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ORIGINAL RESEARCH

Influence of sacroiliac joint variation on clinical features of axial spondyloarthritis: a comparative analysis

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ABSTRACT

Objectives Anatomical variation of the sacroiliac (SI) joints is common and specific variants are associated with erosions and bone marrow oedema on imaging. Our investigation aims to evaluate whether anatomical variations influence the clinical presentation of axial spondyloarthritis (axSpA).

Methods In this propensity score matched post hoc analysis documented clinical data from four prospective clinical cohorts was assessed. Classification of back pain as inflammatory (=IBP), human leucocyte antigen-B27 positivity, family history, disease activity according to Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), symptom duration, elevated acute phase reactants, peripheral and extramusculoskeletal manifestations were evaluated. Statistical analyses were done using (generalised) linear models, t-tests, χ^2 tests and analysis of variances. Multiple testing was corrected according to Bonferroni.

Results A total of 165 patients (86 women) were included. Atypical SI joints, defined by the presence of accessory joint facets, iliosacral complex or crescent-shaped ilii on MRI, were identified in 61 out of 165 patients with axSpA. Disease activity, assessed by BASDAI and symptom duration were similar in both groups (adjusted ß=−0.118 (95% CI -0.713, 0.476), p=0.696 and 120.0 (107.4) vs 116.5 (98.3) months, p=0.838, respectively). There was no significant difference in IBP between the groups (adjusted OR=0.614 (95% CI 0.274, 1.377), p=0.236). Sex-stratified analysis revealed no statistically significant results.

Conclusion Our analysis suggests that clinical phenotypes do not significantly differ between patients with axSpA with and without atypical joints.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Variants of sacroiliac joint anatomy are common in patients with low back pain and have been shown to influence imaging changes in patients with axial spondyloarthritis (axSpA).

⇒ Certain variants have been hypothesised to be radiological mimicker of sacroiliitis, but they may also modulate disease by changing biomechanical conditions within the joint.

WHAT THIS STUDY ADDS

⇒ The overall clinical presentation of axSpA is not significantly influenced by the anatomy of the sacroiliac joint, results reveal a similar distribution of clinical features of axSpA between the groups with normal and atypical sacroiliac joints.

⇒ The individual subtypes of the sacroiliac joints may modulate the disease mechanically in distinct ways, which requires validation in larger studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Atypical sacroiliac joints do not appear to generally determine the clinical presentation of axSpA; their role in difficult-to-treat axSpA remains a future topic of research.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a common rheumatological disease typically affecting the axial skeleton with the sacroiliac joints (SIJs) being the most frequently affected anatomical site.[1 2] The leading clinical symptom of the disease is chronic low back pain.[2] This pain often shows typical characteristics of inflammatory back pain (IBP), which can be defined according to the Berlin criteria by the presence of various clinical symptoms such as: morning stiffness >30 min, improvement with exercise but no improvement with rest, alternating buttock pain, pain at night with awakening in the second half of the night.[3 4] Peripheral manifestations often accompany axial components, with the most common being peripheral arthritis, enthesitis and dactylitis, as well as extramusculoskeletal manifestations (EMMs) such as uveitis, psoriasis and inflammatory bowel disease (IBD).[5 6] Among these, uveitis is the most frequent EMM.[7] The management of axSpA involves identifying

the clinical features characteristic of the disease, leading to an expert-based diagnosis, followed by an evaluation of disease activity. Disease activity can be assessed using tools such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or the Axial Spondyloarthritis Disease Activity Score.[2 8]

The SIJs play a crucial biomechanical role in force transmission from the lower extremities to the torso and stabilisation of the axial skeleton.[1 9] Current research on the pathophysiology of axSpA postulates an influence of the mechanical joint conditions on disease development and progression.[10 11] Among the six distinguished anatomical variations of the SIJs by Prassopoulos *et al* the accessory SIJ, the iliosacral complex and the crescent-shaped ilium seem to lead to chondral stress and consequently to an increased inflammatory response, suggesting a mechanical contribution of these latter two variations to disease modulation.[12 13] Additionally, an association between anatomical variations of the SIJs and changes on MRI images in axSpA was established: an increase of bone erosion and bone marrow oedema has been demonstrated in such cases, especially in those with accessory SIJs.[14–16] In a study by Schett *et al* it has been displayed that overall mechanical influence is part of the process of enthesitis by triggering or maintaining inflammation at affected sites.[17] In patients with an atypical SIJ form, without axSpA, more subchondral sclerosis has been described, laying additional emphasis on the mechanical properties of these joints.[18] While these studies seem to illustrate a mechanical role of certain SIJ types in disease modulation, at the same time anatomical variation on imaging has also been discussed to be a radiological mimicker of sacroiliitis: dorsally located accessory joint facets in adults may cause local irritation, which may be hard to distinguish from sacroiliitis. In the developing skeleton, so-called joint facet defects may mimic erosion.[19–21] To date, it remains unclear whether patients with axSpA with atypical joint forms constitute a clinically distinct phenotype, in whom mechanical loading plays a more prominent role in the disease process and furthermore, if the described imaging changes may represent a radiological mimicker of sacroiliitis, making false positive diagnoses more likely, as has been hypothesised before.[22]

In this analysis, we evaluated whether clinical phenotypes differ between patients with axSpA with and without atypical joint forms by comparing the distribution of clinical spondyloarthritis (SpA) features and disease activity (BASDAI) between groups and analysing this for both women and men independently.

METHODS

Study-specific sample

This analysis encompasses our study-specific sample, which is aggregated from multiple well-defined clinical cohorts from an Assessment of SpondyloArthritis international Society expert centre. The German Spondyloarthritis Inception Cohort (GESPIC) which contributed with three separate subgroups: GESPIC-ankylosing spondylitis (GESPIC-AS; patients with radiographic axSpA), GESPIC-Crohn (patients with Crohn's disease, with or without axSpA) and GESPIC-uveitis (patients with non-infectious acute anterior uveitis, with or without axSpA).[23–25] The Identification of Optimal Referral Strategy for Early Diagnosis of axial spondyloarthritis (OptiRef) cohort included patients with chronic back pain lasting for at least 3 months, with symptom onset before the completion of 45 years of age.[26 27] The SIJ MRI and CT cohort involved patients presenting with chronic low back pain and suspected axSpA.[28–30] Finally, the virtual non-contrast susceptibility-weighted imaging cohort included patients referred for MRI due to suspected axSpA, based on symptoms as IBP or confirmed axSpA diagnoses.[31]

684 patients had sufficient data to be assessed across these cohorts, with 379 receiving a clinical diagnosis of axSpA and 305 being excluded after axSpA was ruled out.[14] Patients with axSpA and atypical joints were matched by age and sex, with those patients with axSpA with normal joints. The presence of a duplicate file for the same patient led to the exclusion of 18 patients.

MRI assessment and final patient inclusion

The MRI evaluation of SIJs was conducted on the entire sample of 684 patients. A semi-quantitative scoring system was used to classify joints as either normal or atypical. Atypical joints were defined by the presence of specific features, including accessory joints, iliosacral complexes and crescent-shaped iliac bones, due to their distinctive biomechanical properties compared with normal joints.[14 18] Examples of these variants are illustrated in figure 1.

Patients were included in the analysis based on the presence of these atypical joint forms, which have been associated with imaging changes in prior studies.[18] Figure 2 depicts the inclusion process and detailed assessment steps.

Clinical features

In addition to age and sex, which were adjusted for during matching, the following clinical factors were considered as potential confounders: body mass index (BMI), symptom duration, human leucocyte antigen (HLA)-B27 positivity, elevated C-reactive protein (CRP) values, positive family history of SpA and treatment with biological disease-modifying anti-rheumatic drugs (bDMARDs). Elevated CRP was defined as any value equal to or above 5 mg/L. For BASDAI (n=9, 5.5%), BMI (n=3, 1.8%) and symptom duration (n=13, 8%), mean imputation was applied. All other variables showed complete data sets.

Outcome variables

We evaluated the association between atypical joint shapes and other clinical characteristics of axSpA, namely characterisation of the low back pain as IBP by the treating rheumatologist, documented current or ever diagnosed extra-axial manifestations of the disease such

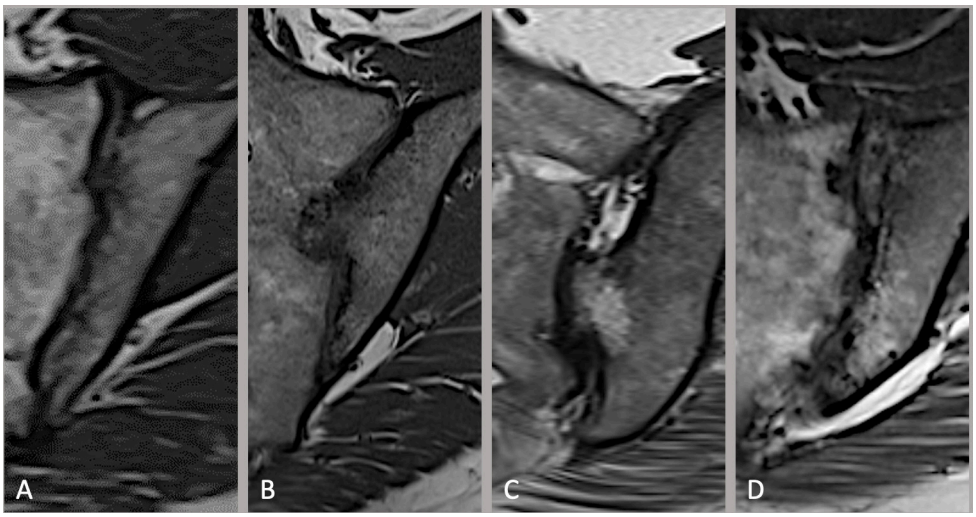

Figure 1 Normal and atypical sacroiliac joint forms as seen on T1-weighted MRI-images: (A) normal sacroiliac joint, (B) iliosacral complex, (C) accessory joint facet, (D) crescent-joint shape.

as peripheral SpA manifestations (peripheral arthritis, enthesitis, dactylitis) and EMMs (uveitis, psoriasis and IBD). Furthermore, we analysed whether there was an association between the joint shapes and disease activity as measured by BASDAI.

Propensity score matching

We a priori assumed sex and age to be the most important predictors of heterogeneity regarding the clinical characteristics of axSpA in our patient cohort. Sex is known to be related to the incidence of axSpA and its phenotype, and associated with the presence or absence of an SIJ variation; we have regarded it in our study as the principal influencer of the clinical picture in the overall cohort.[32 33] Additionally, we matched for age, as axSpA typically begins before the age of 40 and progresses over the course of the patient's lifetime.[2] Matching patients with and without atypical joints was performed using propensity score matching with an intended ratio of 1:2; matching variables were age and sex, and matching tolerance was set to 0.01. While this approach aimed to address key confounders, we acknowledge that additional variables were considered in subsequent analyses, as detailed in the Results and Discussion sections. Group differences in the matched cohort were also evaluated to explore other factors potentially influencing outcomes.

Statistical analysis

Group differences were assessed using χ^2 tests for categorical variables and t-tests or one-way analysis of variance (ANOVA) for continuous variables. We applied linear and logistic regression models for the outcome analysis, adjusting for all factors with a p value<0.15. This threshold was chosen based on simulations

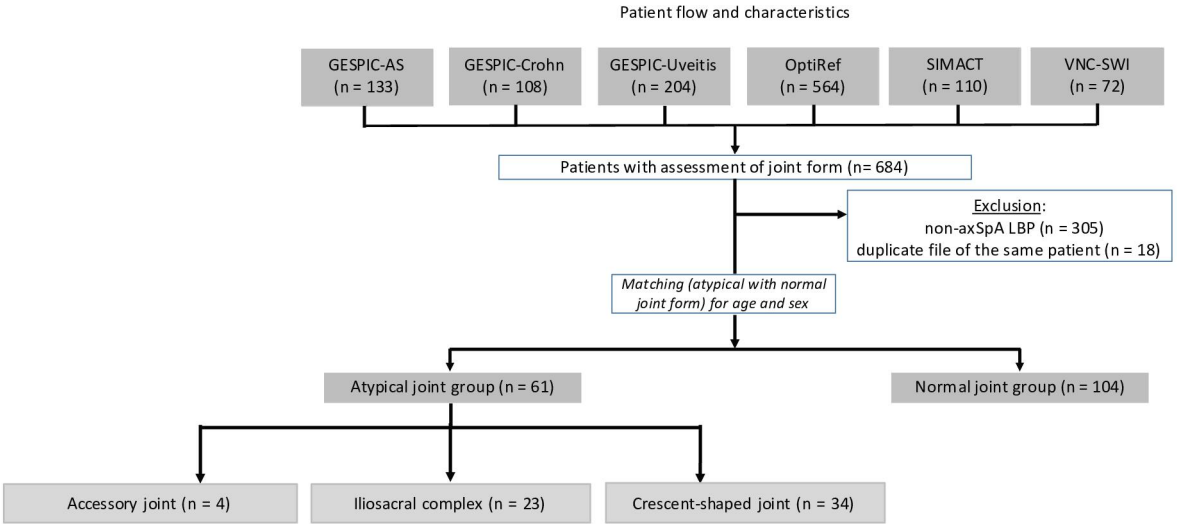

Figure 2 Flow chart illustrating patient inclusion and exclusion. AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; GESPIC, German Spondyloarthritis Inception Cohort; LBP, low back pain; OptiRef, Identification of Optimal Referral Strategy for Early Diagnosis of axial spondyloarthritis; SIMACT, sacroiliac joints MRI and CT; VNC-SWI, virtual non-contrast susceptibility-weighted imaging.

demonstrating its adequacy for including confounding variables that may not reach significance in univariate analyses.[34] Furthermore, using both propensity score matching and regression adjustment can help improve the precision of effect estimates and reduce residual confounding, providing a more robust analysis by combining the strengths of both methods.[35] Additionally, a sex-specific sensitivity analysis was conducted separately for men and women. Finally, a sensitivity analysis was performed in the bDMARD-naïve group and according to SIJ type. The analysis according to joint type was carried out descriptively, given the small sample size of the subtypes. To adjust for multiple testing, we employed the Bonferroni method, prespecifying 4 subgroup analyses (all patients, women, men, joint type) for 8 primary outcomes, totalling 32 tests (8×4). Since ANOVA tests the null hypothesis in one step, we considered the multigroup joint type comparison as one test. Thus, we set the Bonferroni-adjusted significance threshold at $p<0.002$ (0.05÷32, rounded). The sensitivity analyses were purely confirmatory and not aimed at new insights, so no extra corrections were made. Nonetheless, we consistently applied the stricter $p<0.002$ threshold for all tests and provided raw p values for transparency. All statistical analyses were performed using SPSS V.29.0.1.1 (IBM, New York, New York, USA) and R V.4.3.3 (The R Project for Statistical Computing).

RESULTS

Study cohort

A total of 165 patients were included in this analysis. Patients with an atypical SIJ had a mean age of 38.7 years (SD 12.9), while patients with a normal SIJ had a mean age of 36.1 years (SD 11.2)—per study design, there was no significant difference between the two groups (p=0.175). Similarly, sex distribution was nearly identical in both groups: in the group of atypical joints 34 (55.7%) were women, in the normal joint group 52 (50.0%) were women (p=0.582). Table 1 summarises the baseline characteristics of the groups with normal and atypical SIJs in the matched cohort. No statistically significant differences in distribution or mean were found for any clinical parameters under investigation. HLA-B27 positivity was documented in 88 (84.6%) of patients with normal SIJs and in 50 (82.0%) in those in the atypical SIJ cohort (p=0.821). No significant difference was found regarding the prevalence of elevated CRP (40.4% vs 47.5%, p=0.463). A positive family history of SpA was reported in 28 (26.9%) of patients with a normal SIJ and in 16 (26.2%) of those with an anatomical variation (p>0.999). Most included patients were bDMARD-naïve (n=147, 89%). There were no significant differences in BMI (24.4 (4.7) vs 25.8 (4.4), p=0.073), however, the p value was below the predefined threshold for inclusion in the regression analysis and therefore it was included in the outcome analysis.

Table 1 Clinical characteristics in patients with normal and atypical sacroiliac joints

	Normal joint (n=104)	Atypical joint (n=61)	P value
Age, years (mean (SD))	36.1 (11.2)	38.7 (12.9)	0.175
Female patients (n (%))	52 (50.0)	34 (55.7)	0.582
BMI (mean (SD))	24.4 (4.7)	25.8 (4.4)	0.073
Symptom duration, months (mean (SD))	120.0 (107.4)	116.5 (98.3)	0.838
HLA-B27 positivity (n (%))	88 (84.6)	50 (82.0)	0.821
Elevated CRP (n (%))	42 (40.4)	29 (47.5)	0.463
Positive family history of SpA (n (%))	28 (26.9)	16 (26.2)	>0.999
bDMARD therapy (n (%))	12 (11.5)	6 (9.8)	0.936
Cohort (%)			0.609
GESPIC-AS cohort (%)	34 (32.7)	22 (36.1)	
GESPIC-Crohn cohort (%)	5 (4.8)	0 (0.0)	
GESPIC-uveitis cohort (%)	22 (21.2)	13 (21.3)	
OptiRef cohort (%)	15 (14.4)	11 (18.0)	
SIMACT cohort (%)	19 (18.3)	11 (18.0)	
VNC-SWI cohort (%)	9 (8.7)	4 (6.6)	

Elevated CRP was defined as any value equal or above 5 mg/L.
AS, ankylosing spondylitis; bDMARD, biological disease-modifying anti-rheumatic drug; BMI, body mass index; CRP, C-reactive protein; GESPIC, German Spondyloarthritis Inception Cohort; HLA-B27, human leucocyte antigen B27; OptiRef, Identification of Optimal Referral Strategy for Early Diagnosis of axial spondyloarthritis; SIMACT, sacroiliac joint MRI and CT; SpA, spondyloarthritis; VNC-SWI, virtual non-contrast susceptibility-weighted imaging.

Table 2 Regression analysis of clinical characteristics in patients with normal and atypical sacroiliac joints

	Unadjusted estimate (95% CI)	Unadjusted p value	Adjusted estimate (95% CI)	Adjusted p value
BASDAI	–0.021 (–0.617, 0.575)	0.945	–0.118 (–0.713, 0.476)	0.696
Inflammatory back pain	OR 0.61 (0.274, 1.358)	0.226	OR 0.614 (0.274, 1.377)	0.236
Uveitis ever	OR 1.915 (0.843, 4.35)	0.121	OR 1.777 (0.774, 4.076)	0.175
Psoriasis ever	OR 1.157 (0.445, 3.011)	0.765	OR 1.112 (0.424, 2.919)	0.829
IBD ever	OR 0.972 (0.273, 3.467)	0.966	OR 1.173 (0.32, 4.306)	0.810
Peripheral arthritis current	OR 0.675 (0.276, 1.652)	0.390	OR 0.622 (0.251, 1.54)	0.304
Enthesitis current	OR 1.215 (0.575, 2.571)	0.610	OR 1.244 (0.583, 2.656)	0.572
Dactylitis current	OR 1.293 (0.28, 5.981)	0.742	OR 1.215 (0.26, 5.675)	0.804

Estimates for BASDAI are calculated using linear regression and presented as β (95% CI), reflecting the mean difference in outcome per unit change. Estimates for the other outcomes are calculated using logistic regression and are presented as OR (95% CI), indicating the OR of the outcome occurring. Adjusted p values were adjusted for BMI.
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying anti-rheumatic drugs; BMI, body mass index; IBD, inflammatory bowel disease.

Outcomes and adjusted results

We observed no differences in disease activity, expressed by mean BASDAI, between patients with normal and atypical joints (adjusted ß=–0.118 (95% CI -0.713, 0.476), p=0.696). IBP revealed a similar distribution between the groups (adjusted OR 0.614 (95% CI 0.274, 1.377), p=0.236). None of the EMMs (uveitis, psoriasis, IBD) or peripheral manifestations (peripheral arthritis, enthesitis, dactylitis) were more prevalent in patients with normal SIJs than in those with atypical joint shapes—details on unadjusted and adjusted results are displayed in table 2.

Sex-specific analysis: outcomes and adjusted results

Table 3 and table 4 display the distribution of clinical characteristics in our subgroup analysis for women and men, respectively. Individual female cohorts show a similar distribution of most clinical parameters under investigation, as, for example, for HLA-B27 positivity (76.9% vs 82.4%, p=0.738) and rates of a positive family history for SpA (25.0% vs 32.4%, p=0.619). Age revealed to be different in female patients with an atypical SIJ with a mean age of 40.7 years (SD 12.8), while those with a normal SIJ had a mean age of 35.0 years (SD 10.9)

Table 3 Clinical characteristics in women with normal and atypical sacroiliac joints

	Normal joint (n=52)	Atypical joint (n=34)	P value
Age, years (mean (SD))	35.0 (10.9)	40.7 (12.8)	0.031
BMI (mean (SD))	23.6 (5.5)	25.9 (5.3)	0.063
Symptom duration, months (mean (SD))	115.7 (110.9)	130.8 (108.1)	0.534
HLA-B27 positivity (n (%))	40 (76.9)	28 (82.4)	0.738
Elevated CRP (n (%))	18 (34.6)	16 (47.1)	0.353
Positive family history of SpA (n (%))	13 (25.0)	11 (32.4)	0.619
bDMARD therapy (n (%))	3 (5.8)	4 (11.8)	0.555
Cohort (%)			0.812
GESPIC-AS cohort (%)	18 (34.6)	13 (38.2)	
GESPIC-Crohn cohort (%)	2 (3.8)	0 (0.0)	
GESPIC-uveitis cohort (%)	12 (23.1)	7 (20.6)	
OptiRef cohort (%)	6 (11.5)	6 (17.6)	
SIMACT cohort (%)	10 (19.2)	5 (14.7)	
VNC-SWI cohort (%)	4 (7.7)	3 (8.8)	

Elevated CRP was defined as any value equal or above 5 mg/L.
AS, ankylosing spondylitis; bDMARD, biological disease-modifying anti-rheumatic drug; BMI, body mass index; CRP, C-reactive protein; GESPIC, German Spondyloarthritis Inception Cohort; HLA-B27, human leucocyte antigen B27; OptiRef, Identification of Optimal Referral Strategy for Early Diagnosis of axial spondyloarthritis ; SIMACT, sacroiliac joint MRI and CT; SpA, spondyloarthritis; VNC-SWI, virtual non-contrast susceptibility-weighted imaging.

Table 4 Clinical characteristics in men with normal and atypical sacroiliac joints

	Normal joint (n=52)	Atypical joint (n=27)	P value
Age, years (mean (SD))	37.2 (11.5)	36.2 (13.0)	0.745
BMI (mean (SD))	25.2 (3.7)	25.6 (3.1)	0.623
Symptom duration, months (mean (SD))	124.2 (104.7)	98.5 (82.9)	0.272
HLA-B27 positivity (n (%))	48 (92.3)	22 (81.5)	0.288
Elevated CRP (n (%))	24 (46.2)	13 (48.1)	>0.999
Positive family history of SpA (n (%))	15 (28.8)	5 (18.5)	0.466
bDMARD therapy (n (%))	9 (17.3)	2 (7.4)	0.388
Cohort (%)			0.741
GESPIC-AS cohort (%)	16 (30.8)	9 (33.3)	
GESPIC-Crohn cohort (%)	3 (5.8)	0 (0.0)	
GESPIC-uveitis cohort (%)	10 (19.2)	6 (22.2)	
OptiRef cohort (%)	9 (17.3)	5 (18.5)	
SIMACT cohort (%)	9 (17.3)	6 (22.2)	
VNC-SWI cohort (%)	5 (9.6)	1 (3.7)	

Elevated CRP was defined as any value equal or above 5 mg/L.
AS, ankylosing spondylitis; bDMARD, biological disease-modifying anti-rheumatic drug; BMI, body mass index; CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; OptiRef, Identification of Optimal Referral Strategy for Early Diagnosis of axial spondyloarthritis ; SIAMCT, sacroiliac joint MRI and CT; SpA, spondyloarthritis; VNC-SWI, virtual non-contrast susceptibility-weighted imaging.

(p=0.031). Additionally, differences in BMI of the female cohorts were noted: 23.6 (SD 5.5) versus 25.9 (SD 5.3) (p=0.063), again the p value was below the predefined threshold for inclusion in the regression analysis. Consequently, age and BMI were adjusted for in a female-sex-specific regression analysis, as illustrated in table 5. No statistically significant results were noted in this outcome evaluation. Uveitis was the only outcome variable close to reaching statistical significance, observed more often in female patients with an atypical joint than with a normal joint (adjusted OR=5.174 (95% CI 1.464, 18.285), p=0.011). In the male cohort distribution of clinical parameters was similar, no statistically significant differences were detected. In the male cohort, no values were adjusted since no variables surpassed the established threshold. Further details on sex-specific differences in the male cohort as shown in table 6.

Sensitivity analysis in a subset of bDMARD-naïve patients

A sensitivity analysis was conducted in the subset of bDMARD-naïve patients (n=147, 89%). Clinical characteristics were analysed both in the overall cohort and

Table 5 Regression analysis of clinical characteristics in women with normal and atypical sacroiliac joints

	Unadjusted estimate (95% CI)	Unadjusted P value	Adjusted estimate (95% CI)	Adjusted p value
BASDAI	−0.099 (−0.839, 0.641)	0.793	−0.224 (−0.972, 0.524)	0.559
Inflammatory back pain	OR 0.757 (0.211, 2.706)	0.668	OR 0.747 (0.203, 2.749)	0.660
Uveitis ever	OR 5.739 (1.648, 19.985)	0.006	OR 5.174 (1.464, 18.285)	0.011
Psoriasis ever	OR 2.816 (0.626, 12.662)	0.177	OR 2.577 (0.562, 11.82)	0.223
IBD ever	OR 1.022 (0.266, 3.928)	0.974	OR 1.297 (0.32, 5.258)	0.716
Peripheral arthritis current	OR 1.378 (0.42, 4.52)	0.597	OR 1.213 (0.361, 4.082)	0.755
Enthesitis current	OR 1.25 (0.475, 3.293)	0.652	OR 1.282 (0.476, 3.455)	0.623
Dactylitis current	OR 3.187 (0.278, 36.597)	0.352	OR 2.87 (0.244, 33.739)	0.402

Estimates for BASDAI are calculated using linear regression and presented as β (95% CI), reflecting the mean difference in outcome per unit change. Estimates for the other outcomes are calculated using logistic regression and are presented as OR (95% CI), indicating the OR of the outcome occurring. Adjusted p-values were adjusted for BMI.
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying anti-rheumatic drugs; BMI, body mass index; IBD, inflammatory bowel disease.

Table 6 Regression analysis of clinical characteristics in men with normal and atypical sacroiliac joints

	Unadjusted estimate (95% CI)	Unadjusted p value
BASDAI	–0.019 (–0.955, 0.916)	0.968
Inflammatory back pain	OR 0.476 (0.166, 1.369)	0.169
Uveitis ever	OR 0.525 (0.132, 2.096)	0.362
Psoriasis ever	OR 0.597 (0.147, 2.419)	0.470
IBD ever	OR 0 (0,>1000)	0.997
Peripheral arthritis current	OR 0.267 (0.055, 1.292)	0.101
Enthesitis current	OR 1.086 (0.324, 3.634)	0.894
Dactylitis current	OR 0.628 (0.062, 6.346)	0.694

Estimates for BASDAI are calculated using linear regression and presented as β (95% CI), reflecting the mean difference in outcome per unit change. Estimates for the other outcomes are calculated using logistic regression and are presented as OR (95% CI), indicating the OR of the outcome occurring.
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying anti-rheumatic drugs; BMI, body mass index; IBD, inflammatory bowel disease.

stratified by sex, as displayed in online supplemental tables 1.2, 2.2 and 3.2. Detailed results are provided in online supplemental tables 1.3, 2.3 and 3.3. The outcomes of these analyses were consistent with our initial observations, showing no statistically significant differences in the evaluated features.

Outcomes according to subtype of atypical sacroiliac joint

Finally, we assessed the differences in frequency of the documented clinical parameters according to the specific joint shapes in a descriptive manner: accessory SIJ (n=4), crescent-shaped ilium (n=34) and iliosacral complex (n=23). IBP was found to be significantly different among the three analysed subtypes (88.2% in the crescent-shaped ilium group vs 73.9% in the iliosacral complex group vs 0.0% in the accessory joint group, p<0.001). Apart from this finding, no other statistically significant distinctions were observed between the subgroups. Details on this subanalysis are displayed in online supplemental table 4.

DISCUSSION

To the best of our knowledge, this is the first analysis investigating potential differences in clinical presentation between patients with axSpA with and without atypical SIJ forms.

Our analysis did not yield tangible differences between both groups when compared individually. Reassuringly, the results of our analysis, especially the presence of disease activity according to laboratory findings by CRP or clinically according to the BASDAI score in patients with atypical joint forms, question the hypothesis, that the imaging findings in atypical joints lead to false positive diagnoses.[36] These results accentuate the possibility of mechanical and inflammatory pathways concomitantly modulating disease in axSpA, as assumed in previous studies.[10 11] Similarly, all other known SpA features were equally prevalent in patients with atypical SIJs, indicating that no distinct phenotype could be identified between the two cohorts based on anatomical sacroiliac differences. In the performed subanalysis according to joint shape classification of back pain as inflammatory showed to be statistically significantly different among the subgroups, most frequently documented in patients with a crescent-shaped ilium and lacking any prevalence in the group with an accessory joint. An individual analysis in a larger cohort should be performed to confirm this result, as it is important to note, that our accessory SIJ group consisted of only four patients, which remains a viable alternate justification for the low prevalence of this clinical characteristic in the respective subgroup.

Results from sex-disaggregated analyses were comparatively less revealing, showing no statistically significant differences in the evaluated clinical parameters. In the female cohort, uveitis revealed an increased frequency in those with atypical SIJs with a rather low p value, however without reaching statistical significance after correction for multiple testing with the Bonferroni method. The possible result of women with atypical SIJs being more frequently affected by uveitis than women with normal joints would be interesting to be validated in larger studies, as the exploratory nature of our analysis does not allow a conclusion to be drawn in this case. A possible explanation for the frequency of this EMM in this specific cohort is the fact that a diagnosis of acute anterior uveitis represents one of the inclusion criteria for the GESPIC-uveitis-subcohort, possibly contributing to the increased frequency of this EMM in our overall study population.

Although analysed patients differed in inclusion criteria and cohort-specific methodologies, results regarding BMI and bDMARD therapy display no statistically relevant differences between the matched cohorts. Most included patients were bDMARD-naïve at the time of the investigation, enabling a homogenous comparison of groups. Despite matching patients based solely on age and sex, we are aware that other confounders, such as BMI or therapy, influence the clinical picture of axSpA.[37 38] In order to question and discuss the impact cohort discrepancies might have on our regressively

analysed findings, we included adjusted results according to BMI for women. Additionally, we performed a sensitivity analysis on a smaller subset of bDMARD-naïve patients as online supplemental data. As for the results presented initially in the overall cohort, no statistically significant differences in the distribution of clinical characteristics among bDMARD-naïve groups with atypical and normal SIJs were observed. When analysing groups according to specific joint variants, no statistically significant differences were stated. However, the rather small sample size becomes apparent, as only four patients have an accessory SIJ. Differences in the classification of back pain as inflammatory are also statistically significant in this group, likely emphasised by the limited data source.

This analysis has several limitations to its generalisability. First, despite drawing from different patient cohorts, our study design with age-matched and sex-matched controls limits the available data sets substantially, thus reducing the statistical power. This was also the reason why matching was performed for the overall presence of atypical joint form rather than for each shape separately, although we concede that the impact of each of the variants in question may differ. A variant-specific analysis in a larger cohort would be valuable to further validate our findings, especially given the low frequency of certain variants, such as in the subgroup with accessory SIJ types, which included only four patients. Additionally, our approach of using matching followed by multivariate regression may have resulted in a more cautious analysis, as the exclusion of unmatched individuals during the matching process, coupled with regression on the reduced sample, likely impacted statistical power. Future propensity score analyses could be more inclusive, as the incorporation of cofounders before matching could further enhance the homogeneity in the compared cohorts. Selection bias may arise from the inclusion and exclusion criteria, however, matching of patients by age and sex and inclusion of eligible patients with complete data attempted to minimise this effect. While this approach ensures comparability, it may limit the generalisability of findings to broader populations. Furthermore, certain clinical information had to be gathered from electronic patient records, with the known limitations of this source of information, such as the lack of standardised/systematic data documentation. For instance, the history of childbirth in women, which is associated with mechanical joint disease (eg, osteitis condensans ilii), was unavailable but would be valuable for future analyses.[39] Similarly, information on physical activity, a cornerstone of axSpA therapy that improves quality of life, spinal mobility and reduces disease activity, was not systematically documented.[11] Including these variables in future studies would enhance understanding of their impact on clinical outcomes. Tied in with this fact, it is important to acknowledge that, although data collection in these cohorts was conducted prospectively and in a standardised manner, the current analysis represents a post hoc evaluation of pooled data from different cohorts. This distinction highlights the inherent challenges in interpreting the clinical picture, as retrospective analyses may not always fully capture the clinical reality as initially recorded. We applied mean imputation for variables with minor proportions of missing data (BASDAI, BMI and symptom duration). Although we acknowledge that mean imputation has limitations, as it may underestimate variability and could potentially bias results under certain conditions, the overall low proportion of missing data across all variables minimises the risk of significant bias. Finally, longitudinal data, for example, on patients with axSpA with limited response to therapy, would further illuminate the connection between clinical symptoms and anatomical joint form variations.

In summary, our findings suggest that clinical phenotypes do not significantly differ between patients with axSpA with normal and atypical SIJs and rather weaken the role of these variants in radiological disease mimicking. We believe additional research on the topic is crucial to further evaluate the need for diagnosing such anatomical variations and clarify their individual influence on symptomatic joint disease.

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