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Clinical characteristics of peripheral joint disease in axial and peripheral spondyloarthritis: findings from a multicentre cross-sectional study

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Abstract

Peripheral joint disease (PJD) is the most common peripheral manifestation in spondyloarthritis (SpA) patients. This study aimed to determine PJD characteristics and associated factors in patients with axial SpA (AxSpA) and peripheral SpA (pSpA). This cross-sectional and multicenter study involved 13 different rheumatology and physical medicine & rehabilitation clinics, and patients diagnosed with axSpA or pSpA were included in the study. PJD was defined as the 'ever' related to SpA according to the physician. Multivariable analyses were conducted to identify factors associated with PJD. A total of 394 patients were enrolled in the study (57.6% male, mean age 40.8 years), of whom 359 (91.1%) were classified as AxSpA and 35 (8.9%) as pSpA. Peripheral arthritis was reported in 118 patients (29.9%), comprising 85 (72%) with AxSpA and 33 (28%) with pSpA. Among the whole population with PJD, the main joint involvement pattern was monoarticular (33.9%, $n=40$) and oligoarticular (49.2%, $n=58$). The rate of predominantly lower limb and large joint involvement was approximately 60% ($n=68$) and the major course of PJD was transient (42.4%, $n=50$) and intermittent (40.7%, $n=48$). pSpA patients had a higher rate of persistent (33.3% vs. 14.3%, $p=0.021$) and progressive arthritis (15.2% vs. 1.2%, $p=0.007$). The coexistence of PJD with other peripheral involvement and extra-articular manifestations excluding psoriasis was widespread. Dactylitis, enthesitis, and high CRP level were positively associated with PJD; on the contrary, ever alcohol intake, presence of sacroiliitis on MRI, and family history for SpA were negatively associated. PJD was accompanied by both other peripheral involvements and extra-articular manifestations, excluding psoriasis and the course of PJD was more persistent in pSpA patients. This undoubtedly contributes to an increased disease burden.

Keywords Spondyloarthritis · Enthesitis · Dactylitis · Arthritis · Disease burden

Introduction

Spondyloarthritis (SpA) is an umbrella term for a group of chronic inflammatory diseases which share common clinical features, genetic susceptibility and pathophysiological mechanisms [1]. The Assessment of SpondyloArthritis international Society (ASAS) determined the classification criteria of axial SpA (axSpA) in 2009 and peripheral SpA (pSpA) in 2011, based on the predominant pattern of axial or predominantly peripheral involvement, respectively [2, 3]. AxSpA primarily affects the axial skeleton, including the spine and sacroiliac joint (SIJ) whereas the predominant clinical manifestations in pSpA are arthritis, enthesitis, and/or dactylitis. In addition to these musculoskeletal

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symptoms, extra- musculoskeletal manifestations (EMMs) such as acute anterior uveitis (AAU), psoriasis or inflammatory bowel disease (IBD) are also common in SpA [4].

Peripheral joint disease (PJD) is the most frequent peripheral musculoskeletal manifestation in SpA patients. The typical clinical presentation is an asymmetric, monoarthritis or oligoarthritis that involves the lower limbs more frequently than the upper limbs [5]. Most studies evaluating PJD are focused on axSpA. Among this population, PJD prevalence varies between 30 and 51% and the presence of PJD independently leads to more functional impairment over time [6–9]. Non-smoking, HLA-B27 negativity, enthesitis, dactylitis, abnormal CRP level, absence of uveitis, and absence of chronic inflammatory back pain are factors associated with PJD [7, 8].

Peripheral arthritis is one of the entry items of the ASAS classification criteria for pSpA [3]. Although these criteria were introduced in 2011, most clinical studies have not addressed this clinical entity as a separate disease. Therefore, the characteristics of pSpA, which is a neglected disease, have not been thoroughly investigated [10]. PJD is the most frequent clinical manifestation, occurring in 85–98% of pSpA patients [3, 11, 12]. Current and detailed PJD characteristics in patients with pSpA have been obtained from the ASAS-perSpA study. In this study, the prevalence of PJD in SpA patients was highest in pSpA group (95%). Half of the patients exhibited lower limbs large joint involvement, and the pattern of joint involvement was predominantly oligoarticular and polyarticular. PJD varied significantly regarding geographic distribution and the highest prevelance was in patients from Latin American countries (80%) [12]. Geographic differences may affect the localization and course of peripheral arthritis in addition to the PJD prevalence.

Therefore, in this study, using data from Türkiye contributed to the ASAS-perSpA cohort, we aimed to characterize the clinical features, distribution, and associated factors of PJD in AxSpA and pSpA patients.

Methods

The ASAS-PerSpA is an observational, cross-sectional, multicentre, and international study involving 24 participating countries. Full details of the study have been published previously [12]. Türkiye, which made the largest contribution to the research, participated through 13 different rheumatology and physical medicine & rehabilitation clinics. Our study includes the Türkiye dataset from the ASAS-perSpA study. This study was conducted in full accordance with the ethical principles outlined in the latest version of the Declaration of Helsinki (December 2024 version). The research protocol was reviewed and approved by the relevant institutional ethics committee prior to data collection. The study was approved by the Marmara University Clinical Research Ethics Committee (approval number 09.2018.576). All participants were thoroughly informed about the purpose, procedures, potential risks, and benefits of the study, and written informed consent was obtained from each participant before enrolment.

Patient recruitment

Patients diagnosed with axSpA and/or pSpA by their treating physician were included in the study between July 2018 and February 2020. Eligible participants were selected from consecutive adult patients (i.e., at least 18 years old) attending the outpatient clinic who were able to understand and complete the questionnaires. The ASAS classification criteria for axSpA and pSpA criteria were applied to all participants. Patients diagnosed with psoriatic arthritis (PsA) were excluded from our study because they would cause differences in the clinical expression of SpA (i.e., high frequency of dactylitis, distal interphalangeal joint involvement, increased comorbidities) [13]. Written informed consent was obtained from all subjects before enrollment.

Data collection

All data were collected from four different categories during a face-to-face interview at one single study visit: demographic, disease features, peripheral musculoskeletal involvement, and disease activity. The demographic data included age, gender, body mass index (BMI), smoking, alcohol intake, and education level. SpA characteristics, family history, disease duration, date of symptom onset, and treatment history were stated in the disease features. Peripheral musculoskeletal manifestation contained PJD, root joint involvement, midfoot arthritis (tarsitis), enthesitis, and dactylitis. Specific treatments used for these peripheral symptoms were also recorded.

Assessment of PJD

PJD (excluding isolated root joint) was identified as a positive answer by the researcher to the following question: ‘Do you think that the patient has ever been affected by PJD related to SpA in the past?’. In cases of a positive response the following parameters were evaluated: the existence of objective synovitis (physical examination or confirmed by ultrasonography), the pattern of affected joint (mono, oligo, or polyarticular type), localisation (predominantly in the lower limbs/large joints), involved joints since the onset of SpA, natural history (transient, continuous, intermittent or progressive), specific treatments prescribed for PJD, and

surgery history for the affected peripheral joint. The localization of affected joints since the onset of SpA was assessed using the 66 Swollen Joints Index [14].

Other variables

HLA-B27 status, extra-musculoskeletal manifestations such as uveitis, psoriasis and IBD, the presence of sacroiliitis on X-ray or MRI, and disease activity outcome measures were also recorded. Current disease activity was measured with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score-C reactive protein (ASDAS-CRP) [15, 16], whereas function and health assesment were evaluated with the Bath Ankylosing Spondylitis Functional Index (BASFI) and the ASAS Health Index [17, 18]. To assess the current tender joint count, the Ritchie Articular Index was used [19]. Furthermore, current Patient Global Assessment of well-being (PGA) was determined with a numerical scale from 0 to 10. Ultimately, a coexistence with secondary fibromyalgia according to a rheumatologist was also enrolled and the self-reported Fibromyalgia Rapid Screening Tool (FiRST) was completed [20].

Statistical analysis

Statistical analysis was performed using the SPSS software (version 25.0; IBM Corporation, Armonk, NY, USA). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov, skewness, and kurtosis) to determine whether they are normally distributed or not. Continuous data were described as median (interquartile range, IQR) or mean (standard deviation, SD) and categorical variables as percentages. Chi-square test was used to compare categorical variables and Mann–Whitney U test/Student's T test was used to compare continuous variables. To find risk factors associated with PJD, the variables with $p<0.2$ as a result of univariate analysis were included in the multivariate analysis. Factors associated with PJD were analyzed by the logistic regression analysis. Hosmer–Lemeshow goodness-of-fit statistics were used to assess model fit. P values of <0.05 were considered as signifcant.

Results

Definition of SpA cohort

A total of 489 patients from 13 different centers in Türkiye were included in the ASAS-perSpA study. In this study which we present the Turkish data of the ASAS-perSpA study, 73 patients with PsA who fulfilled CASPAR criteria were excluded. Of the remaining 394 patients, 359 (91.1%) were grouped as AxSpA and 35 (8.9%) as pSpA. In the overall population, the mean age was 40.8 (±10.7) years and 57.6% were male. Demographics and clinical characteristics were presented for AxSpA and pSpA in **Table** 1. There was no difference between the groups in terms of age, gender, and BMI. Past or current history of smoking and alcohol use was more common in the AxSpA group. AxSpA patients had a higher rate of family history for SpA (52.6% vs. 26.5%, $p=0.004$), inflammatory back pain (94.9% vs. 74.3%, $p<0.001$), and sacroiliitis on MRI (95% vs. 80.6%, $p=0.008$), while pSpA patients had more frequently PJD (94.3% vs. 23.7%, $p<0.001$), dactylitis (11.4% vs. 2.8%, $p=0.028$), and psoriasis (14.3% vs. 2.8%, $p=0.007$). Disease activity and disease burden were similar in both groups. The presence of current swollen joints in the pSpA patients was five times more frequent than in the AxSpA ones (25.7% vs. 5%, $p<0.001$). The rate of ever used csDMARD was significantly higher in pSpA patients (85.7% vs. 54.6%, $p<0.001$).

Assessment of the patients according to the presence of PJD

118 (29.9%, 95%CI:25.4–34.5) patients had at least one peripheral arthritis history. Of these patients, 85 (72%, 95%CI:63.9–80.1) were in the AxSpA group and 33 (28%, 95%CI:19.9–36.1) were in the pSpA group. The comparison of the patients' demographics and disease characteristics according to the presence of PDJ were shown in **Table** 2. The rate of male gender (61.2% vs. 49.2%, $p=0.026$), current smoking (30.1% vs. 19.5%, $p=0.031$), and family history for SpA (55.8% vs. 37.6%, $p=0.001$) was higher in PJD- patients. Dactylitis (8.5% vs. 1.4%, $p=0.001$), enthesitis (69.5% vs. 34.8%, $p<0.001$), uveitis (23.7% vs. 12%, $p=0.003$), IBD (6.8% vs. 2.2, $p=0.024$), and root joint disease (33.9% vs. 19.6%, $p=0.002$) at any time were more frequently observed in PJD+patients. The presence of sacroiliitis on MRI (95.8% vs. 88.3%, $p=0.011$) was more common in the PDJ- group while the distribution of sacroiliitis on X-ray was similar for both groups. Compared to the disease activity and burden, PJD+patients had significantly worse average PGA (4.6 vs. 3.9, $p=0.011$), BASDAI (5.5 vs. 4.4, $p<0.001$), ASDAS-CRP (3 vs. 2.8, $p<0.001$) and ASAS-HI score (8.3 vs. 7.5, $p<0.001$). Similarly, the mean FIRST score (3.3 vs. 1.8, $p<0.001$) and the rate of fibromyalgia according to FIRST (36% vs. 13.7%, $p<0.001$) were higher in PDJ+group. Finally, the use of csDMARDs during the disease was more widespread in the patients with PJD.

Table 1 Comparison of the demographic and disease characteristics of the patients with AxSpA and pSpA

	AxSpA ($n=359$)	pSpA ($n=35$)	p
Age (mean, SD)	40.7 (10.7)	41.8 (10.2)	0.571
Gender (male)	211 (58.8)	16 (45.7)	0.136
BMI (kg/m^2), mean (SD)	26.6 (5.6)	27.3 (6.4)	0.517
Ever smoker	188 (52.4)	12 (34.3)	**0.041**
Ever alcohol	104 (29)	3 (8.6)	**0.011**
Age at SpA onset, mean (SD)	32.7 (10.7)	34.9 (12.6)	0.263
Family history for SpA	185 (52.6)	9 (26.5)	**0.004**
Disease duration, years, med (IQR)	5 (8)	6 (9)	0.387
Diagnostic delay, years, med (IQR)	2 (5)	2.5 (10.7)	0.503
İnflammatory back pain (ever)	337 (94.9)	26 (74.3)	**<0.001**
Peripheral joint disease (ever)	85 (23.7)	33 (94.3)	**<0.001**
Dactylitis (ever)	10 (2.8)	4 (11.4)	**0.028**
Enthesitis (ever)	157 (43.7)	21 (60)	0.065
Uveitis (ever)	53 (14.8)	8 (22.9)	0.206
Psoriasis (ever)	10 (2.8)	5 (14.3)	**0.007**
IBD (ever)	12 (3.3)	2 (5.7)	0.358
Root joint disease (ever)	82 (22.8)	12 (34.3)	0.129
HLA-B27 positivity	150 (68.5)	12 (60)	0.437
Sacroiliitis on X-ray	237 (69.1)	22 (66.7)	0.773
Sacroiliitis on MRI	287 (95)	25 (80.6)	**0.008**
High level CRP at the diagnosis	229 (64.5)	24 (72.7)	0.343
PGA, mean (SD)	5.2 (2.5)	5.3 (2.1)	0.532
BASDAI, mean (SD)	4.8 (2.5)	4.7 (2)	0.739
High BASDAI (binary, ≥4)	144 (40.1)	14 (40)	0.991
ASDAS-CRP, mean (SD)	2.9 (1)	3 (1)	0.724
BASFI, mean (SD)	3.4 (2.7)	3.6 (2.3)	0.296
ASAS-HI, mean (SD)	7.7 (4.8)	7.9 (3.7)	0.446
Presence of current swollen joint	18 (5)	9 (25.7)	**<0.001**
Number of current tender Joints, med (IQR)	3 (5)	4 (9)	0.073
Fibromyalgia according to the rheumatologist	65 (18.1)	2 (5.7)	0.063
Fibromyalgia according to the FIRST	61 (19.9)	2[a] (22.2)	0.999
FIRST score, mean (SD)	2.2 (2.1)	2.3 (1.9)	0.898
csDMARDs using during the disease	196 (54.6)	30 (85.7)	**<0.001**
bDMARDs using during the disease	197 (54.9)	19 (54.3)	0.947

Categorical variables are presented as percentages

ASAS-HI: ASAS Health Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score, AxSpA: Axial spondyloarthritis, BASDAI: Bath Ankylosing Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, bDMARDs: Biological disease-modifying antirheumatic drugs, BMI: Body mass index, CRP: C reactive protein, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, FiRST: Fibromyalgia Rapid Screening Tool, IBD: Inflammatory bowel disease, PGA: Patient's global assesment, pSpA: Peripheral spondyloarthritis

[a] The FIRST questionnaire was completed by only 9 patients

Details of the PJD

Among the whole population with PJD, the main joint involvement patterns were monoarticular (33.9%) and oligoarticular (49.2%). The rate of predominantly lower limb and large joint involvement was approximately 60% and the major course of PJD was transient (42.4%) and intermittent (40.7%). The comparison of the PJD characteristics according to AxSpA and pSpA was presented in **Table 3** and **Figure 1**. The number and localization of affected joints were similar in both groups whereas the presence of objective synovitis was higher in pSpA patients. Continuous (33.3% vs. 14.3%, $p=0.021$) and progressive (15.2% vs. 1.2%, $p=0.007$) peripheral arthritis forms in terms of the PJD course were more common in pSpA group. Any specific treatments given for PJD were not different between groups except for csDMARD use (84.8% in pSpA vs. 61.2% in AxSpA, $p=0.014$).

Associated factors with PJD

Predictors of the PJD were determined using logistic regression analysis in **Table 4**. PJD was associated with male gender, enthesitis, dactylitis, uveitis, IBD, sacroiliitis on MRI, and family history for SpA in the univariate analysis. In multivariate analysis, enthesitis [aOR 3.83 (2.16–6.78) 95% CI; $p<0.001$], dactylitis [aOR 5.05 (1.38–18.47) 95%CI; $p=0.014$], and high CRP level at diagnosis [aOR 1.98 (1.06–3.69) 95%CI; $p=0.033$] were positively associated with PJD, whereas ever alcohol intake [aOR 0.48 (0.24–0.92) 95%CI; $p=0.029$], sacroiliitis on MRI [aOR 0.25 (0.09–0.69) 95%CI; $p=0.008$], and family history for SpA [aOR 0.51 (0.29–0.91) 95%CI; $p=0.022$] were negatively associated with PJD.

Discussion

In this multicenter study investigating 394 patients diagnosed with AxSpA or pSpA, the prevalence of peripheral joint disease (PJD) was 30%, and 4 times more common in pSpA patients than AxSpA patients. Dactylitis, enthesitis, uveitis, IBD, and root joint disease were more frequently observed among PJD + patients. Enthesitis, dactylitis, and high CRP level at diagnosis were positively associated with PJD, whereas current smoking, the presence of sacroiliitis on MRI, and family history for SpA were negatively associated.

Spondyloarthritis is among the most common inflammatory rheumatic diseases and its global prevalence differs between 0.20% and 1.61% [21]. In a nationwide study, the standardized SpA prevalance for the general population of Türkiye is 0.46% [22]. Beyond disease prevalence, peripheral manifestations vary according to geographical regions. In the ASAS-perSpA study, the prevalance of PJD was found 49% in the geographical region where Türkiye was located, while it was the most prevelant in Latin American countries (80%) [12]. In our study, we stated that the prevalence of PDJ was 30%. This decrease in the frequency of PJD seems to be related to the exclusion of PsA patients from the study.

Little is known about the prevalence, phenotype, and burden of pSpA, as most studies investigating the SpA spectrum have focused on patients with AxSpA and PsA [10]. Peripheral arthritis, one of the entry items in the ASAS classification criteria for pSpA, is observed in over 95% of patients with pSpA, and this rate is 3–6 times more frequent than in AxSpA patients [11, 23, 24]. This prevalence was also confirmed by the ASAS-perSpA study, which reported that PJD was detected in 95% of patients with pSpA and was approximately three times more prevalent than in AxSpA patients [12]. Our results support previous studies that compared AxSpA and pSpA and reported the prevalence of PJD.

The classical clinical presentation of PJD in AxSpA and pSpA is monoarthritis or oligoarthritis, predominantly affecting the lower extremities and large joints [5, 25]. This joint involvement preference is a fundamental phenotypic difference from PsA, which principally affects the upper extremities and small joints. As expected, in the ASAS-COMOSPA study including PsA patients, oligoarthritis was the most common joint involvement pattern at 40%, while the rate of polyartricular involvement was 16% and the majority consisted of PsA patients [8]. Unfortunately, the features of peripheral arthritis in AxSpA and pSpA were not specified in most studies. In the SPACE cohort, the frequency of asymmetric lower limb arthritis in AxSpA patients fulfilling the ASAS criteria was reported to be 13.3% [26] while in another study that included only pSpA patients, this rate was stated as 72% [27]. Moreover, the ASAS-perSpA study revealed that peripheral involvement of the large joints of the lower extremities was present in 39% of patients, and differently, PsA patients predominantly had upper extremity and small joint involvement [12]. In our study, the frequency of PJD at large joint of the lower limbs was 60%, and the main patterns of joint involvement were oligoarthritis and monoarthritis. This distribution was similar in AxSpA and pSpA patients. In addition, 17% of the patients had polyarticular involvement although we excluded PsA patients. Although upper extremity small joint involvement is primarily seen in PsA and RA, it should be kept in mind that it can also occur in AxSpA and pSpA patients.

It is well established that peripheral joint disease contributes to the disease burden in patients with SpA. A cluster analysis demonstrated that high disease activity was associated with the presence of peripheral arthritis in patients

Table 2 Patients and disease's characteristics according to the presence of PJD

	History of at least one PJD		*p*
	Yes (*n* = 118)	No (*n* = 276)	
Age (mean, SD)	41.1 (11.7)	40.7 (10.2)	0.751
Gender (male)	58 (49.2)	169 (61.2)	**0.026**
BMI (kg/m^2), mean (SD)	25.9 (6.5)	26 (5.5)	0.862
Current smoking	23 (19.5)	83 (30.1)	**0.031**
Ever smoking	54 (45.8)	146 (52.9)	0.194
Ever alcohol	26 (22)	81 (29.3)	0.135
Age at SpA onset, mean (SD)	32.7 (12.4)	32.9 (10.3)	0.867
Family history for SpA	44 (37.6)	150 (55.8)	**0.001**
Disease duration, years, med (IQR)	6 (9)	4 (8)	0.701
Diagnostic delay, years, med (IQR)	2.5 (7)	2 (7)	0.989
İnflammatory back pain (ever)	107 (90.7)	256 (94.1)	0.219
Dactylitis (ever)	10 (8.5)	4 (1.4)	**0.001**
Enthesitis (ever)	82 (69.5)	96 (34.8)	**< 0.001**
Uveitis (ever)	28 (23.7)	33 (12)	**0.003**
Psoriasis (ever)	7 (5.9)	8 (2.9)	0.151
IBD (ever)	8 (6.8)	6 (2.2)	**0.024**
Root joint disease (ever)	40 (33.9)	54 (19.6)	**0.002**
HLA-B27 positivity	37 (63.8)	125 (69.1)	0.455
Sacroiliitis on X-ray	79 (68.7)	180 (69)	0.958
Sacroiliitis on MRI	83 (88.3)	229 (95.8)	**0.011**
High level CRP at the diagnosis	84 (72.4)	169 (62.1)	0.052
Disease activity and burden			
PGA, mean (SD)	4.6 (2.6)	3.9 (2.6)	**0.011**
BASDAI, mean (SD)	5.5 (2.6)	4.4 (2.4)	**< 0.001**
High BASDAI (binary, ≥4)	61 (51.7)	97 (35.1)	**0.002**
ASDAS-CRP, mean (SD)	3 (1.2)	2.8 (0.9)	**< 0.001**
BASFI, mean (SD)	3.5 (2.9)	3.5 (2.5)	**0.016**
ASAS-HI, mean (SD)	8.3 (4.6)	7.5 (4.7)	**< 0.001**
Number of current tender Joints, med (IQR)	3 (7)	3 (5)	0.566
Fibromyalgia according to the rheumatologist	22 (18.6)	45 (16.3)	0.571
Fibromyalgia according to the FIRST	32 (36)	31 (13.7)	**< 0.001**
FIRST score, mean (SD)	3.3 (2.1)	1.8 (1.9)	**< 0.001**
csDMARDs using during the disease	99 (83.9)	127 (46)	**< 0.001**
bDMARDs using during the disease	71 (60.2)	145 (52.5)	0.163

Categorical variables are presented as percentages

ASAS-HI: ASAS Health Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score, AxSpA: Axial spondyloarthritis, BASDAI: Bath Ankylosing Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, bDMARDs: Biological disease-modifying antirheumatic drugs, BMI: Body mass index, CRP: C reactive protein, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, FiRST: Fibromyalgia Rapid Screening Tool, IBD: Inflammatory bowel disease, PGA: Patient's global assesment, PJD: Peripheral joint disease, pSpA: Peripheral spondyloarthritis

Table 3 Comparison of arthritis and treatment features of AxSpA and pSpA patients with PJD

	axSpA ($n=85$)	pSpA ($n=33$)	p
The number of affected joints	30 (35.3)	10 (30.3)	0.607
Monoarticular	42 (49.4)	16 (48.5)	0.928
Oligoarticular	13 (15.3)	7 (21.2)	0.442
Polyarticular			
Peripheric arthritis localization	56 (65.9)	26 (78.8)	0.172
Lower limb predominancy	53 (62.4)	21 (63.6)	0.897
Large joint predominancy			
Objective synovitis	65 (76.5)	31 (93.9)	**0.029**
Root joint disease (ever)	29 (34.1)	11 (33.3)	0.936
Arthritis history	40 (47.1)	10 (30.3)	0.098
Transient	12 (14.3)	11 (33.3)	**0.021**
Continuous	34 (40.5)	14 (42.4)	0.847
Intermittent	1 (1.2)	5 (15.2)	**0.007**
Progressive			
PGA, mean (SD)	4.6 (2.6)	4.6 (2.5)	0.974
BASDAI, mean (SD)	4.5 (2.6)	3.6 (2.4)	0.081
High BASDAI (binary, ≥4)	47 (55.3)	14 (42.4)	0.209
ASDAS-CRP, mean (SD)	2.8 (1.1)	2.6 (1.1)	0.296
BASFI, mean (SD)	3 (2.8)	3.1 (2.4)	0.831
ASAS-HI, mean (SD)	7.4 (4.7)	6.8 (4.1)	0.531
Any specific treatment for PJD	70 (83.3)	27 (81.8)	0.845
NSAIDs	74 (87.1)	31 (93.9)	0.284
Systemic glucocorticoid	23 (27.1)	14 (42.4)	0.106
csDMARDs	52 (61.2)	28 (84.8)	**0.014**
bDMARDs	25 (29.4)	15 (45.5)	0.098
Local glucocorticoid	13 (15.3)	4 (12.1)	0.660
Surgery	3 (3.5)	0	NA

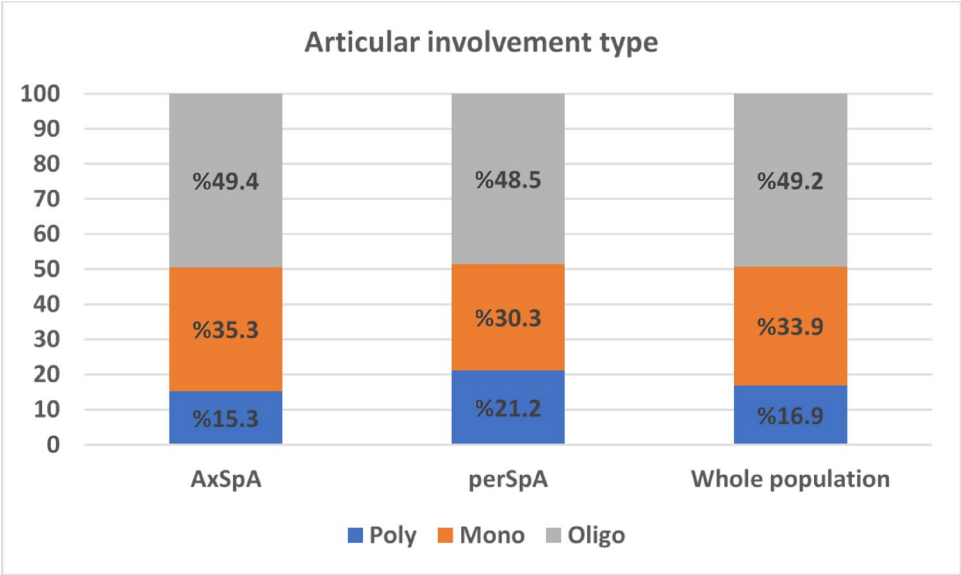
Categorical variables are presented as percentages

ASAS-HI: ASAS Health Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score, AxSpA: Axial spondyloarthritis, BASDAI: Bath Ankylosing Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, bDMARDs: Biological disease-modifying antirheumatic drugs, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, PGA: Patient's global assesment, PJD: Peripheral joint disease, pSpA: Peripheral spondyloarthritis

with AxSpA, while it is associated with elevated CRP levels in patients with pSpA. In addition, disease activities were not different in AxSpA patients with peripheral involvement compared to non-PsA pSpA patients [24]. Seemingly, peripheral arthritis contributes to the disease burden in both disease groups. In our study, PDJ + AxSpA patients and PJD + pSpA patients had similar disease activity. However, the course of peripheral arthritis was different. We found that persistent and progressive arthritis was significantly more prevalent in patients with pSpA, whereas monophasic arthritis was more common in patients with AxSpA despite not statistically significant. This course has generally been investigated in PsA studies. To our knowledge, the ASAS-perSpA study is the first study to evaluate it in all SpA subgroups.

The coexistence of peripheral manifestations is common in SpA. Studies comparing SpA patients with and without peripheral arthritis have demonstrated that enthesitis and dactylitis are more common in the peripheral arthritis group [7, 8]. A similar association is valid for pSpA patients [3, 27]. These associations bring to mind the role of biomechanical factors in SpA. It has been proposed that biomechanical microtrauma in the enthesal regions causes the secretion of pro-inflammatory factors, which may trigger simultaneous seconder synovitis and osteitis [28]. Consistently, we found that the rate of enthesitis and dactylitis was higher in the PJD + group. Moreover, EAMs such as uveitis and IBD were also observed more frequently in this group. This result can be explained with the increased incidence of peripheral arthritis in IBD and the possibility that uveitis may be triggered by atypical enthesitis of the extra-ocular muscles. In addition, the rates of male gender, current smoking, family history of SpA, and the presence of sacroiliitis on MRI were more abundant in the PJD- group. This finding is likely attributable to the fact that almost all patients in this group were AxSpA patients (99.3%).

Factors associated with peripheral arthritis in SpA have been explored in only a few studies [7, 8, 29]. The DESIR cohort including AxSpA patients displayed that non-smoking, HLA-B27 negativity, elevated CRP level, the absence of uveitis history, and pervious history of dactylitis and enthesitis were associated with peripheral arthritis [7]. In the ASAS-COSMOPA study, which also included pSpA patients, HLA-B27 negativity, absence of chronic IBP,



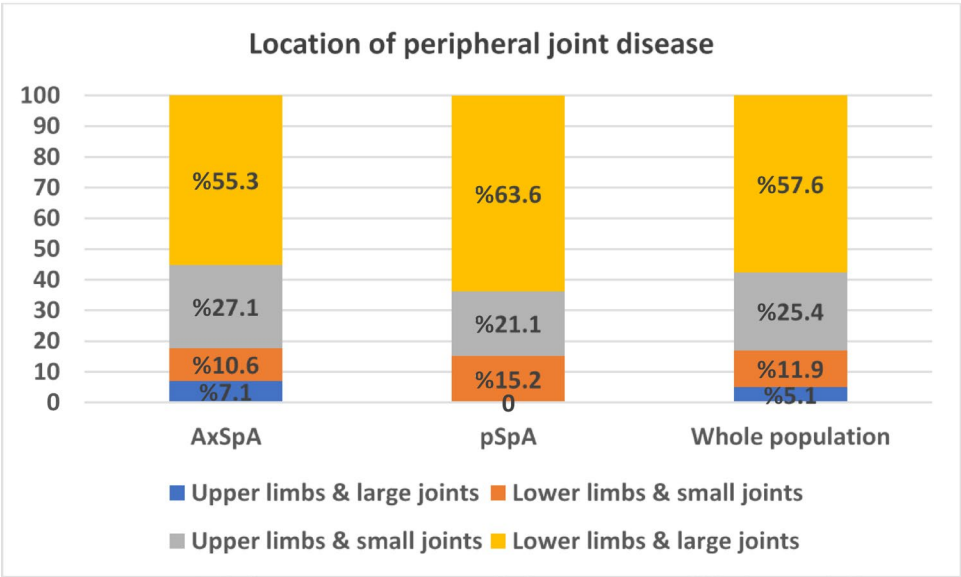


Fig. 1 The distribution of affected joints according to AxSpA and pSpA

enthesitis, dactylitis, psoriasis, family history of psoriasis, never smoking and never alcohol intake were associated with peripheral arthritis [8]. The impact of smoking and alcohol consumption on peripheral manifestations was investigated in detail and updated in the ASAS-perSpA study [29]. This study showed that smoking and alcohol use were associated with a lower prevalence of peripheral manifestations in SpA patients. Furthermore, ever smoking was negatively associated with ever peripheral arthritis and current alcohol consumption was associated with a lower prevalence of current arthritis in AxSpA patients. However, the similar association was not valid in pSpA group. In an another study investigating the effect of alcohol intake on disease activity in AxSpA, the frequency of peripheral arthritis was not different in drinking and non-drinking groups [30]. We found that enthesitis, dactylitis, and high CRP level at diagnosis were positively associated with PJD, whereas ever alcohol intake, sacroiliitis on MRI, and family history of SpA were negatively associated. Unlike other studies, the negative association of sacroiliitis on MRI and family history for SpA with PJD can be clarified by the fact that almost all patients in the PJD- group are AxSpA patients.

Unsurprisingly, in our study, the rate of csDMARD use was significantly higher in the PJD + group. This rate was lower in the AxSpA group when comparing PJD + AxSpA and pSpA patients. According to ASAS-EULAR recommendations, sulfasalazine is a treatment option in case of

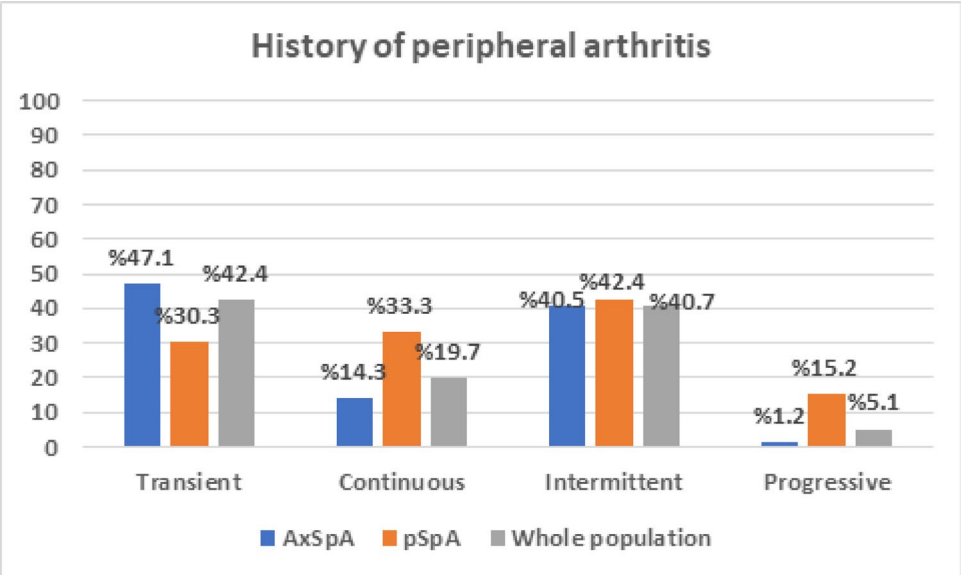


Fig. 1 (continued)

Table 4 Results of univariable and multivariable analyses for the associated factors of PJD in axSpA and perSpA patients

Predictors	Univariable analysis		Multivariable analysis regression model (Backward) ($n=321$)	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex (male)	0.61 (0.39–0.94)	0.027		
Smoking (ever)	0.75 (0.49–1.15)	0.194		
Alcohol (ever)	0.68 (0.41–1.13)	0.135	0.48 (0.24–0.92)	0.029
Inflammatory back pain	0.61 (0.27–1.35)	0.223		
Enthesitis	4.27 (2.68–6.79)	<0.001	3.83 (2.16–6.78)	<0.001
Dactylitis	6.29 (1.93–20.51)	0.002	5.05 (1.38–18.47)	0.014
Uveitis	2.29 (1.31-4.00)	0.004		
Psoriasis	2.11 (0.75–5.96)	0.158		
Inflammatory bowel disease	3.27 (1.11–9.65)	0.032		
High CRP at diagnosis	1.6 (0.99–2.57)	0.053	1.98 (1.06–3.69)	0.033
Sacroiliitis on MRI	0.32 (0.13–0.80)	0.015	0.25 (0.09–0.69)	0.008
Family history for SpA	0.47 (0.31–0.74)	0.001	0.51 (0.29–0.91)	0.022

peripheral arthritis [31] This recommendation includes the management of peripheral arthritis in AxSpA patients. To date, no specific treatment recommendations for pSpA have been published. We consider that this deficiency has led to an increased use of csDMARDs in pSpA patients. In data from a recently published Irish axial spondyloarthritis cohort, peripheral arthritis and dactylitis were frequently observed together; however, each manifestation was independently associated with worse clinical outcomes. It has been reported that patients with peripheral arthritis have a higher disease burden and therefore use csDMARDs, such as methotrexate and sulfasalazine, more frequently [32].

Our study has several strengths and some limitations. One limitation is that our results cannot be generalized to all AxSpA and pSpA patients due to the cross-sectional design of the study. Another limitation is the difficulty in correctly assessing peripheral manifestations, including PJD, that occurred before the study visit. The final limitation is that the number of pSpA patients is much lower than those with AxSpA, which may limit the validity of our results for pSpA patients. Despite these limitations, the strengths of the study are as follows: The participation of 13 different centers from Turkey in the study increases the possibility that our results reflect the Turkish population. The objective confirmation of synovitis in 80% of PJD + patients indicates that peripheral arthritis is correctly detected. Since the ASAS-perSpA study is the first to present the course of peripheral arthritis in AxSpA and pSpA patients, our study provides actual information on this subject.

In conclusion, we have presented the characteristics of peripheral joint disease and its associated factors in AxSpA and pSpA patients. The prevalence of PJD in our cohort was 30%, and it was four times more common in pSpA patients. The coexistence of PJD with other peripheral involvements and extra-musculoskeletal manifestations excluding psoriasis was widespread. Dactylitis, enthesitis, and high CRP level were positively associated with PJD; on the contrary, alcohol intake, presence of sacroiliitis on MRI, and family history of SpA were negatively associated. It is clear that studies with a large number of pSpA patients are needed to investigate the characteristics and course of PJD, which is the most prevelant peripheral finding in SpA patients.

Disclosure of interest

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Author contributions ES, MTD, HHG, and UK conceived and designed the study. ES, HHG, İA, SA, SH, NŞ, ÖA, MAM, İS, ŞA, FGUN, EÇ, and FY collected and analyzed the data. ES and UK contributed to the interpretation of the results. ES, MTD, HHG and UK drafted and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for the integrity and accuracy of all aspects of the work.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interest.

Ethical approval The study has been approved by the Marmara University Clinical Research Ethics Committee (09.2018.576).

Informed consent Informed consent was obtained from all individual participants included in the study.

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