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Original article

Root joint involvement in spondyloarthritis: a *post hoc* analysis from the international ASAS-PerSpA study

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Abstract

Objectives. The primary objective was to compare the clinical characteristics of SpA patients with and without root joint disease (RJD+ and RJD–). The secondary objectives were to compare the prevalence of RJD across various SpA subtypes and in different world regions, and to compare the SpA axial severity and SpA burden between RJD+ and RJD–.

Methods. This is a *post hoc* analysis of the Assessment of Spondyloarthritis International Society PerSpA study (PERipheral involvement in SpondyloArthritis), which included 4465 patients with SpA [axial (axSpA), peripheral (pSpA), PsA, IBD, reactive and juvenile] according to the rheumatologist's diagnosis. RJD was defined as the 'ever' presence of hip or shoulder involvement related to SpA, according to the rheumatologist. Patient characteristics were compared between RJD+ and RJD–. Multivariable stepwise binary logistic regression analyses were conducted to identify factors associated with 'RJD', 'hip' and 'shoulder' involvement.

Results. RJD was significantly associated with the SpA main diagnosis (highest in pSpA), a higher prevalence of HLA-B27 positivity, enthesitis, tender and swollen joints, CRP, conventional synthetic DMARDs, loss of lumbar lordosis and occiput-wall distance >0. RJD was more prevalent in Asia, and occurred in 1503 patients (33.7%), with more hip (24.2%) than shoulder (13.2%) involvement. Hip involvement had a distinct phenotype, similar to axSpA (including younger age at onset, HLA-B27 positivity), whereas shoulder involvement was associated with features of pSpA (including older age at onset).

Conclusion. RJD+ SpA patients had a distinctive clinical phenotype compared with RJD–. Hip involvement, based on the rheumatologist's diagnosis, was more prevalent than shoulder involvement and was clinically distinct.

Key words: spondyloarthritis, root joint disease, hip, shoulder, disease phenotype, epidemiology

Rheumatology key messages

- Root joint disease occurs in 33.7% of patients with SpA and is more prevalent in the hip than the shoulder.
- Root joint disease occurs more frequently in Asia.
- Hip involvement had a distinct phenotype resembling axSpA, whereas shoulder involvement was associated with features of peripheral SpA.

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CLINICAL SCIENCE

Introduction

SpA is a group of inflammatory rheumatic disorders that mostly involve the axial skeleton, starting in the sacroiliac joints [1]. The Assessment of SpondyloArthritis international Society (ASAS) introduced the classification criteria of axial SpA (axSpA) in 2009 and peripheral SpA (pSpA) in 2011, depending on the existence of predominantly axial or predominantly peripheral involvement, respectively [2–4]. Peripheral joint involvement may exist in both entities but is expectedly more severe and frequent among patients with pSpA [5].

The concept of root joint disease (RJD) started emerging in the 1980s, when hip involvement was observed to conjoin the axial form of SpA, as part of a same disease spectrum [6]. Further reports confirmed that both hip and shoulder involvement were correlated with a more severe course of the axial involvement and worse spinal mobility [6–11]. This observation prompted the concept that hips, along with the shoulders, should be considered as 'root joints' [6, 9, 12], which behave more comparatively to the spine than to the peripheral joints, and can have a different impact on the disease than for example small joint involvement. Nevertheless, there is no universal agreement on the root joint definition or on its classification within the axial or the peripheral skeleton.

Most studies evaluating hip involvement are focussed on radiographic axSpA. Among this population, clinical hip impairment prevalence varies between 9 and 36% [8–10, 13]. Ethnic and geographic differences may explain this variability, as, for example, North African patients seem to have more frequent hip involvement than French patients [14].

It is consistent in all datasets that hip involvement is associated with early age at disease onset [6, 8, 13, 15–18]. This may explain why patients with juvenile onset of axSpA (i.e. age at disease onset $<$16 years) showed higher frequency of functional impairment and surgical hip replacement [13].

Furthermore, less data are available regarding shoulder involvement in SpA, and this localization is sometimes overlooked [19]. The reported prevalence ranges from 7 to 33% when based on clinical evaluation and reaches 49% when based on MRI studies [20], with a higher prevalence among patients with long-standing axSpA [21–23]. The pattern of shoulder involvement is more heterogeneous compared with hip involvement, and may include sternoclavicular joint or acromioclavicular joint involvement, increased joint fluid in the glenohumeral joint, entheseal bone marrow oedema and tendonitis [19, 20, 23]. Shoulder involvement may be less linked with disability [21] but is associated in other reports with hip and knee joints involvement and with a worse spinal mobility [21, 22].

Apart from the relationship between RJD and axial disease, the information about the association between RJD and other SpA features, such as HLA-B27 status or extra-musculo-skeletal manifestations, is inconsistent [9, 17, 24]. Moreover, when studying the overall SpA population, the radiographic hip findings were not associated with inflammatory back pain or radiographic sacroiliitis [25]. This emphasizes the need to study RJD in the overall SpA population, along with isolated axSpA.

The ASAS-PerSpA (PERipheral involvement in SpondyloArthritis) study [26] includes one of the largest ever international SpA cohorts and therefore represents a unique opportunity to investigate these pending queries and identify regional differences in RJD prevalence.

The primary objective of the present *post hoc* analysis was to compare the clinical characteristics of SpA patients with and without RJD (RJD+ and RJD–). Secondary objectives were to compare the prevalence of RJD across the various SpA subtypes and in different world regions, and to compare the SpA axial severity as well as the disease burden in terms of patient-reported outcomes (PROs) between RJD+ and RJD– SpA patients.

Methods

Study design

This is a *post hoc* analysis of ASAS-PerSpA, which was an observational, cross-sectional, multicentre, international study that involved 4465 patients in 24 countries and aimed at evaluating the peripheral involvement of SpA and PsA [26].

Patients

All participants from the ASAS-PerSpA study were included in this analysis. To be enrolled in the study, patients had to be diagnosed by their treating physician with axSpA, pSpA and/or PsA. Thereafter, the treating physician had to choose only one answer (main disease) to the following question: 'In your opinion which is the disease that better describes your patient?', with the following possible answers: axSpA, pSpA, PsA, IBD-associated SpA (IBD-SpA), reactive arthritis or juvenile SpA (Juv-SpA).

The study was approved by all local the Ethics Committees of the participating sites. All patients signed an informed consent form prior to enrolment in the study.

Data collected

The details of the collected data in ASAS-PerSpA have been previously reported [26]. The data were collected during a single routine visit to the rheumatologist and included:

i. The involved joints including RJD related to SpA. RJD was defined as a positive answer by the investigator to the following question: 'Do you consider that the patient has ever suffered from RJD (e.g. hip, shoulder) related to SpA?' In case of a positive answer, a

potential specific treatment (e.g. total articular replacement) was investigated. There was no obligation to document the involvement by imaging in the original protocol.

ii. The demographic data including age, gender, BMI, smoking, socio-educational level and family history of SpA, PsA, uveitis and IBD.

iii. The disease phenotype including the age at first SpA symptom, diagnostic delay, HLA-B27, tender joint count (TJC) using the Ritchie Articular Index [27], 66 swollen joint count (SJC) [28], Mander enthesitis index [29], dactylitis and treatment with conventional synthetic DMARDs (csDMARDs) and biological DMARDs (bDMARDs).

iv. The indicators of axial disease severity: bamboo spine, loss of lumbar lordosis, thoracic kyphosis, occiput-to-wall distance (OWD) >0 and spinal vertebrotomy.

v. The markers of disease activity: CRP, BASDAI [30] and Ankylosing Spondylitis Disease Activity Score calculated with CRP (ASDAS) [31].

vi. The PROs: Patient Global Assessment of well-being (PGA) collected on a numerical scale from 0 to 10, BASFI [32], ASAS Health Index (ASAS-HI) [33], Work Productivity and Activity Impairment Instrument (WPAI) [34], EuroQOL-5D (EQ-5D) [35] and Fibromyalgia Rapid Screening Tool (FiRST) [36].

Statistical analysis

The prevalence and CIs of RJD, hip or shoulder involvement alone or in combination were calculated.

The clinical characteristics (demographic data and disease characteristics) were compared between patients with and without RJD (RJD+ and RJD−), and among patients with different RJD sites: hip, shoulder and both involvements. The characteristics were also compared between patients with hip (hip+) and shoulder (shoulder+) involvement, and patients without hip (hip−) or shoulder (shoulder−) involvement, respectively.

The prevalence of RJD was compared across five categories of SpA (axSpA, pSpA, PsA, ReA + IBD-SpA, Juv-SpA + Other SpA) and across four regions of the world [Europe + North America, Middle East and North Africa (MENA), Latin America and Asia], following the adopted grouping in the main manuscript.

The indicators of disease severity, disease activity and PROs were also compared between patients with and without RJD, with and without hip or shoulder involvement, and among the RJD sites.

Continuous variables were expressed by mean (S.D.) and categorical variables as counts and percentages. Comparison of the characteristics between patients with and without RJD, with and without hip involvement and with and without shoulder involvement and among RJD sites was performed using the Pearson χ^2 or Fisher test for the categorical variables and the *t*-test or analysis of variance for the continuous variables.

Moreover, among patients with hip involvement, the characteristics of those who had hip replacement were compared with those without hip replacement, using the Pearson χ^2 or Fisher test for the categorical variables and the *t*-test for the continuous variables. A multivariable stepwise binary logistic regression analysis was conducted to identify factors associated with hip replacement.

Furthermore, three multivariable stepwise binary logistic regression analyses were conducted to identify factors associated with the dependent binary variable 'RJD', 'hip involvement' and 'shoulder involvement'. Age at first symptom was transformed in a binary variable in this analysis, using the median as a cut-off. All independent variables with a *P*-value <0.1 in the univariate analysis were considered in the multivariable logistic regression analysis; adjusted odds ratios after controlling for all the variables in the model were presented with their CIs; *P*-values <0.05 were accepted as statistically significant. All statistical analyses were performed using SPSS v20 (IBM, online).

Results

Patients' demographics according to the presence of RJD

Patients with RJD had a significantly younger age at study inclusion (43.2 *vs* 45.0 years, $P < 0.001$), a higher prevalence of male gender (64.9 *vs* 59.0%, $P < 0.001$), a lower BMI (25.9 *vs* 26.5 kg/m^2, $P = 0.001$) and a lower smoking rate (39.5 *vs* 44.2%, $P = 0.003$) compared with patients without RJD. RJD was negatively associated with a family history of psoriasis (9.9 *vs* 12.3%, $P < 0.001$) (Table 1).

Disease characteristics and phenotype according to the presence of RJD

RJD+ patients had a significantly younger age at SpA onset (28.9 *vs* 30.9 years, $P < 0.001$), a younger age at first axial symptoms (28.6 *vs* 30.8 years, $P < 0.001$) and had different association with SpA categories ($P < 0.001$): more frequent axSpA (61.3 *vs* 60.7%), pSpA (12.8 *vs* 8.1%) and Juv-SpA + Other SpA (3.9 *vs* 1.8%) compared with RJD– patients.

Furthermore, RJD+ patients had more frequently positive HLA-B27 (49.4 *vs* 44.7%, $P < 0.001$), more enthesitis (55.1 *vs* 39.1%, $P < 0.001$), more uveitis (19.2 *vs* 15.2%, $P = 0.001$), a higher TJC (3.4 *vs* 2.1 joints, $P < 0.001$) and SJC (1.0 *vs* 0.7 joints, $P = 0.002$), and a higher use of cs-DMARDs (76.4 *vs* 62.1%, $P < 0.001$) compared with RJD– patients. Nevertheless, they had less psoriasis (21.8 *vs* 29.9%, $P < 0.001$) and PsA (18.4 *vs* 25.6%, $P < 0.001$) (Table 1).

The comparison of the patients' demographics and disease characteristics among different RJD sites is shown in Table 1. The comparison between patients with hip+ *vs* hip− and shoulder+ *vs* shoulder−, respectively, is shown in supplementary Table S1, available at *Rheumatology* online.

Table 1 Patients and disease's characteristics according to the presence of RJD and to presence of hip, shoulder and both sites involvement

	All	RJD involvement +	RJD involvement –	*P*-value	Hip involvement	Shoulder involvement	Hip and shoulder involvement	*P*-value
Number of patients	4465	1503	2962		783	290	299	
Patients' demographics								
Age (years), mean (s.d.)[a]	44.40 (13.97)	43.22 (13.91)	45.00 (13.97)	<0.001	40.79 (13.26)	47.45 (13.91)	44.86 (14.14)	0.002
Male gender, *N* (%)[a]	2724 (61.0)	975 (64.9)	1749 (59.0)	<0.001	544 (69.5)	158 (54.5)	196 (65.6)	<0.001
BMI, mean (s.d.)[b]	26.34 (5.39)	25.95 (5.71)	26.54 (5.22)	0.001	25.74 (5.54)	25.92 (5.61)	26.10 (6.34)	0.141
Ever smokers, *N* (%)[b]	1900 (42.6)	593 (39.5)	1307 (44.2)	0.003	306 (39.1)	117 (40.3)	109 (36.5)	0.257
Socio-educational level, *N* (%)				0.329				0.066
Primary school	737 (16.5)	231 (15.4)	506 (17.1)		126 (16.1)	41 (14.1)	47 (15.7)	
Secondary school	1909 (42.8)	649 (43.2)	1260 (42.6)		312 (39.8)	140 (48.3)	138 (46.2)	
University	1815 (40.7)	623 (41.5)	1192 (40.3)		345 (44.1)	109 (37.6)	114 (38.1)	
Family history of SpA, *N* (%)	659 (14.8)	225 (15.5)	434 (15.7)	0.901	125 (16.6)	38 (13.8)	50 (17.3)	0.125
Family history of psoriasis, *N* (%)[a]	512 (11.5)	149 (9.9)	363 (12.3)	<0.001	44 (5.6)	61 (21.0)	19 (6.4)	<0.001
Family history of uveitis, *N* (%)	92 (2.1)	34 (2.3)	58 (2.0)	0.632	15 (2.0)	8 (2.9)	9 (3.2)	0.595
Family history of IBD, *N* (%)	92 (2.1)	30 (2.0)	62 (2.1)	0.701	15 (2.1)	7 (2.6)	7 (2.5)	0.674
Diagnosis								
Age at first SpA symptom, mean (s.d.)[a]	30.27 (12.94)	28.88 (12.73)	30.98 (12.99)	<0.001	26.96 (11.65)	33.67 (13.53)	29.90 (14.08)	0.005
Age at first axial symptom, mean (s.d.)[a]	30.3 (12.01)	28.60 (12.06)	30.82 (11.92)	<0.001	27.16 (11.07)	33.07 (12.91)	29.81 (13.39)	<0.001
Diagnostic delay, mean (s.d.)[c]	6.60 (8.59)	6.29 (7.95)	6.76 (8.89)	0.081	5.62 (7.16)	6.91 (8.77)	6.85 (8.18)	0.007
SpA category, *N* (%)[a]				<0.001				
1 axSpA	2719 (60.9)	921 (61.3)	1798 (60.7)		549 (70.1)	118 (40.7)	177 (59.2)	
2 PsA	1033 (23.1)	276 (18.4)	757 (25.6)		92 (11.7)	101 (34.8)	42 (14.0)	
3 pSpA	433 (9.7)	192 (12.8)	241 (8.1)		90 (11.5)	38 (13.1)	59 (19.7)	
4 ReA + IBD SpA	168 (3.8)	55 (3.7)	113 (3.8)		26 (3.3)	17 (5.9)	10 (3.3)	
5 Juvenile + Other SpA	112 (2.5)	59 (3.9)	53 (1.8)		26 (3.3)	16 (5.5)	11 (3.7)	
Disease phenotype								
Hip involvement, *N* (%)[a]	1082 (24.2)	1082 (71.9)	0 (0	<0.001	783 (72.4) (of all hip)	0 (0	299 (27.6) (of all hip)	<0.001
Shoulder involvement, *N* (%)[a]	589 (13.2)	589 (39.2)	0 (0	<0.001	0 (0	290 (49.2) (of all shoulder)	299 (50.8) (of all shoulder)	<0.001
HLA-B27, *N* (%)[a]	2066 (46.3)	743 (49.4)	1323 (44.7)	<0.001	423 (77.2)	89 (50.9)	168 (78.1)	<0.001
Enthesitis, *N* (%)[a]	1984 (44.4)	828 (55.1)	1156 (39.0)	<0.001	381 (48.7)	165 (56.9)	193 (64.5)	<0.001
Dactylitis, *N* (%)[c]	685 (15.3)	245 (16.3)	440 (14.9)	0.205	76 (9.7)	80 (27.6)	66 (22.1)	<0.001
TJC, Mean (s.d.)[a]	3.5 (8.6)	3.39 (7.59)	2.07 (5.03)	<0.001	2.17 (5.59)	4.18 (9.26)	4.92 (8.76)	<0.001

(continued)

TABLE 1 Continued

	All	RJD involvement +	RJD involvement –	*P*-value	Hip involvement	Shoulder involvement	Hip and shoulder involvement	*P*-value
SJC, Mean (S.D.)[a]	0.82 (3.2)	1.05 (3.91)	0.70 (2.76)	0.002	0.65 (3.32)	1.49 (5.14)	1.31 (3.89)	<0.001
Psoriasis, *N* (%)[a]	1212 (27.1)	327 (21.8)	885 (29.9)	<0.001	117 (14.9)	111 (38.3)	55 (18.4)	<0.001
Uveitis, *N* (%)[a]	738 (16.5)	288 (19.2)	450 (15.2)	0.001	160 (20.4)	22 (11.4)	69 (23.1)	0.002
IBD, *N* (%)[c]	275 (6.2)	102 (6.8)	173 (5.8)	0.120	50 (6.4)	30 (10.3)	18 (6.0)	0.033
csDMARDs, *N* (%)[a]	2987 (66.9)	1148 (76.4)	1839 (62.1)	<0.001	561 (71.6)	245 (84.5)	244 (81.6)	<0.001
bDMARDs, *N* (%)	2647 (59.3)	916 (60.9)	1731 (58.4)	0.107	500 (63.9)	124 (42.8)	130 (43.5)	0.073

[a]All percentages are calculated in columns. *P*-value <0.05 for RJD+/RJD– comparison and RJD site comparison. [b]*P*-value <0.05 for comparison RJD+/RJD– only. [c]*P*-value <0.05 for RJD site comparison only. axSpA: axial SpA; bDMARDS: biological DMARDs; csDMARDs: conventional synthetic DMARDs; pSpA: peripheral SpA; ReA: reactive SpA; RJD: root joint disease; SJC: swollen joint count; TJC: tender joint count.

Prevalence of RJD, hip and shoulder involvement in the cohort

RJD occurred in 1503/4465 patients [33.7% (95% CI 32.3, 35.1)]. The location (hip/shoulder) of RJD was not available in 131/4465 patients (2.9%). For the remaining 1372 patients with known location, hip involvement was mentioned in 1082 patients [24.2% (95% CI 23.0, 25.5) of the total 4465 patients], shoulder involvement in 589 patients [13.2% (95% CI 12.2, 14.2)], and involvement of both in 299 patients [6.7% (95% CI 6.0, 7.5)] (supplementary Fig. S1, available at *Rheumatology* online). Hip and shoulder involvement were significantly associated with each other, i.e. patients with hip involvement had significantly more frequently shoulder involvement compared with those without hip involvement ($P < 0.001$).

Prevalence of RJD in the different SpA categories

RJD showed differences in its prevalence among the different SpA subtypes, with the highest prevalence in Juv-SpA + Other SpA (52.7%), followed by pSpA (44.3%) and axSpA (33.9%) ($P < 0.001$) (Fig. 1). The highest prevalence of hip involvement only was found in pSpA (34.4%), Juv-SpA + Other SpA (33.0%) and axSpA (26.7%). Shoulder involvement was more frequent in Juv-SpA + Other SpA (24.1%) and pSpA (22.4%), while it was the least prevalent in axSpA (10.8%).

Prevalence and characteristics of RJD in patients with SpA across the regions

The highest prevalence of RJD, hip and shoulder involvement across the world regions was found in Asia (57.4, 44.3 and 23.3%, respectively) ($P < 0.001$) (Fig. 2). The lowest prevalence in all categories were found in Europe and North America.

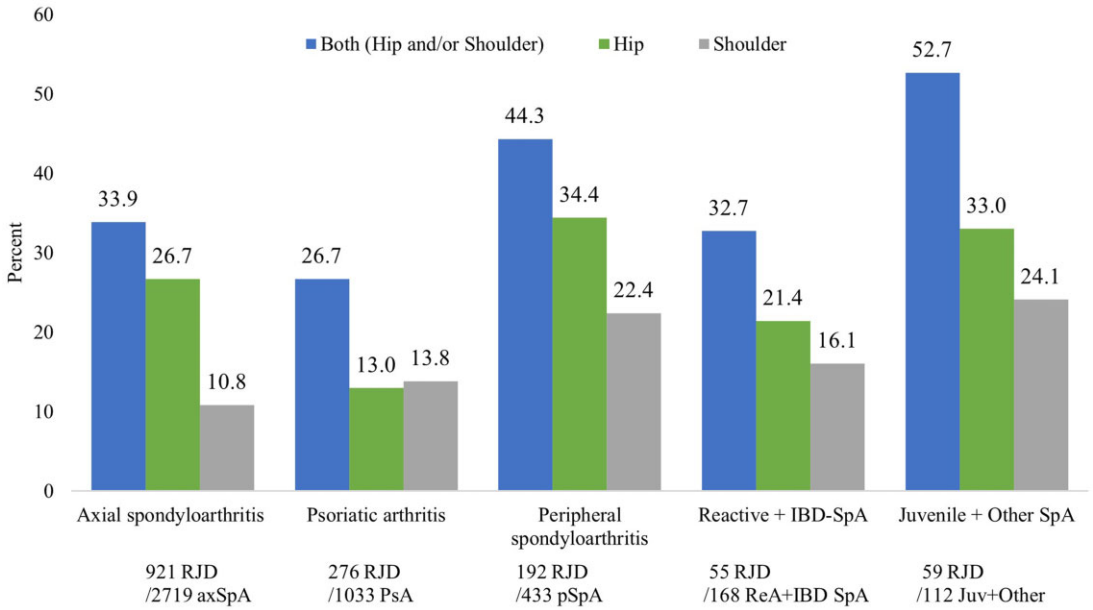
In addition to the difference in RJD prevalence between various regions, patients from Asia were younger, had the youngest age at initial symptoms of hip and shoulder involvement and the shortest duration of hip and shoulder involvement, and, interestingly, the shortest diagnostic delay (Table 2).

Regarding treatment specifically given for RJD, patients from Asia significantly had the highest use of treatments for RJD in general. Patients from Latin America had the highest use of NSAIDS and csDMARDS, whereas patients from Europe and North America had the highest use of bDMARDS and local steroid injections. Among patients with hip involvement, 6.0% had a history of hip replacement (highest in the MENA region and Latin America); among patients with shoulder involvement, 0.8% had a history of shoulder replacement.

Axial disease severity according to the presence of RJD

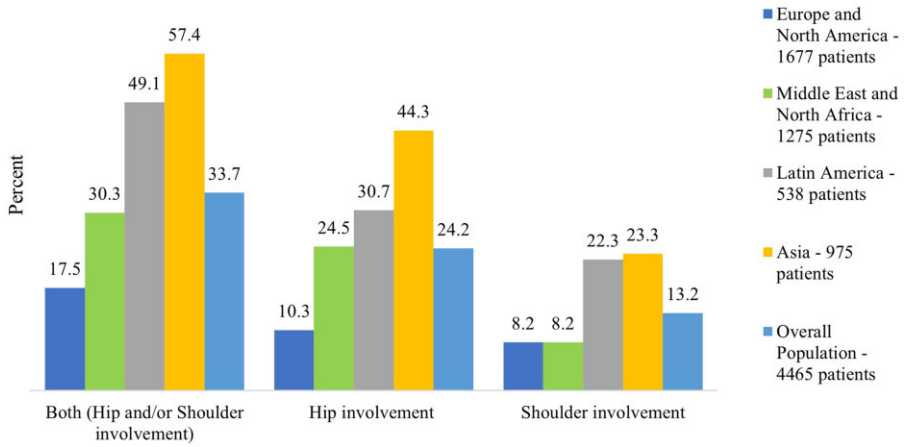
Patients with RJD had a significantly higher prevalence of bamboo spine, of loss of lumbar lordosis, of thoracic kyphosis and of OWD >0 cm compared with patients without RJD (Table 3, all $P < 0.001$).

Fig. 1 Prevalence of involvement of hip, shoulder or both according to SpA subtypes



axSpA: axial SpA; Juv-SpA: juvenile SpA ; pSpA: peripheral SpA; ReA: reactive SpA; RJD: root joint disease.

Fig. 2 Prevalence of root joint involvement across the regions



The comparison of the axial disease severity among different RJD sites is shown in Table 3, and between patients with hip+ *vs* hip− and shoulder+ *vs* shoulder−, respectively, in supplementary Table S2, available at *Rheumatology* online.

Burden of SpA according to the presence of RJD

RJD+ patients as a group, as well as hip and shoulder involvement taken individually, were significantly associated with higher disease activity as measured by CRP, BASDAI and ASDAS-CRP ($P < 0.001$) (Table 3, supplementary Table S2, available at *Rheumatology* online) compared with patients without RJD, hip and shoulder involvement, respectively. They also had worse PROs, i.e. PGA, BASFI, ASAS-HI, WPAI, EQ-5D and FiRST scores.

Regarding the RJD sites, patients with hip involvement had a higher CRP and a higher ASDAS compared with patients with shoulder involvement. However, patients with both hip and shoulder involvement had the highest disease activity scores compared with each RJD site alone. Similarly, patients with both hip and shoulder involvement had the worse PROs scores (PGA, BASFI, ASAS-HI, WPAI, EQ-5D and FiRST) compared with each RJD site alone (Table 3).

Table 2 Characteristics of patients with RJD across the world

	All	Europe and North America	MENA	Latin America	Asia	*P*-value[c]
Patients with RJD, *N* (%)[a]	1503 (33.7)	293 (17.5)	386 (30.3)	264 (49.1)	560 (57.4)	<0.001
Age of participants (years), mean (S.D.)	43.22 (13.91)	50.17 (13.07)	41.68 (12.50)	46.55 (13.74)	39.08 (15.60)	<0.001
Age at first SpA symptom (years), mean (S.D.)	28.88 (12.73)	30.22 (13.68)	28.65 (11.71)	30.61 (13.05)	27.50 (12.60)	0.002
Age at first hip involvement (years), mean (S.D.)	32.36 (13.55)	37.3 (14.64)	32.3 (12.65)	35.30 (14.19)	29.30 (12.66)	<0.001
Age at first shoulder involvement (years), mean (S.D.)	36.29 (13.69)	41.41 (13.98)	38.96 (12.88)	35.20 (12.54)	33.93 (14.27)	0.007
Duration of hip involvement (years), mean (S.D.)	9.52 (8.77)	13.15 (11.15)	8.44 (7.26)	10.95 (9.29)	8.31 (7.99)	<0.001
Duration of the shoulder involvement (years), mean (S.D.)	8.50 (8.92)	11.94 (9.66)	7.58 (6.18)	11.37 (10.35)	5.37 (7.27)	<0.001
Diagnostic delay (years), mean (S.D.)	6.30 (7.94)	7.47 (9.56)	6.21 (6.71)	7.40 (8.65)	5.19 (7.27)	<0.001
Treatments specifically for RJD, *N* (%)[a]	1257 (28.2)	273 (16.3)	236 (18.5)	249 (46.3)	499 (51.2)	<0.001
NSAIDs[b]	1191 (79.2)	248 (84.6)	216 (56.0)	241 (91.3)	486 (86.8)	<0.001
csDMARDS[b]	686 (45.6)	129 (44.0)	90 (23.3)	185 (70.1)	282 (50.4)	<0.001
bDMARDS[b]	455 (30.3)	113 (38.6)	85 (22.0)	79 (29.9)	178 (31.8)	<0.001
Local steroid injection[b]	215 (14.3)	84 (28.7)	60 (15.5)	28 10.6)	43 (7.7)	<0.001
Hip replacement[b]	65 (4.3)	17 (5.8)	24 (6.2)	16 (6.1)	8 (1.4)	<0.001
Shoulder replacement[b]	5 (0.3)	2 (0.7)	1 (0.3)	1 (0.4)	1 (0.2)	0.358

[a]Percentage from the overall population. [b]Percentage from patients with RJD. [c]The *P*-value reflects the statistical significance of the difference between the 4 regions of the world. bDMARDS: biological DMARDs; csDMARDs: conventional synthetic DMARDs; MENA: Middle East and North Africa region; RJD: root joint disease.

Phenotype of patients with hip replacement

Among patients with hip involvement, 5.4% had a hip replacement. In addition to being more prevalent in the MENA region, hip replacement was positively associated in the univariate analysis with age, disease duration, more frequent use of bDMARDs, bamboo spine, loss of lumbar lordosis, thoracic kyphosis, OWD >0 and BASFI. It was negatively associated with enthesitis, dactylitis and FiRST score. In the multivariable analysis, patients with hip replacement had a higher use of bDMARDs, a lower prevalence of enthesitis and a lower FiRST score compared with patients without hip replacement.

There was no difference with regards to other outcome measures (BASDAI, ASDAS, ASAS-HI, ASDAS, WPL, EQ-5D), nor to gender, HLA-B27 and extra-musculoskeletal manifestations.

Patients and disease characteristics associated with RJD in the multivariable analysis

In the multivariable analysis, RJD was significantly associated with the world region (highest in Asia), the SpA main diagnosis (highest in pSpA), a higher prevalence of HLA-B27 positivity and of enthesitis, higher TJC, SJC and CRP, more frequent treatment with csDMARDs, more loss of lumbar lordosis and OWD >0 (supplementary Table S3, available at *Rheumatology* online).

Compared with patients without hip involvement, hip involvement was significantly associated with the world region (highest in Asia), the SpA main diagnosis (highest in pSpA, lowest in PsA), a younger age at first SpA symptom, a higher prevalence of HLA-B27 positivity, more frequent treatment with csDMARDs and bDMARDs, more OWD >0, and a lower prevalence of family history of psoriasis (Fig. 3, supplementary Table S4, available at *Rheumatology* online).

Compared with patients without shoulder involvement, shoulder involvement was associated in the multivariable analysis with the world region (highest in Asia), the SpA main diagnosis (highest in Juv-SpA, pSpA and PsA), an older age at first SpA symptom, a higher prevalence of enthesitis, dactylitis, TJC, IBD, OWD >0, treatment with csDMARDs and EQ-5D (Fig. 3, supplementary Table S4, available at *Rheumatology* online).

Discussion

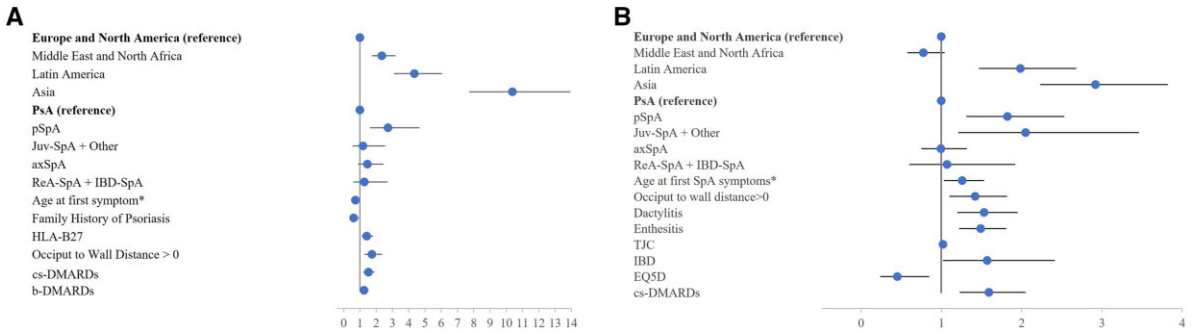
This is the first and largest observational study to describe the prevalence and the clinical characteristics of both hip and shoulder involvement across a whole spectrum of SpA patients. This worldwide analysis through

Table 3 Axial disease severity and SpA global burden according to the presence of RJD, hip and shoulder involvement

	All	RJD involvement +	RJD involvement -	*P*-value	Hip involvement	Shoulder involvement	Hip and shoulder involvement	RJD with unspecified site	*P*-value
Number of patients	4465	1503	2962	<0.001	783	290	299	131	<0.001
Axial disease severity, *N* (%)									
Bamboo spine[a]	496 (11.1)	237 (15.8)	259 (8.7)	<0.001	151 (19.3)	20 (6.9)	45 (15.1)	21 (16.0)	<0.001
Loss of lumbar lordosis[a]	1292 (28.9)	566 (37.7)	726 (24.5)	<0.001	325 (41.5)	84 (29.0)	105 (35.1)	52 (39.7)	<0.001
Thoracic kyphosis[a]	812 (18.2)	371 (24.7)	441 (14.9)	<0.001	216 (27.6)	41 (14.1)	82 (27.4)	32 (24.4)	0.002
OWD >0[a]	951 (21.3)	459 (30.5)	492 (16.6)	<0.001	265 (33.8)	46 (15.9)	109 (36.5)	39 (29.8)	<0.001
Spinal vertebrotomy	52 (1.2)	21 (1.4)	31 (1.0)	0.302	15 (1.9)	1 (0.3)	3 (1.0)	2 (1.5)	0.215
Disease activity, mean (S.D.)									
CRP (mg/l)[a]	11.93 (26.67)	15.05 (28.8)	10.34 (25.38)	<0.001	14.02 (26.36)	11.47 (24.73)	21.55 (39.51)	14.38 (18.67)	<0.001
BASDAI[a]	3.86 (2.43)	4.14 (2.46)	3.71 (2.40)	<0.001	3.82 (2.37)	4.08 (2.48)	4.73 (2.53)	4.84 (2.48)	<0.001
ASDAS[a]	2.54 (1.14)	2.77 (1.18)	2.42 (1.09)	<0.001	2.67 (1.55)	2.59 (1.11)	3.09 (1.24)	3.12 (1.16)	<0.001
PROs, mean (S.D.)									
PGA[a]	4.37 (2.70)	4.81 (2.68)	4.15 (2.68)	<0.001	4.61 (2.61)	4.47 (2.66)	5.30 (2.73)	5.65 (2.71)	<0.001
BASFI score[a]	2.98 (2.65)	3.57 (2.88)	2.69 (2.48)	<0.001	3.39 (2.84)	3.11 (2.78)	4.11 (2.96)	4.36 (2.86)	<0.001
ASAS-HI[a]	6.58 (4.58)	7.53 (4.70)	6.09 (4.44)	<0.001	7.11 (4.68)	7.32 (4.61)	8.44 (4.69)	8.46 (4.66)	<0.001
Work productivity loss[a]	26.10 (18.70)	29.97 (26.72)	24.34 (25.25)	<0.001	27.12 (18.41)	25.96 (18.37)	30.55 (18.63)	31.76 (20.65)	0.001
EQ-5D[a]	0.65 (0.24)	0.61 (0.24)	0.68 (0.23)	<0.001	0.64 (0.25)	0.62 (0.23)	0.56 (0.24)	0.56 (0.26)	<0.001
FiRST score[a]	2.33 (1.94)	2.52 (2.03)	2.24 (2)	<0.001	2.25 (1.98)	2.50 (2.00)	2.95 (2.03)	3.16 (2.09)	<0.001

All percentages are calculated in columns. [a]*P*-value < 0.001 for total RJD comparison and RJD site comparison. ASAS-HI: ASAS Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; EQ-5D: EuroQOL-5D; FiRST: Fibromyalgia Rapid Screening Tool; OWD: occiput-to-wall distance; PGA: Patient Global Assessment of well-being; PROs: patient-reported outcomes; RJD: root joint disease.

FIG. 3 Results of the multivariable analysis



axSpA: axial SpA; bDMARDs: biological DMARDs; csDMARDs: conventional synthetic DMARDs; EQ-5D: EuroQOL-5D; Juv-SpA: Juvenile SpA; pSpA: peripheral SpA; ReA-SpA: reactive SpA; TJC: total joint count;. *Age at first symptom: >28 years *vs* ≤28 years.

four continents showed that the prevalence of RJD was 33.7% and was mostly driven by the hip involvement, which instigated a separated analysis for the hip and for the shoulder involvement.

The prevalence of hip involvement (24.2% among patients with SpA in general, and 26.7% in patients with axSpA) was consistent with the published prevalence of 9–36% of hip involvement in the axSpA population [8–10, 13, 25]. Moreover, hip involvement was strongly associated with Juv-SpA as well (33%), an association that was previously reported [6, 8, 13, 15–18]. However, hip involvement was unexpectedly highly prevalent in patients diagnosed as pSpA according to the rheumatologist (34.4%), whereas it was the least prevalent in patients with PsA (13.0%), highlighting an important phenotypical difference between the two SpA subtypes. This association with pSpA may indicate either a true relationship that was overlooked in the past due to the high focus on axSpA subtype only [6–11], or a possible classification bias. Nevertheless, these findings emphasize the importance of a systematic iterative check of hip involvement in patients diagnosed with or monitored for SpA, particularly due to negative prognostic value of this involvement. In fact, our study confirmed the association of hip involvement with a more severe axial disease, previously described by Amor *et al.* [37]. It was also associated with a higher use of csDMARDs and bDMARDs, which mirrors more severe disease in general.

Regarding shoulder involvement, this is the first study, to our knowledge, assessing shoulder involvement in thousands of patients with all subtypes of SpA. In contrast to the hip, shoulder involvement was the least prevalent in patients with axSpA (10.8%) compared with patients with Juv-SpA (24.1%) and pSpA (22.4%). The lack of association with axSpA is poorly consistent with previous results [22, 23] and may represent a first argument that contradicts the idea that the shoulder should be classified as a root joint, and as part of the axial rather than the peripheral skeleton. In addition, shoulder involvement was not associated with the use of bDMARDs or with the indices of axSpA severity, except for OWD >0, the clinical significance of which is unexplainable and warrants further dedicated studies.

When analysing the prevalence and characteristics of RJD across the world, our data showed, for the first time, that patients from Asia had the highest prevalence of RJD. In addition, patients from Asia were younger, had the earliest age at hip or shoulder involvement and, interestingly, also had the shortest diagnostic delay. These findings indicate that hip involvement—which was associated with lower age at first SpA symptoms—may be an appealing SpA feature that is useful for an early diagnosis of the disease. This high prevalence of RJD in Asia was associated with a higher use of treatments intended specifically for RJD, which may reflect a higher disease severity, especially when associated with an earlier disease onset [6–11]. Nevertheless, bDMARDS were more frequently used by patients from Europe and North America, which may be related to socio-economical differences between the regions rather to the disease severity *per se* [38]. Moreover, the highest prevalence of hip replacement was found in patients from the MENA region (6.2%), whereas the lowest was found in patients from Asia (1.4%). This result may be partially explained by the lowest use of bDMARDs for RJD in the MENA region.

Regarding the phenotype profile, hip involvement was associated with HLA-B27, after adjusting for other factors such as disease category and world region. This finding settles the inconsistent previous literature about this association [13, 17, 25, 39] and, taken together with earliest disease onset and the correlation with axial disease severity, reinforces that the profile of hip involvement is indeed like the profile of axSpA. Also, this association may indicate that HLA-B27 might also be a genetic risk marker for RJD severity, similar to its relevance to axial disease, although this association needs to be confirmed in further studies using imaging data.

On the other hand, shoulder involvement was not associated with HLA-B27 in our study. Moreover, it was associated with older age at onset and features of peripheral disease, such as dactylitis, enthesitis and peripheral TJC and SJC. This phenotypical profile, which is distinct from the hip profile, is a second argument against considering the shoulder as similar to hip involvement, and against estimating that the shoulder behaves more similarly to the spine than to other peripheral joints [6, 9]. Moreover, shoulder involvement was associated with PsA and IBD, both entities being clearly distinct from axSpA in general and from hip involvement in particular. The association of shoulder involvement with IBD was also in the Swiss IBD Cohort Study (SIBDCS) [40]. Nevertheless, RJD was not necessarily confirmed by imaging in our study. Therefore, shoulder involvement may in fact include patients with rotator cuff disease and acromioclavicular affection [19], which may add to the confusion in the interpretation of this phenotypical profile.

Finally, hip and shoulder involvement were significantly associated with a higher prevalence of OWD >0, indicating changes in postural controls, worse spinal mobility [21] and a significant impact on physical impairment, despite the advancements in SpA management [41]. Moreover, shoulder involvement was also associated with worse EQ-5D, thus indicating a significant impact on the quality of life.

This study has some weaknesses but also some major strengths. One major limitation is the possibility of misclassifying the patient as having pSpA (as main SpA disease) because of the RJD involvement, thus explaining the high percentage of RJD in the pSpA category. Another limitation is that the number of patients with axSpA was larger compared with the other groups, which could have driven the overall prevalence of RJD in this study. Also, the cross-sectional design of the study does not allow for evaluation of cause–effect relationships and may introduce some recall bias regarding manifestations that occurred before the study visit. Hence, a longitudinal study design, with multiple PROs measurements, would be more suitable to draw firm results about the severity and the burden of disease related to RJD. Finally, information about confirmatory imaging was not requested in the electronic case report form and therefore was not available for this analysis. Thus, the decision whether shoulder or hip involvement was solely due to SpA was made by the investigator. Also, the identification of a precise aetiology of the involvement (i.e. articular *vs* periarticular) might have been challenging.

The most important strengths of this study are the large sample of SpA patients (>4400), recruited from several countries and continents of the globe with different ethnic and genetic background, which increases the external validity and the generalizability of the results, as well as the coverage of the whole spectrum of the disease. This *post hoc* study is the first to focus on hip and shoulder involvement as the main outcome and has identified some associations that were not described previously. Furthermore, we can expect that not only was patient recruitment and classification well achieved, but also the identification of manifestations has been well assessed, since all patients were recruited from centres of investigators who are ASAS members with a long-standing expertise in the field of SpA.

In summary, we presented the phenotype profile of patients with RJD in a worldwide SpA population. Our results suggest analysing hip and shoulder involvement separately rather than lumping them together under the root joint entity. Both entities were more prevalent in patients from Asia. Hip involvement was more prevalent in the overall SpA population, and was associated with both pSpA and axSpA, earlier disease onset, HLA-B27 and the use of DMARDs, a phenotype resembling axial disease; in contrast, shoulder involvement was more associated with pSpA, older age and peripheral disease features. Further longitudinal studies including imaging modalities are recommended to help in additional characterization of root joint phenotypes in SpA.

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Data availability statement

The data underlying this article were provided by the PerSpA main authors by permission. Data will be shared on request to the corresponding author with permission of the PerSpA main authors.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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