI of the sacroiliac joints; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; X-spine, radiograph of the spine; N, number; mNY, modified New York; ASDAS, axial spondyloarthritis disease activity score; EMM; extra musculoskeletal manifestations; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biological DMARDs; REF, reference. Bold values indicate statistically significant ($p < 0.05$) results. Models for SPARCC MRI-spine, SPARCC MRI-SIJ and N fatty lesions on MRI-SIJ are quadratic, the remaining are linear.

Table 4
Effect of baseline latent class on BASFI and SF36 PCS stratified on treatment status with TNFi at 1 year.

	BASFI (0–10)		SF36 PCS (0–100)	
	Treated ($N = 129$) β (95 % CI)	Untreated ($N = 375$) β (95 % CI)	Treated ($N = 129$) β (95 % CI)	Untreated ($N = 375$) β (95 % CI)
Unadjusted				
Axial	REF	REF	REF	REF
IBP+Peripheral	0.7 (−0.1; 1.5)	0.3 (−0.2; 0.8)	**−5.5 (−9.2; −1.8)**	−2.2 (−4.7; 2.3)
At risk	**1.3 (0.6; 2.0)**	**0.5 (0.1; 1.0)**	**−6.6 (−9.7; −3.4)**	**−2.9 (−4.8; −1.0)**
Adjusted*				
	Treated ($N = 129$) β (95 % CI)	Untreated ($N = 373$) β (95 % CI)	Treated ($N = 129$) β (95 % CI)	Untreated ($N = 373$) β (95 % CI)
Axial	REF	REF	REF	REF
IBP+Peripheral	0.5 (−0.1; 1.1)	0.1 (−0.2; 0.5)	**−3.6 (−6.3; −0.9)**	−1.3 (−3.2; 0.5)
At risk	**0.6 (0.1; 1.2)**	**0.5 (0.1; 0.8)**	**−3.1 (−5.6; −0.6)**	**−2.5 (−3.9; −1.0)**

Interaction between class and treatment with TNFi at 1 years: BASFI: $p = 0.076$; SF36 PCS: $p = 0.071$. Model for BASFI and for SF36 PCS are adjusted for age, sex, HLA-B27 status, educational status (university vs not university), job type (blue collar vs white collar), ASDAS, EMM (AAU, psoriasis or IBD), treatment with NSAIDs, csDMARDs and number of comorbidities. BASFI, Bath Ankylosing Spondylitis Functional Index; SF36 PCS, short form 36 physical component score; ASDAS, axial spondyloarthritis disease activity score; EMM; extra musculoskeletal manifestations; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; TNFi, TNF inhibitors; REF, reference; CI, confidence interval; Bold values indicate statistically significant ($p < 0.05$) results. Polynomial (4th order) models are used both for BASFI and SF36 PCS.

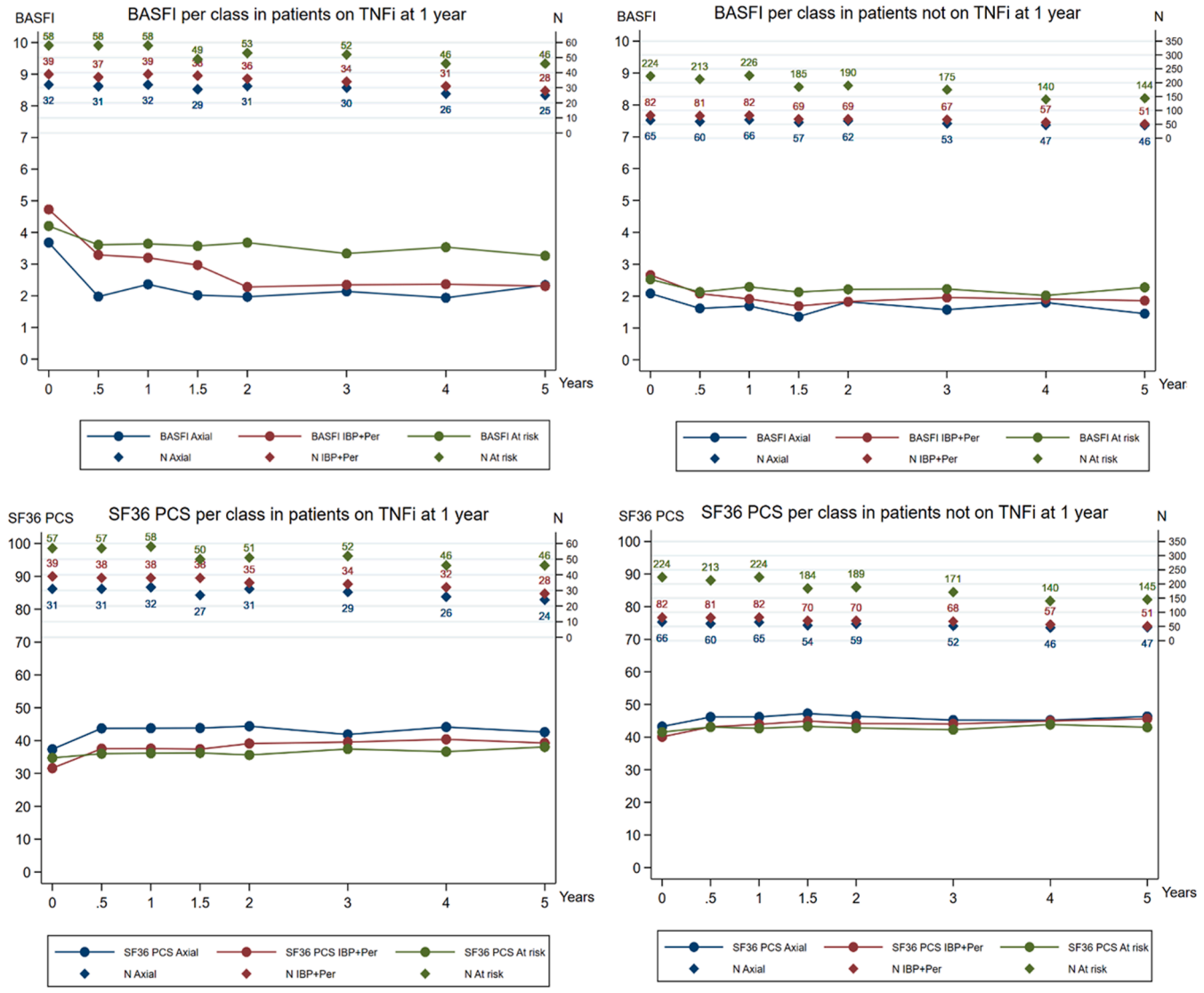

Fig. 2. Change in BASFI and SF36 PCS over time in patients treated and not treated with bDMARDs at the 1-year visit.
BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; SF36 PCS, short form 36 physical component score; TNFi, TNF inhibitors.

socio-economic factors also are associated with more MRI inflammation and more structural damage in axSpA.

Intuitively, one would think 'Axial' patients, with a high inflammatory burden at study entry, will have worse outcomes over time than patients with other phenotypes and minimal or no signs of objective inflammation. However, that is not what we observed. 'Axial' patients, who had features associated with worse structural outcomes (e.g., male sex and elevated CRP) [21,22], had indeed more structural progression over time than the other phenotypes, but this did not translate into worse clinical outcomes. On the contrary, disability and quality of life improved more in 'Axial' than in 'At risk' patients, especially in patients receiving bDMARDs, which were used during follow-up in about half of the 'Axial' (and also 'IBP+Peripheral') patients and in one third of the 'At risk' patients. And though 'Axial' patients were more often unemployed at baseline, most were at work by the end of follow-up. Although this study was not designed to test treatment effects, it seems possible that appropriately treated patients with real inflammatory disease improve and will return to work. This improvement was not only noted in PROs (i.e., BASFI and SF36) and work outcomes but also in the objective MRI inflammation scores.

Previous studies have shown an association between high disease activity and worse function and quality of life in patients with axSpA [23–26]. We have previously shown that there was a small probability (11 %) for 'At risk' patients at baseline to transition to the 'IBP+peripheral' phenotype over time, due to the occurrence of peripheral features [6]. However, the large majority of the patients remained in their original phenotype without ever showing objective signs of inflammation. Therefore, our finding that 'At risk' patents had worse function and quality of life than patients with an inflammatory 'Axial' phenotype is seemingly counterintuitive, but not without precedent; In a previous study performed in the SPACE cohort, patients with an axSpA diagnosis had better physical function after 2 years compared with patients with CBP but without an axSpA diagnosis [27]. It has previously been shown that 13 % of the patients in DESIR have, at study entry, extreme PROs, a validated surrogate for fibromyalgia [28]. Therefore, our current findings in DESIR, a cohort which includes only patients with a clinical diagnosis of axSpA, could, at least in part, be explained by concomitant widespread pain syndromes in the 'At risk' patients. These syndromes occur more often in women and the 'At risk' class is indeed a predominantly female phenotype. the fact that the difference in disability between the 'Axial' and the 'At risk' phenotypes was exclusively found in female (HLA-B27 positive) patients is also

concordant with this explanation. Moreover, patients with axSpA and widespread pain conditions are not expected to respond well to bDMARDs [29], Indeed, even though several 'At risk' patients received these drugs, the improvement in disability was only marginal at best.

Patients who have an 'IBP+Peripheral' phenotype present with IBP and peripheral features, such as arthritis (86 %). Even though these patients had almost no axial imaging abnormalities, they had the highest values for ASDAS and BASFI of all phenotypes at baseline. Patients with an 'IBP+peripheral' phenotype were also less often HLA-B27 positive than those of the 'Axial phenotype' (52% vs 93 %). These findings are concordant with previous evidence showing that peripheral disease is more common in HLA-B27 negative axSpA patients [30,31], and that the presence of arthritis significantly contributes to a high disease burden of disease in axSpA [25,32-34]. Given the high prevalence of peripheral arthritis it is not surprising that almost half the 'IBP+Peripheral' patients received csDMARDs, as these drugs, especially sulfasalazine, have been shown efficacious in these patients [35]. Similar to the 'Axial' patients many 'IBP+Peripheral' patients were also treated with bDMARDs and similar levels of improvement of disability and quality of live over time were found for these two phenotypes resulting in better outcomes as compared to the 'At risk' patients.

A previous study, performed in DESIR, has shown that patients with axSpA with peripheral features (labelled as 'Cluster B') have a higher disease burden (e.g., more disability) and receive more DMARDs over time than patients with only axial disease (labelled as 'Cluster A') [36] It should be noted that a different clustering method (cluster analysis) was used in that study. LCA and cluster analysis rely on different 'grouping-assumptions' and can yield different results [37]. Therefore, the previously identified 'Cluster A' and 'Cluster B' do not necessarily include the same patients as the current 'Axial' and 'IBP+Peripheral' classes. In fact, patients from the 'Axial' phenotype were more often male (73% vs 58 %), had more elevated CRP (56% vs 30 %) and BME on MRI-SIJ (88% vs 35 %) than patients from 'Cluster A' in the previous work [6]. These baseline differences might justify, at least in part, why here we found similar levels of disability over time between the 'Axial' and 'IBP+Peripheral' classes whereas a higher disability was found for 'Cluster B' compared with the ('less severe') 'Cluster A' in the previous study. In addition, only in the current study, the 'At risk' class emerged as a distinct phenotype, which might again be a consequence of our methodological choice for LCA. Contrary to cluster analysis, LCA allows for some degree of overlap across classes and therefore might more easily recognize less well-defined groups such as the 'At risk' phenotype.

Our study is not without limitations. One important limitation is that we could not ascertain how many patients with axSpA in DESIR have concomitant fibromyalgia. However, previously proposed surrogate markers of this condition, such as extreme PROs, help us to some extent interpret some of the differences in prognosis noted across phenotypes. Another limitation is that our prognostic analysis was done in patients under treatment, and therefore our study cannot be said to reflect the natural history of the disease. However, a 5-year study without treatment will not be feasible (e.g., for ethical reasons) and we did take treatment into account in the analysis, for instance by comparing the outcomes across classes after adjusting for treatment received during follow-up.

In summary, patients with axSpA can present with a spectrum of phenotypes, ranging from a highly inflammatory disease to cases with risk factors and only sporadic additional features. Practicing rheumatologists, who will recognize these patients from their practice, should be aware that different phenotypes have different prognostic implications. Patients with axSpA with typical lesions on axial imaging and those with axial complaints (without positive imaging) and swollen joints will fare better than the patients with axial complaints and only risk factors for the disease present. Even under bDMARDs, clinical outcomes improve the least in the latter group. In principle, these anti-inflammatory drugs should only be offered to patients with objective inflammatory markers (e.g., CRP, inflammation on MRI or swollen joints). Alternative management strategies, pharmacologically or non-pharmacologically, should be sought for those without.

Data availability statement

The data that support the findings of this study was made available by the Scientific Committee of the DESIR cohort (http://www.lacohortedesir.fr/desir-in-english/ and la.cohorte.desir.cch@aphp.fr). Restrictions may apply to the availability of these data used for this study.

Ethics approval

The study was conducted according to Good-Clinical-Practice-guidelines and approved by the appropriate local ethical committees. Written informed consent was obtained from participating patients before inclusion in each cohort.

Author contributions

All authors made contributions to conception and/or development of the study. AS performed the analysis. All authors contributed to the interpretation of the results. AS wrote the first draft of the manuscript and all authors were involved in reviewing the manuscript and gave final approval to the version to be published.

Funding

The DESIR study is under the umbrella of the French Society of Rheumatology, which financially supports the cohort. The DESIR cohort is run with the support of unrestricted grants from (in order of decreasing support) Pfizer France, Biogen, AbbVie, UCB, Lilly, Galapagos, Novartis, MSD, Fresenius and Celltrion HealthCare.

Patient and public involvement

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

Declaration of competing interest

Alexandre Sepriano: speaking and/or consulting fees from Abbvie, Novartis, UCB and Lilly. Sofia Ramiro: research grants and/or consultancy fees: AbbVie, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer, UCB, Sanofi. Désirée van der Heijde: Received consulting fees from AbbVie, Argenx, Bayer, BMS, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Lilly, Novartis, Pfizer, Takeda, UCB Pharma and is Director of Imaging Rheumatology bv. Anna Moltó: Received consulting fees from AbbVie, Biogen, BMS, Gilead, Galapagos, Janssen, Lilly, Novartis, MSD, Pfizer, UCB Pharma. Cécile Gaujoux-Viala: reports serving as a consultant and on a speaker's bureau for AbbVie; Amgen; Biogen;Boehringer Ingelheim, Bristol-Myers Squibb; Celgene; Eli Lilly; Galapagos; Gilead Sciences, Inc.; Janssen; Medac; Merck-Serono; Mylan; Nordic Pharma; Novartis; Pfizer; Roche; Sandoz; Sanofi; and UCB Pharma. Maxime Dougados: Received consulting fees from AbbVie, BMS, Galapagos, Janssen, Lilly, Novartis, Pfizer, UCB Pharma, Merck. Robert Landewé: Received consulting fees from AbbVie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Roche, UCB and is Director of Rheumatology Consultancy bv

Acknowledgments

The DESIR cohort is conducted with Assistance Publique-Hopitaux de Paris (AP-HP, Paris France) as the sponsor and under the umbrella of the French Society of Rheumatology. The DESIR cohort is run with the support of unrestricted grants from (in order of decreasing support) Pfizer France, Biogen, AbbVie, UCB, Lilly, Galapagos, Novartis, MSD, Fresenius and Celltrion HealthCare. We thank the Clinical Research Unit Paris Centre (AP-HP, Paris France), and the Institut national de la sante

et de la recherche medicale (Inserm). We also thank the investigators: Pr Maxime Dougados, Pr André Kahan, Dr Julien Wipff and Dr Anna Moltó (Paris-Cochin), Pr Olivier Meyer, Pr Philippe Dieudé (Paris-Bichat), Pr Pierre Bourgeois, Pr Laure Gossec (Paris-La Pitie-Salpétriere), Pr Francis Berenbaum (Paris-Saint-Antoine), Pr Pascal Claudepierre (Creteil), Pr Maxime Breban, Pr Maria-Antonietta D'Agostino, Pr Félicie Costantino (Boulogne-Billancourt), Pr Michel De Bandt, Dr Bernadette Saint-Marcoux (Aulnay-sous-Bois), Pr Philippe Goupille (Tours), Pr Jean-Françis Maillefert (Dijon), Pr Xavier Puechal, Dr Emmanuelle Dernis (Le Mans), Pr Daniel Wendling, Pr Clément Prati (Besançon), Pr Bernard Combe, Pr Cédric Lukas (Montpellier), Pr Liana Euller-Ziegler, Pr Véronique Breuil (Nice), Pr Pascal Richette (Paris Lariboisière), Pr Pierre Lafforgue, Pr Thao Pham (Marseille), Pr Patrice Fardellone, Dr Patrick Boumier, Dr Pauline Lasselin (Amiens), Pr Jean-Michel Ristori, Pr Martin Soubrier, Pr Anne Tournadre (Clermont-Ferrand), Dr Nadia Mehsen (Bordeaux), Pr Damien Loeuille (Nancy), Pr Rene-Marc Flipo (Lille), Pr Alain Saraux (Brest), Pr Corinne Miceli, Dr Stephan Pavy (Le Kremlin-Bicêtre), Pr Alain Cantagrel, Pr Adeline Ruyssen-Witrand (Toulouse), Pr Olivier Vittecoq, Pr Thierry Lequerre (Rouen).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152424.

References

[1] Navarro-Compan V, Sepriano A, El-Zorkany B, van der Heijde D. Axial spondyloarthritis. Ann Rheum Dis 2021;80(12):1511–21.
[2] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27(4):361–8.
[3] Marques ML, Ramiro S, Lunteren MV, Stal R, Berg IJ, Fagerli KM, et al. OP0005Can axial spondyloarthritis unequivocally be diagnosed by rheumatologists in patients with chronic back pain of less than two years duration? main result of the spondyloarthritis caught early (space) cohort. Ann Rheum Dis 2023;82(Suppl 1):3.
[4] Capelusnik D, Benavent D, van der Heijde D, Landewe R, Poddubnyy D, van Tubergen A, et al. Treating spondyloarthritis early: does it matter? Results from a systematic literature review. Rheumatol (Oxf) 2023;62(4):1398–409.
[5] Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68(6):777–83.
[6] Sepriano A, Ramiro S, van der Heijde D, van Gaalen F, Hoonhout P, Molto A, et al. What is axial spondyloarthritis? A latent class and transition analysis in the SPACE and DESIR cohorts. Ann Rheum Dis 2020;79(3):324–31.
[7] Dougados M, d'Agostino MA, Benessiano J, Berenbaum F, Breban M, Claudepierre P, et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. Joint Bone Spine 2011;78(6):598–603.
[8] Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21(12):2281–5.
[9] Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473–83.
[10] Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21(9):1694–8.
[11] Nikiphorou E, Carvalho PD, Boonen A, Fautrel B, Richette P, Machado PM, et al. Sick leave in early axial spondyloarthritis: the role of clinical and socioeconomic factors. Five-year data from the DESIR cohort. RMD Open 2021;7(2).
[12] Nikiphorou E, Boonen A, Fautrel B, Richette P, Landewe R, van der Heijde D, et al. How do clinical and socioeconomic factors impact on work disability in early axial spondyloarthritis? Five-year data from the DESIR cohort. Rheumatol (Oxf) 2022;61(5):2034–42.
[13] Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Krishnananthan R, Stone M, et al. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. Arthritis Rheum 2005;53(4):502–9.
[14] Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64(1):127–9.
[15] Krabbe S, Sorensen IJ, Jensen B, Moller JM, Balding L, Madsen OR, et al. Inflammatory and structural changes in vertebral bodies and posterior elements of the spine in axial spondyloarthritis: construct validity, responsiveness and discriminatory ability of the anatomy-based CANDEN scoring system in a randomised placebo-controlled trial. RMD Open 2018;4(1):e000624.
[16] Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Williams M, Stone M, et al. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. Arthritis Rheum 2005;53(5):703–9.
[17] Weber U, Lambert RG, Ostergaard M, Hodler J, Pedersen SJ, Maksymowych WP. The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. Arthritis Rheum 2010;62(10):3048–58.
[18] Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68(1):18–24.
[19] Nikiphorou E, Ramiro S, Sepriano A, Ruyssen-Witrand A, Landewe RBM, van der Heijde D. Do smoking and socioeconomic factors influence imaging outcomes in axial spondyloarthritis? Five-year data from the DESIR cohort. Arthritis Rheumatol 2020;72(11):1855–62.
[20] Ramiro S, Landewe R, van Tubergen A, Boonen A, Stolwijk C, Dougados M, et al. Lifestyle factors may modify the effect of disease activity on radiographic progression in patients with ankylosing spondylitis: a longitudinal analysis. RMD Open 2015;1(1):e000153.
[21] Dougados M, Sepriano A, Molto A, van Lunteren M, Ramiro S, de Hooge M, et al. Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. Ann Rheum Dis 2017;76(11):1823–8.
[22] Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Marker-Hermann E, Zeidler H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70(8):1369–74.
[23] Carvalho PD, Ruyssen-Witrand A, Marreiros A, Machado PM. Long-term association between disease activity and disability in early axial spondyloarthritis: results from a prospective observational study of inflammatory back pain. Arthritis Care Res (Hoboken) 2022;74(5):768–75.
[24] Carvalho PD, Vieira-Sousa E, Hmamouchi I, Marreiros A, Machado PM. Determinants of health-related quality of life in spondyloarthritis and rheumatoid arthritis - data from the COMOSPA and COMORA studies. Semin Arthritis Rheum 2022;57:152086.
[25] Capelusnik D, Ramiro S, Schneeberger EE, Citera G. Peripheral arthritis and higher disease activity lead to more functional impairment in axial spondyloarthritis: longitudinal analysis from ESPAXIA. Semin Arthritis Rheum 2021;51(3):553–8.
[26] Putrik P, Ramiro S, Molto A, Keszei AP, Norton S, Dougados M, et al. Individual-level and country-level socioeconomic determinants of disease outcomes in SpA: multinational, cross-sectional study (ASAS-COMOSPA). Ann Rheum Dis 2019;78(4):486–93.
[27] Boel A, Lunteren MV, Fagerli KM, Exarchou S, Ramonda R, MVd Sande, et al. POS0954Quality of life in chronic back pain patients, a 2-year comparison between patients with and without a diagnosis of axial spondyloarthritis: data from the spondyloarthritis caught early cohort. Ann Rheum Dis 2021;80(Suppl 1):741.
[28] Meghnathi B, Claudepierre P, Dougados M, Molto A. Evaluation of extreme patient-reported outcome in early spondyloarthritis and its impact on the effect of TNF-alpha blockers treatment. Clin Exp Rheumatol 2018;36(6):1043–8.
[29] Alunno A, Carubbi F, Stones S, Gerli R, Giacomelli R, Baraliakos X. The impact of fibromyalgia in spondyloarthritis: from classification criteria to outcome measures. Front Med (Lausanne) 2018;5:290.
[30] Arevalo M, Gratacos Masmitja J, Moreno M, Calvet J, Orellana C, Ruiz D, et al. Influence of HLA-B27 on the Ankylosing Spondylitis phenotype: results from the REGISPONSER database. Arthritis Res Ther 2018;20(1):221.
[31] Rusman T, van Bentum RE, van der Horst-Bruinsma IE. Sex and gender differences in axial spondyloarthritis: myths and truths. Rheumatol (Oxf) 2020;59(Suppl4):iv38-iv46.
[32] de Winter JJ, Paramarta JE, de Jong HM, van de Sande MG, Baeten DL. Peripheral disease contributes significantly to the level of disease activity in axial spondyloarthritis. RMD Open 2019;5(1):e000802.
[33] Lopez-Medina C, Dougados M, Ruyssen-Witrand A, Molto A. Evaluation of concomitant peripheral arthritis in patients with recent onset axial spondyloarthritis: 5-year results from the DESIR cohort. Arthritis Res Ther 2019;21(1):139.
[34] Lopez-Medina C, Molto A, Dougados M. Peripheral manifestations in spondyloarthritis and their effect: an ancillary analysis of the ASAS-COMOSPA study. J Rheumatol 2020;47(2):211–7.
[35] Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2023;82(1):19–34.
[36] Costantino F, Aegerter P, Schett G, De Craemer AS, Molto A, Van den Bosch F, et al. Cluster analysis in early axial spondyloarthritis predicts poor outcome in the presence of peripheral articular manifestations. Rheumatol (Oxf) 2022;61(8):3289–98.
[37] Magidson J, Vermunt J. Latent Class Models for Clustering: a Comparison with K-means. Can J Market Res 2001. 11/30; 20.