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Clinical science

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

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Abstract

Objectives: The aim of our study was to identify the potential distinct phenotypes within a broad SpA population.

Methods: We conducted a cross-sectional study using the REGISPONSER registry, which has data from 31 specialist centres in Spain, including patients with SpA who have fulfilled the 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 five-classes LCA model yielded the best fit. Classes named 'Axial with spine involvement' and 'Axial with isolated SI joint involvement' showed a primarily axial SpA phenotype defined by inflammatory back pain and high HLA-B27 prevalence. Patients in class 'Axial + peripheral' showed a similar distribution of manifest variables to previous classes but also had 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' were 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 exhibited increased probability of axial involvement both clinically and radiologically.

Conclusion: The identification of five 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) influenced the phenotype of both axial and peripheral manifestations.

Keywords: spondyloarthritis, axial spondyloarthritis, peripheral spondyloarthritis, unsupervised methods.

Rheumatology key messages

- Unsupervised latent class analysis identified five distinct clinical SpA entities defined by a combination of both axial and peripheral manifestations, and psoriasis.
- A model with patients with a history of psoriasis and/or nail disease suggested a difference between the concept of axial PsA and axial SpA with psoriasis.
- The identification of these classes provides a better understanding of the broad SpA spectrum.

Introduction

The concept of SpA, including both axial SpA (axSpA) and several predominantly peripheral forms of arthritis such as PsA, reactive arthritis (ReA), and arthritis associated with IBD, was first described by Moll and Wright in Leeds, in 1974 [1]. Subsequently, the Amor and the 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

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early axial disease with MRI, proposed a new set of classification criteria aimed at facilitating research in this area. These criteria introduced the terms 'axSpA' to cover the spectrum of axial phenotypes and 'peripheral SpA' (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 with 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 utilize 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 utilizing baseline data from the multicentre REGISPONSER registry. The REGISPONSER registry has been previously described [11]. Briefly, adults ($\geq$18 years) with a clinical diagnosis of SpA and meeting the 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, and cervical and lumbar spine) were systematically collected in all patients regardless of their primary diagnosis and clinical symptoms. Radiographs were graded using the BASRI by the local investigator [12]. All patients gave informed written consent to participation in the REGISPONSER registry, which was approved centrally by the ethics committee of the Reina Sofia University Hospital from Cordoba (Spain).

A LCA was performed with preselected features (manifest variables) that 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—AS, PsA, ReA, IBD-related arthritis or undifferentiated SpA); inflammatory back pain (IBP) (fulfilling Calin Criteria) [13]; peripheral arthritis, enthesitis, and dactylitis as confirmed on physical examination by a rheumatologist; anterior uveitis, IBD, nail disease, skin psoriasis (confirmed diagnosis); HLA-B27 positivity; elevated CRP (>5 mg/l); high grade sacroiliitis (BASRI $\geq$ 2), radiographic cervical involvement (BASRI $\geq$ 2), radiographic lumbar spine involvement (BASRI $\geq$ 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 the 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 utilized 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 visualizing missingness distribution (Supplementary Material 1, available at *Rheumatology* online). Bivariate residuals were explored to determine local independence between variables, and a simpler model with fewer variables was constructed. As sensitivity analyses, the final model was run again using only individuals with complete data available for all variables, together with another analysis with an additional variable capturing disease duration (defined from symptom onset to last visit). 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 characterize the demographic, clinical and radiographic characteristics of each class. LCA was performed utilizing MPlus V8 [14]. 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 IBP. A latent class model with five classes was determined as providing the best fit. The supplementary material contains all models ranging from two to eight classes, along with their corresponding model fit statistics and clinical interpretation. After examining bivariate residuals and the exclusion of covariate variables, it was determined that a simpler model did not exhibit greater robustness, particularly with respect to less clinically recognizable classes (see Supplementary Material 13 and Supplementary Tables 14–18, available at *Rheumatology* online). The sensitivity analysis with five classes performed only in patients with complete data yielded similar results (Supplementary Table 19, available at *Rheumatology* online). A sensitivity analysis including a disease

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)

duration variable (early/late) determined by median disease duration (5 years) showed consistency of the five classes (see Supplementary Tables 20–24, available at *Rheumatology* online).

Fig. 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 the 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 involvement' and 'Axial with isolated SI joint involvement' classes demonstrated similar distributions, with a significant likelihood of IBP (0.99 and 0.95) and axial as first symptom (both 0.97). As noted in the labels, the difference was 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 of ≥2 at each region. The rest of the classes displayed a greater probability of presenting with peripheral arthritis, as well as this being the presenting symptom. The 'Axial + peripheral' class shared similar characteristics with the 'Axial with

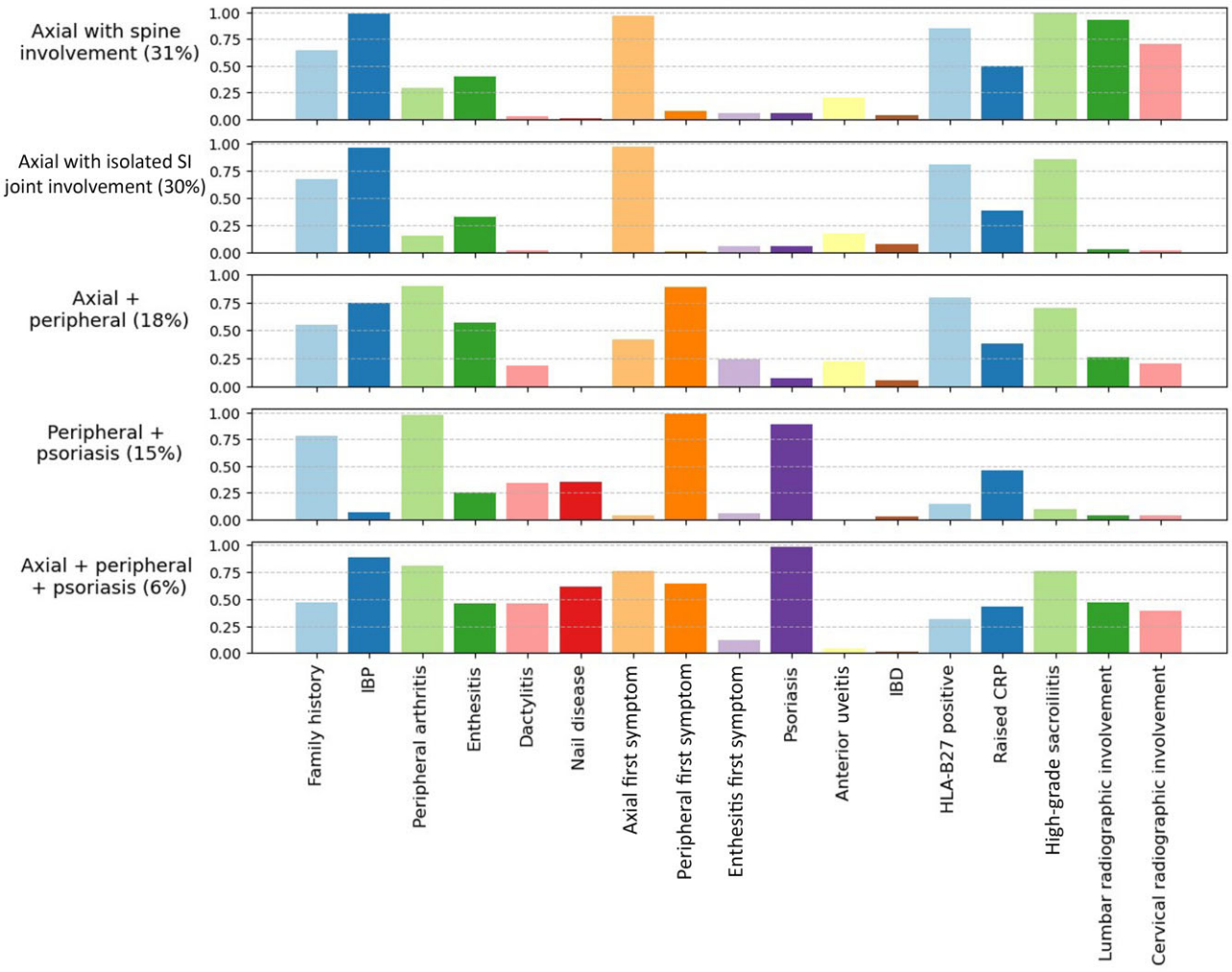

Figure 1. Bar chart of the distribution of the conditional probabilities of each feature according to the final latent class analysis model in REGISPONSER. The *y*-axis shows the probability of each feature within each class. Labels are constructed based on clinical interpretation and for further reference. Classes are ordered by the percentage of each class (from highest to lowest). IBP: inflammatory back pain; high-grade sacroiliitis: S.I. joint BASRI score of ≥2; lumbar radiographic involvement: lumbar BASRI score of ≥2; cervical radiographic involvement: cervical BASRI score of ≥2

spine/SI joint involvement' 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' were 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 was the probability of presenting with IBP and radiographic involvement of the SI joints and spine, which is mainly observed in the 'Peripheral + axial + psoriasis' class.

The 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, the patients in classes 'Peripheral + psoriasis' and 'Axial + peripheral + psoriasis' were diagnosed at an older age, and those in class 'Peripheral + psoriasis' demonstrated a female predominance (47.6% *vs* 25.2%, $P < 0.001$). The median CRP (mg/l) was higher in the 'Axial with spine involvement' class (5.0 *vs* 3.5, $P < 0.001$), as were BASRI scores at the SI joint (4.0 *vs* 2.0, $P < 0.001$), and lumbar (3.0 *vs* 0.0, $P < 0.001$) and cervical spine (2.0 *vs* 0.0, $P < 0.001$) level, compared with 'Axial with isolated SI joint involvement'. Patient-reported outcomes (PROs) did not exhibit any significant differences, except for higher BASFI scores in classes 'Axial with spine damage' (4.6 *vs* 2.3, $P < 0.001$) and 'Axial + peripheral + psoriasis'(3.7 *vs* 2.3, $P = 0.002$) 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 three classes (see Fig. 2 and Supplementary Material 10, available at *Rheumatology* online). The main class was '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' exhibited similar probability distributions, with a high likelihood of IBP and radiographic sacroiliitis. Some differences were, 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 characterize 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 LCA conducted in a SpA setting performed by Sepriano *et al.* [10]. Analysing cohorts focusing on early axSpA (SPACE and DESIR), four 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, available at *Rheumatology* online), 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 aligned with the findings from the previous LCA. Interestingly, Sepriano *et al.* did not identify an additional class that could account for the differences between non-radiographic (nr-axSpA) and radiographic axSpA (r-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 the differences within the axial phenotype subgroup, which supports the view that this 'division' between nr- and r-axSpA is an artificial construct [17–19]. Nonetheless, caution must be exercised when comparing our cohort with DESIR and SPACE, as their inclusion criteria significantly differed. Furthermore, it is worth noting that the sample sizes of DESIR and SPACE were relatively modest; therefore, the possibility of additional classes representing nr-axSpA may only emerge in a larger sample. Further, 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 SI joints, 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. De Craemer *et al.* [22] also used k-means methodology within the Be Giant cohort to explore peripheral manifestations, also finding two patient clusters (axial and peripheral predominant), and Costantino *et al.* [23] in a similar analysis found a mixed phenotype (axial and peripheral) as well as a purely axial cluster in DESIR, further validated in the Be Giant cohort. 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 our analyses and those of others. Interestingly, this mixed phenotype would only be classified as axSpA according to the existing criteria if IBP is considered a 'current' feature [4]. Yet, the fluctuating nature of clinical manifestations in the various phenotypes adds to the understanding of the concept or 'gestalt' of SpA, whereby if a specific clinical feature has 'ever' been present it 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. The heterogeneity seen in some SpA diseases, such as in IBD-related arthritis or ReA hampers the assignment of a class to a primary diagnosis. Instead, we aimed to characterize the classes as comprehensively as possible, to provide the readership with a better understanding of the implications of subgrouping 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

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

Variable	'Axial with spine involvement' $N = 725$	'Axial with isolated SI joint involvement' $N = 708$	'Axial + peripheral' $N = 409$	'Peripheral + psoriasis' $N = 334$	'Axial + peripheral + psoriasis' $N = 143$
Demographic characteristics					
Age, mean (S.D.)	52.5 (11.6)	41.0 (11.8)	44.3 (12.8)	50.9 (14.0)	50.4 (12.2)
Age at diagnosis, mean (S.D.)	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, median (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 (S.D.)	27.5 (4.5)	25.6 (4.2)	26.0 (4.3)	27.0 (4.4)	27.9 (5.7)
Family history of SpA[a]	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[a]	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[a]	142/720 (19.7%)	124/700 (17.7%)	91/405 (22.5%)	1/333 (0.3%)	5/140 (3.6%)
IBD[a]	25/724 (3.5%)	54/701 (7.7%)	22/406 (5.4%)	10/332 (3.0%)	1/142 (0.7%)
Psoriasis[a]	39/723 (5.4%)	42/701 (6.0%)	23/408 (5.6%)	298/332 (89.8%)	140/142 (98.6%)
Dactylitis[a]	17/721 (2.4%)	13/703 (1.8%)	67/405 (16.5%)	108/333 (32.4%)	63/142 (44.4%)
Enthesitis[a]	225/719 (31.3%)	157/700 (22.4%)	201/405 (49.6%)	43/333 (12.9%)	61/141 (43.3%)
Peripheral arthritis[a]	185/723 (25.6%)	100/700 (14.3%)	362/409 (88.5%)	329/334 (98.5%)	109/142 (76.8%)
Nail disease[a]	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 (%)[a]	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)[a]	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[a]	713/715 (99.7%)	552/654 (84.4%)	262/376 (69.7%)	33/326 (10.1%)	104/138 (75.4%)
BASRI SI 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)[a]	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)[a]	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)
Treatment					
bDMARD treatment naïve, n (%)	565/725 (77.9%)	635/708 (89.7%)	326/409 (79.7%)	288/334 (86.2%)	106/143 (74.1%)

[a] Variables highlighted were used in the latent class analysis model. ASDAS-CRP: AS DAS–CRP; IQR: interquartile range; VAS: visual analogue scale.

made by the treating rheumatologist. Nevertheless, this cohort represents real-world clinical settings. As conceived by Professor 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 subclasses or phenotypes [2]. The classes we hereby named 'Axial with spine involvement', 'Axial with isolated SI joint involvement', and 'Axial + peripheral + psoriasis' exhibited 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/SI joint involvement' classes may receive a diagnosis of axSpA, and classified as r-axSpA/AS, with 'Axial with spine involvement' corresponding to longstanding disease as reflected by the higher proportion of spinal radiographic damage in addition to sacroiliitis. Patients in the 'Axial + peripheral' class could be diagnosed as axial SpA or pure peripheral SpA, while patients in the 'Peripheral + psoriasis' class would likely be diagnosed as PsA and/or peripheral SpA. 'Axial + peripheral + psoriasis' could be named 'axPsA' or 'axSpA 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 subanalysis and even recognizing the limitations of preselecting a population in these unsupervised methods, it could be argued

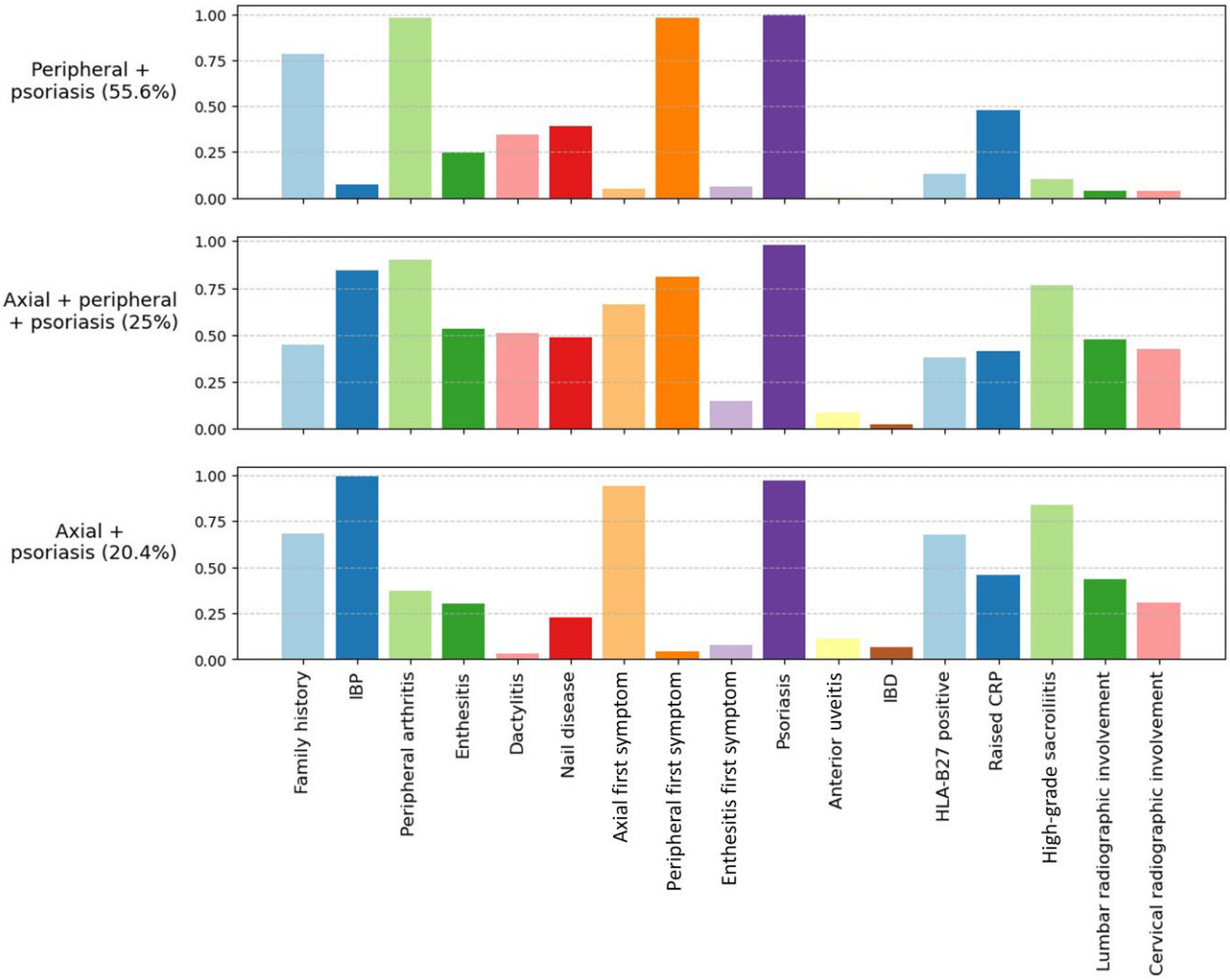

Figure 2. Bar chart of the distribution of the conditional probabilities of each feature according to the final latent class analysis model in the REGISPONSER population with a history of psoriasis or nail disease. The *y*-axis shows the probability of each feature within each class. Labels are constructed 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; high-grade sacroiliitis: S.I. joint BASRI score of ≥2; lumbar radiographic involvement: lumbar BASRI score of ≥2; cervical radiographic involvement: cervical BASRI score of ≥2

that class 'Axial + peripheral + psoriasis' may correspond to 'axPsA' with more dactylitis, nail disease, and peripheral involvement, in comparison with class 'Axial + psoriasis', which could be named 'AxSpA 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's diagnosis of axPsA) [24].

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. Second, the unavailability of MRI data precluded us from characterizing early spinal disease more effectively. Additionally, while the source population comprised the entire SpA spectrum, there was an over-representation of axSpA. Nevertheless, we identified distinct classes that aligned 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, made this a unique dataset for conducting this type of unsupervised analysis. Furthermore, the selection of manifest variables and the LCA methodology were aimed at avoiding the intrinsic circularity associated with clinician or expert input in diagnosis and case ascertainment definitions, which is a critical issue in such analyses.

In conclusion, we identified five latent classes, providing a data-driven perspective on the concept of SpA based on a combination of axial and peripheral phenotypes, which is 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

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

Variable	'Peripheral + psoriasis' N = 304	'Axial + peripheral + psoriasis' N = 133	'Axial + psoriasis' N = 114
Demographic characteristics			
Age, mean (S.D.)	51.9 (13.7)	50.0 (12.5)	48.4 (12.6)
Age at diagnosis, mean (S.D.)	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 (S.D.)	27.1 (4.4)	27.5 (5.9)	27.7 (4.4)
Family history of SpA[a]	24/271 (8.9%)	13/112 (11.6%)	19/105 (18.1%)
Clinical characteristics			
Inflammatory back pain[a]	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[a]	1/303 (0.3%)	11/130 (8.5%)	13/114 (11.4%)
IBD[a]	0/302 (0.0%)	3/133 (2.3%)	7/113 (6.2%)
Psoriasis[a]	302/303 (99.7%)	130/133 (97.7%)	110/113 (97.3%)
Dactylitis[a]	102/303 (33.7%)	63/132 (47.7%)	2/114 (1.8%)
Enthesitis[a]	39/303 (12.9%)	64/132 (48.5%)	28/112 (25.0%)
Peripheral arthritis[a]	299/304 (98.4%)	112/132 (84.8%)	40/112 (35.7%)
Nail disease[a]	119/303 (39.3%)	63/131 (48.1%)	26/112 (23.2%)
Laboratory findings			
HLA-B27 positive, n (%)[a]	24/173 (13.9%)	32/87 (36.8%)	65/96 (67.7%)
CRP (mg/l), median (IQR)[a]	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[a]	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)[a]	0.0 (0.0–0.0)	1.0 (0.0–2.0)	1.0 (0.0–3.0)
BASRI cervical spine, median (IQR)[a]	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)
Treatment			
bDMARD treatment naïve, n (%)	260/304 (85.5%)	99/133(74.4%)	87/114 (76.4%)

[a] Variables highlighted were used in the latent class analysis model. ASDAS-CRP: AS DAS–CRP; IQR: interquartile range; VAS: visual analogue scale.

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 in order to validate these disease classifications, and to enhance our understanding of SpA, and ultimately, improve the lives of affected individuals.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

Contribution statement

X.M., A.S. and H.M.-O. designed the study. X.M. 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.

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