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What is peripheral spondyloarthritis? Identifying proportion, phenotype and burden in post hoc analysis of the ASAS-PerSpA study

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ABSTRACT

Background: Little is known about the prevalence, phenotype, and burden of peripheral spondyloarthritis (pSpA). The objective of the study is to compare the phenotype and burden of disease of pure pSpA to that of pure psoriatic arthritis (PsA), pure axial SpA (axSpA), and combined forms of SpA.

Methods: This is a post hoc analysis of 4,185 patients from the cross-sectional ASAS-Peripheral involvement in SpA (PerSpA) study. Patients were approached in 2 ways: the first approach was based on the rheumatologist's diagnosis (diagnostic approach) and the second one was based on the fulfillment of ASAS or CASPAR classification criteria (classification criteria approach). Demographics, disease phenotype, and burden were compared among pure pSpA, PsA, axSpA, and the combined forms.

Findings: The proportion of pSpA was 31.5% of SpA using the classification criteria approach and 10.3% using the diagnostic approach. pSpA was pure (i.e. without axSpA or PsA) in 16.8% of pSpA using the criteria, and in 62.3% using the diagnostic approach. Using classification criteria and diagnostic approach, respectively, pure pSpA patients had a high prevalence of peripheral joint disease (86 and 96%), synovitis (76 and 91%), and enthesitis (57 and 55%), a positive HLA-B27 in 65 and 59%, a high C-Reactive Protein level in 51% and inflammatory back pain in 52 and 42%. However, compared to pure PsA and pure axSpA, they had a significantly higher disease burden, but lower use of biologics using both approaches.

Interpretation: The proportion of pSpA varies when using the classification criteria or the diagnostic approach. pSpA occurred in a pure form less frequently than PsA and axSpA and had intermediate features but a higher disease burden.

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Introduction

To understand and define a disease is of crucial importance for applying a proper and adequate treatment. Moreover, identifying the epidemiologic features of a disease is the most critical determinant for estimating its burden on the population. If limited healthcare resources are to be appropriately distributed, one must first have a reasonably clear idea about what a disease is, and second, which diseases are most

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worth the investment of time and budget [1]. However, defining a particular disease is sometimes difficult and can be described by different approaches, as is the case for peripheral spondyloarthritis (pSpA).

Spondyloarthritis (SpA) is a group of inflammatory rheumatic disorders that usually involves the axial skeleton [2]. The Assessment of Spondyloarthritis International Society (ASAS) introduced the classification criteria for axial SpA (axSpA) in 2009 and pSpA in 2011, depending on the existence of predominantly axial or predominantly peripheral involvement, respectively [3,4].

However, pSpA shows features that overlap with psoriatic arthritis (PsA), axSpA, and other forms of SpA and seems to be unsatisfactorily defined despite the introduction of the ASAS classification criteria, knowing that all peripheral features can be found in all subtypes of SpA [5,6]. In addition, some studies have shown that these combined forms of SpA were associated with a higher disease burden in comparison with pure ones [7].

Little is known about the prevalence of pSpA in general, particularly pure pSpA, and about the possible differences across the different regions of the world. Moreover, the proportion of pSpA within the whole group of SpA, as a pure form and in combination with axSpA and PsA, has not been well explored yet [8]. Finally, no comparative studies were found between the patient socio-demographic profile or burden of disease of pure pSpA on one hand and those of pure PsA, pure axSpA, and the combined forms of SpA on the other hand.

The ASAS-PerSpA (PERipheral involvement in SpondyloArthritis) study [6] included the largest ever international SpA cohort and therefore represents a unique opportunity to investigate the characteristics of pSpA, compare them with pure PsA, pure axSpA and combined forms of SpA, and identify geographical differences in pSpA prevalence.

The primary objective of the present post hoc analysis of the ASAS PerSpA study is to identify the phenotype and burden of disease in patients with pure pSpA.

The secondary objectives are to compare this phenotype and disease burden with those of pure PsA, pure axSpA and combined forms of SpA and to estimate the proportion of pSpA across the world regions.

Methods

Study design

This is a post hoc analysis of ASAS-PerSpA, an observational, cross-sectional, multicenter, international study that involved 4465 patients from 68 recruiting centers in 24 countries and aimed at evaluating the features of pSpA.

Patients

The ASAS PerSpA study included consecutive patients suffering from any form of SpA (axSpA, pSpA or PsA (one to three diagnoses could be selected at study inclusion)). Patients were adults (ie, at least 18 years old) who were able to understand and complete questionnaires and were included from July 2018 to February 2020 at the participating rheumatology centers. Thereafter, the rheumatologists were asked to select only one main clinical condition from the following list: axSpA, pSpA, PsA, Inflammatory Bowel Disease-related SpA (IBD-SpA), reactive SpA (ReA-SpA), juvenile SpA or other types of SpA. In practice, the rheumatologists may the potential to consider multiple diagnoses for the same patient at study inclusion, however, they were subsequently obliged to select a single main diagnosis per patient.For the current analysis, we included patients in which the rheumatologist has selected axSpA, pSpA or PsA (4185 patients) and excluded patients from whom the rheumatologist has selected either reactive arthritis, IBD related arthritis, juvenile SpA or other types of SpA (280 patients in total). Thereafter, we applied the different sets of classification criteria in the included population: the ASAS axSpA, ASAS pSpA and CASPAR criteria [3,4,9] . Concerning the pSpA criteria, we performed a non-strict application that is, we accepted as fulfillment of pSpA criteria, patients with current axial symptoms and/or patients with only a past history of peripheral symptoms.

Data collection

The data were collected during a single routine visit to the rheumatologist. The details of the collected data in ASAS-PerSpA have been previously reported [6].

A case report form was used to collect four different categories of data: demographics, disease characteristics, peripheral musculoskeletal manifestations, disease activity, and disease burden. Current disease activity at the study visit was measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [10], and the Ankylosing Spondylitis Disease Activity Score was calculated with CRP (ASDAS) [11]. Moreover, the Bath Ankylosing Spondylitis Functional Index (BASFI) and the ASAS Health Index (ASAS-HI) were used to evaluate function and health, respectively [12]. Concomitant fibromyalgia was collected using the self-reported Fibromyalgia Rapid Screening Tool (FiRST) [13]. Finally, the Work Productivity and Activity Impairment Instrument (WPAI) [14] and the EuroQOL-5Dimension (EQ-5D) [15] were collected.

Statistical analysis

Two parallel approaches were used to define the prevalence of the disease subtypes (Fig. 1):

First, the classification criteria approach categorized the patients into 6 groups: pure disease (patients fulfilling either ASAS pSpA classification criteria, ASAS axSpA classification criteria, or CASPAR PsA criteria) and combined disease (patients who fulfill more than one of the criteria mentioned above). The classification criteria were used in a non-strict mannerfor the purpose of the current study only. Normally, a patient fulfilling the axSpA and pSpA ASA criteria simultaneously is classified as axSpA only, which is justified by the need to have a simple unequivocal classification for clinical trials and homogenization of response to certain treatment categories. However, in real life, patients may fulfill both criteria simultaneously and, since this heterogeneity needs to be addressed, it was exceptionally allowed for one patient to fulfill axSpA and pSpA ASAS criteria simultaneously in the current study.

Second, the diagnostic approach categorized the patients in 6 groups as well: pure disease (diagnosed with pSpA, axSpA, or PsA as the main SpA disease, exclusively) and combined disease (patients for whom more than one defining disease subtype were checked by the rheumatologist at study entry).

Socio-demographic characteristics, clinical, biological, imaging phenotype, and disease burden were compared among patients with pure pSpA, PsA, axSpA, and the combined forms of SpA (grouped together), using Chi-square, ANOVA, and Kruskal-Wallis as appropriate. P-values < 0.05 were accepted as statistically significant. All statistical analyses were performed using SPSS v20 (IBM).

The proportion of disease subtypes was compared across the world's regions as defined in the original manuscript: Latin America, Europe, and North America, Asia and Middle East and North Africa (MENA).

Results

Proportion of pSpA among the 3 main spa forms (axSpA, psa, pSpA)

The proportion of all pSpA was 31.5% (95%CI 30.1–32.9) of the SpA population (1317/4185) using the ASAS non-strict criteria approach and 10.3% (95%CI 9.4–11.3) (433/4185) using the diagnostic approach (pSpA as the main form of SpA according to the rheumatologist's diagnosis) (Fig. 1). Overlapping between the three classification criteria

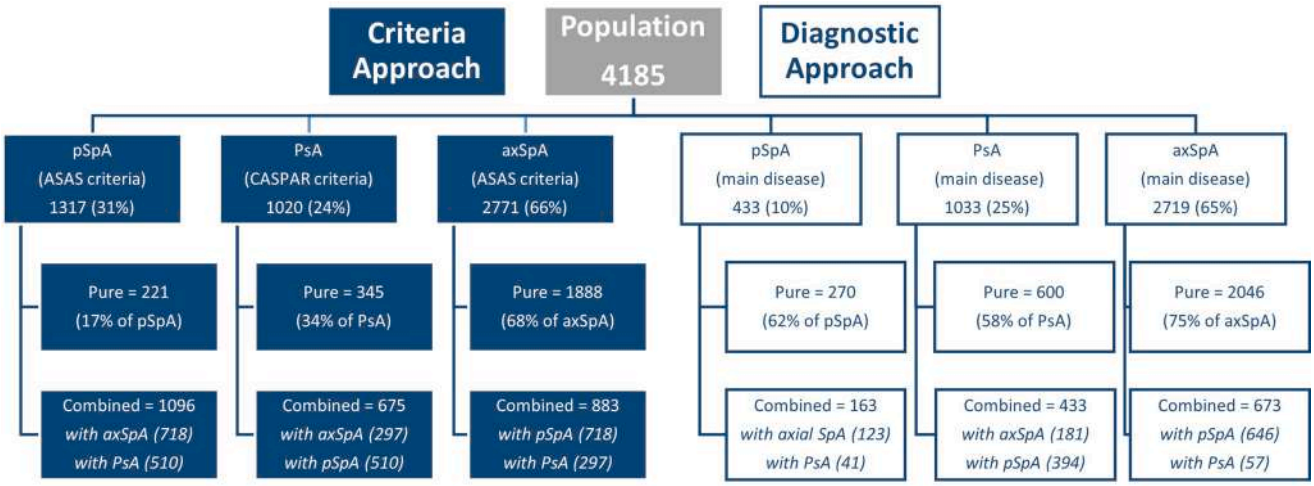

Fig. 1. Proportion of the pure and combined forms of spondyloarthritis (peripheral SpA (pSpA), psoriatic arthritis (PsA) and axial SpA (axSpA), using the classification criteria approach (ASAS and CASPAR classification criteria) and the diagnostic approach (main SpA disease according to the rheumatologist).

systems is presented in a Venn diagram (Fig. 2).

When using the classification criteria approach in a non-strict manner, pSpA was pure in only 16.8% of patients with pSpA (221/1317), compared to 33.8% pure PsA and 68.1% pure axSpA. As for the 1096 patients with a combined form of pSpA, 65.5% were combined with axSpA (718/1096) and 46.5% with PsA (510/1096) (Fig. 1). As a mean of comparison, using the classification criteria in a strict manner (one patient may fulfill axSpA or pSpA ASAS classification exclusively), pSpA was pure in 221/599 patients with pSpA (37%).

When using the diagnostic approach, pSpA was pure in 62.3% of the whole group of patients with pSpA (270/433), compared with 58.1% pure PsA and 75.2% pure axSpA. As for the 163 patients with a combined form of pSpA, 75.5% were combined with axSpA (123/163) and 25.1% with PsA (41/163) (Fig. 1).

To sum up, pure pSpA constituted 5.3% of the whole SpA population (221/4185) using the classification criteria approach, both in the strict and non-strict manner, and 6.4% (270/4185) using the diagnostic approach.

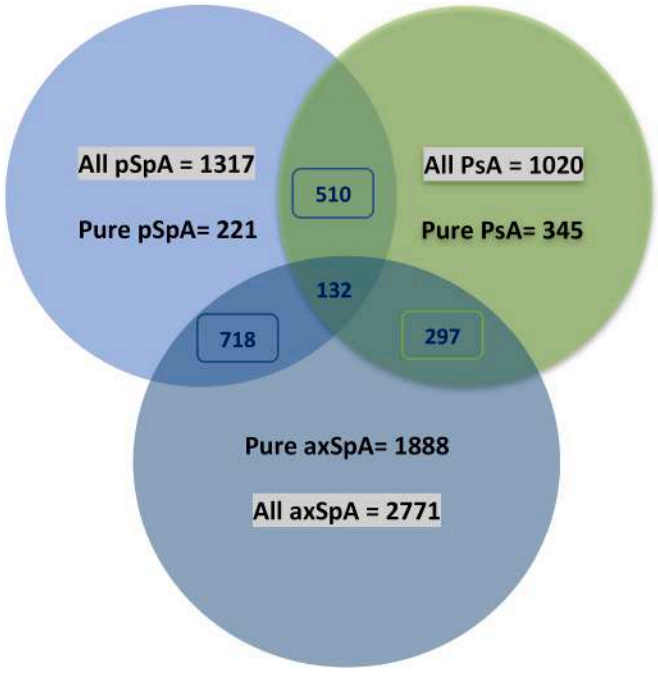

Fig. 2. Overlap between the ASAS axial spondyloarthritis (axSpA), ASAS peripheral SpA (pSpA) and CASPAR (Psoriatic Arthritis (PsA)) classification criteria systems in the 4185 patients with SpA.

Comparison of the patient socio-demographic profile, disease phenotype, disease burden and treatment modalities of pure pSpA with pure PsA, pure axSpA and the combined forms using the classification criteria approach

Using the classification criteria approach (Table 1), patients with pure pSpA had peripheral joint disease in 86%, synovitis in 75.6%, enthesitis in 56.6%, inflammatory back pain in 52.5%, dactylitis in 16.7%, psoriasis in 17.2%, and uveitis in 15.8% (Fig. 3). Their mean CRP level was 16.3 mg/l, 50.9% had a high CRP, 64.9% were positive for HLA-B27, 29.4% had sacroiliitis on x-rays and 24.9% on magnetic resonance imaging.

As for the disease burden, patients with pure pSpA had a mean patient global assessment of 5.1 /10 (± 2.5), BASDAI of 4.5 (± 2.3), ASDAS of 2.8 (± 1.1), BASFI of 3.2 (± 2.8), ASAS-HI 7.5 (± 4.5), WPAI 28.7 (± 17.4); all measures were worse in comparison with the pure forms of PsA and axSpA, respectively, and in a similar range of those of combined forms of SpA.

Some patients with pSpA had spine abnormalities. In addition, they had fibromyalgia (based on their responses to the FiRST screening questionnaire) in 23.1% (more prevalent than the pure PsA and axSpA, respectively, but similar to the combined forms of SpA). The health status as measured by EQ-5D was comparable to that of pure PsA and pure axSpA.

Finally, 82.4% of patients with pure pSpA were treated with conventional synthetic (cs-) and 49.8% of them were treated with biologic (b-) disease modifying anti-rheumatic drugs (DMARDs), the latter prevalence being the lowest in all disease categories.

Comparison of the patient socio-demographic profile, disease phenotype, disease burden, and treatment modalities of pure pSpA with pure axSpA, pure PsA, and the combined forms of SpA using the diagnostic approach

Using the diagnostic approach (Table 2), patients with pure pSpA had peripheral joint disease in 96.3%, synovitis in 90.7%, enthesitis in 54.8%, inflammatory back pain in 42.2%, dactylitis in 24.8%, uveitis in 15.6%, and psoriasis in 6.3% (Fig. 3). Their mean CRP level was 14.1 mg/l, 51.1% had a high CRP level, 58.7% had a positive HLA-B27, 21.1% had sacroiliitis on x-rays, and 18.1% on magnetic resonance imaging.

As for the disease burden, patients with pure pSpA had a mean patient global assessment of 4.7 / 10 (± 2.7), BASDAI of 4.2 (± 2.4), ASDAS of 2.7 (± 1.1); all measures were worse in comparison with the

Table 1
Comparison of the socio-demographic characteristics of the patients, disease phenotype, disease burden, and treatment modalities among patients with pure peripheral spondyloarthritis, pure psoriatic arthritis, pure axial spondyloarthritis, and combined forms of spondyloarthritis according to the classification criteria approach.

	Pure peripheral SpA	Pure Psoriatic Arthritis	Pure axial SpA	Combined forms of SpA
Number of patients	221	345	1888	1731
Socio-Demographic Data				
Age (continuous), years, mean (SD)	46.8 (14.8)	54.0 (13.8)	41.2 (12.6)	46.0 (13.8)
Gender, male, N (%)	113 (51.1)	183 (53.0)	1357 (71.9)	914 (52.8)
BMI Kg/m^2, mean (SD)	26.2 (5.0)	28.2 (6.1)	25.8 (5.0)	26.9 (5.6)
Educational level, N (%)				
Primary school	53 (24.1)	80 (23.3)	253 (13.4)	308 (17.8)
Secondary school	90 (40.9)	158 (45.9)	783 (41.5)	761 (44.0)
University	77 (35.0)	106 (30.8)	850 (45.1)	662 (38.2)
Employed, N (%)	101 (45.7)	180 (52.3)	1235 (65.5)	928 (53.7)
Smoker, N (%)	71 (32.1)	169 (49.1)	845 (44.8)	722 (41.7)
Age at SpA onset, mean (SD)	37.4 (14.8)	37.1 (15.7)	26.7 (9.6)	31.9 (13.6)
Family history of SpA, N (%)	29 (14.1)	6 (2.0)	391 (21.3)	216 (13.4)
Disease duration, Median [IQR]	6.6 [12.0]	14.5 [17.8]	11.8 [14.6]	11.6 [15.0]
Diagnostic delay, Median [IQR]	1.2 [5.8]	4.7 [13.7]	3.0 [7.0]	3.3 [9.61]
Disease Phenotype				
Peripheral Joint Disease, N (%)	190 (86.0)	331 (95.9)	596 (31.6)	1209 (69.8)
Synovitis, N (%)	167 (75.6)	321 (93.0)	504 (26.7)	1099 (63.5)
Enthesitis, N (%)	125 (56.6)	134 (38.8)	671 (35.5)	904 (52.2)
TJC, mean (SD)	4.1 (6.1)	2.1 (5.7)	0.7 (2.5)	4.4 (8.0)
SJC, mean (SD)	2.1 (3.3)	0.01 (0.2)	0.0 (0.0)	1.7 (4.5)
Inflammatory Back Pain, N (%)	116 (52.5)	79 (22.9)	1800 (95.3)	1155 (66.7)
Dactylitis, N (%)	37 (16.7)	154 (44.6)	92 (4.9)	363 (21)
Psoriasis, N (%)	38 (17.2)	334 (96.8)	92 (4.9)	733 (42.2)
Uveitis, N (%)	35 (15.8)	9 (2.6)	416 (22.0)	230 (13.3)
Inflammatory Bowel Disease, N (%)	6 (2.7)	2 (0.6)	93 (4.9)	62 (3.6)
CRP mg/l, mean (SD)	16.3 (31.2)	10.0 (30.0)	9.2 (21.0)	14.5 (30.1)
High CRP, N (%)	111 (50.9)	119 (34.5)	710 (37.8)	822 (47.9)
HLA-B27 positive, N (%)	85 (64.9)	12 (8.2)	1266 (82.2)	629 (55.2)
Sacroiliitis on X-ray, N (%)	65 (29.4)	33 (9.6)	1456 (78.2)	826 (47.7)
Sacroiliitis on MRI, N (%)	55 (24.9)	16 (4.6)	1053 (55.8)	621 (35.9)
Disease Burden				
PGA mean (SD)	5.1 (2.5)	3.7 (2.5)	3.8 (2.6)	5.0 (2.7)
BASDAI, mean (SD)	4.5 (2.3)	3.3 (2.3)	3.2 (2.2)	4.6 (2.5)
High BASDAI (binary, ≥4), N (%)	127 (57.5)	127 (37.5)	641 (34.0)	1014 (58.7)
BASDAI #1, mean (SD) (Fatigue)	4.8 (2.9)	4.1 (2.7)	4.1 (2.7)	5.2 (2.8)
	3.9 (3.4)	3.3 (3.0)		4.9 (3.1)
BASDAI #2, mean (SD) (Axial pain)			4.0 (2.8)	
BASDAI #3, mean (SD) (Peripheral pain)	4.8 (2.9)	3.3 (2.8)	2.3 (2.6)	4.3 (3.1)
BASDAI #4, mean (SD) (Tenderness to pressure)	4.9 (2.9)	3.2 (2.9)	2.8 (2.8)	4.5 (3.2)
BASDAI #5, mean (SD) (Morning stiffness level)	4.5 (3.2)	3.0 (2.8)	3.3 (2.9)	4.5 (3.1)
BASDAI #6, mean (SD) (Morning Stiffness Duration)	3.2 (2.9)	2.1 (2.5)	2.5 (2.5)	3.2 (2.9)
ASDAS, mean (SD)	2.8 (1.1)	2.2 (1.0)	2.3 (1.0)	2.8 (1.7)
High ASDAS (binary ≥2.1), N (%)	157 (72.7)	164 (48.8)	956 (51.3)	1228 (71.9)
S-ASDAS, mean (SD)	23.7 (12.2)	17.5 (11.4)	17.7 (11.3)	16.2 (11.3)
BASFI, mean (SD)	3.4 (2.8)	2.3 (2.3)	2.6 (2.5)	3.5 (2.7)
ASAS-HI, mean (SD)	7.5 (4.5)	5.6 (4.4)	5.7 (4.4)	7.6 (4.6)
Bamboo spine, N (%)	13 (5.9)	3 (0.9)	273 (14.5)	190 (11)
Loss of lumbar lordosis, N (%)	36 (16.3)	20 (5.8)	673 (35.6)	482 (27.8)
Thoracic kyphosis, N (%)	17 (7.7)	7 (2.0)	426 (22.6)	325 (18.8)
Occiput-Wall Distance >0, N (%)	24 (10.9)	8 (2.3)	519 (27.5)	356 (20.6)
FiRST (continuous), mean (SD)	2.6 (2.0)	2.0 (2.0)	2.0 (1.8)	2.7 (2.0)
FiRST score, N (%)	51 (23.1)	58 (16.8)	231 (12.2)	401 (23.2)
WPAI, mean (SD)	28.7 (17.4)	23.2 (16.5)	24.4 (18.8)	28.7 (19.1)
EQ-5D, mean (SD)	0.59 (0.23)	0.71 (0.22)	0.70 (0.22)	0.60 (0.25)
Treatment Modalities				
csDMARDs, N (%)	182 (82.4)	317 (91.9)	909 (48.1)	1337 (77.2)
bDMARDs, N (%)	110 (49.8)	218 (63.2)	1146 (60.7)	1030 (59.5)

(All percentages are presented in columns. Comparison of the four columns simultaneously was statistically significant for all variables ($p<0.001$ in all variables except $p = 0.009$ for bDMARDs)).
ASAS-HI: ASAS Health Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, b-DMARDS: biological disease-modifying anti-rheumatic drugs, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, CRP: C-Reactive Protein, cs-DMARDs: conventional synthetic disease-modifying anti-rheumatic drugs, EQ-5D: EuroQOL-5 Dimension, FiRST: Fibromyalgia Rapid Screening Tool, PGA: Patient Global Assessment of well-being, S-ASDAS: Simplified ASDAS, SJC: Swollen Joint Count, SpA: Spondyloarthritis, TJC: Tender Joint Count, WPAI: Work Productivity Loss.

pure forms of axSpA, and in a similar range of those of pure PsA and the combined forms of SpA, respectively. BASFI (mean 2.9 (± 2.5)), ASAS-HI (mean 6.8 (± 4.3)), fibromyalgia (16.3%), and WPAI (27.4 (± 17.0)) were similar to those observed in pure axSpA. Some patients with pSpA had spine abnormalities. The health status as measured by EQ-5D was comparable to pure PsA and combined forms of SpA.

Finally, 90.4% of patients with pure pSpA were treated with cs-DMARDs, and 44.8% of them were treated with b-DMARDs, the latter proportion being the lowest in all disease categories.

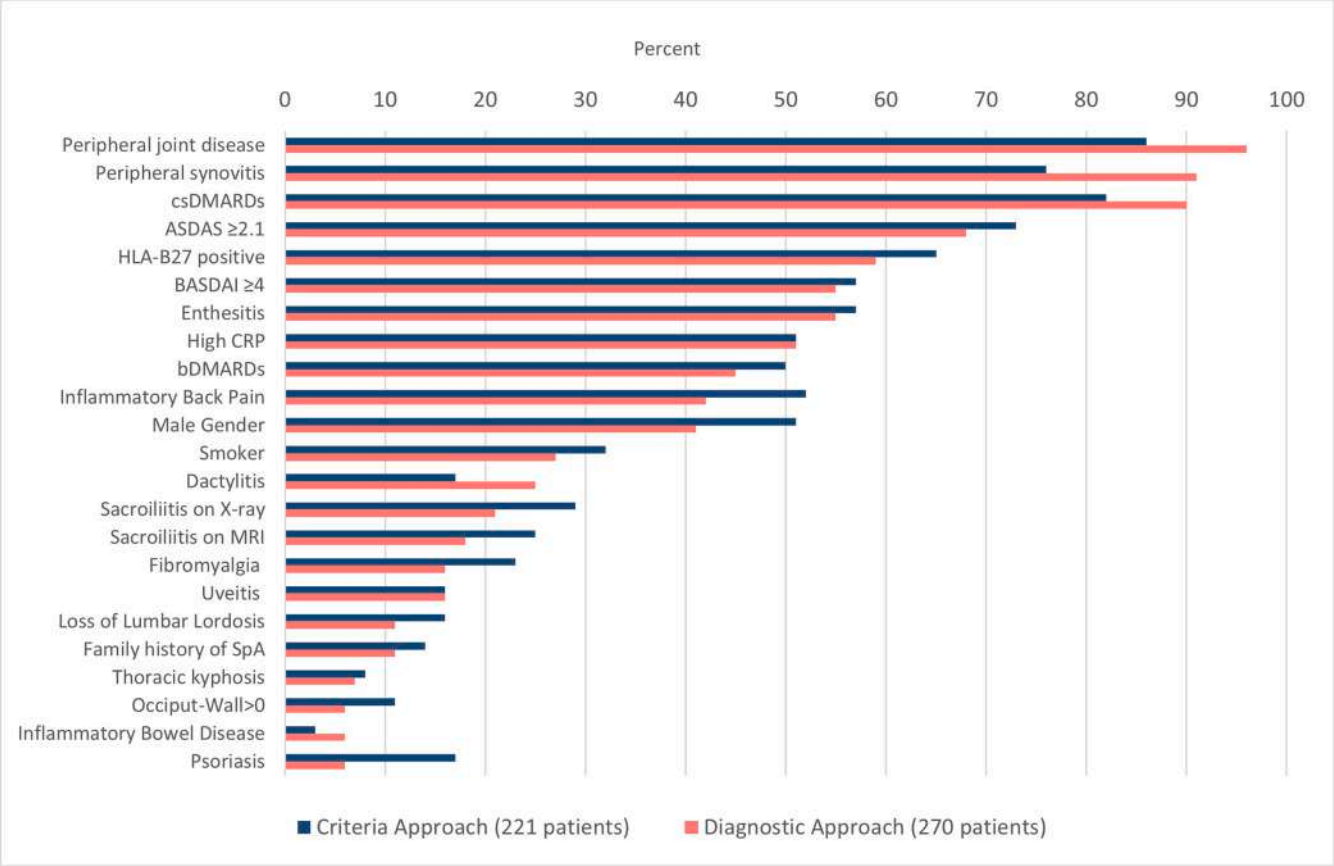

Fig. 3. Phenotypic profile of patients with pure peripheral spondyloarthritis using the classification criteria and the diagnostic approaches Footnote: ASDAS: Ankylosing Spondylitis Disease Activity Score, bDMARDS: biological disease-modifying anti-rheumatic drugs, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-Reactive Protein, c-DMARDs: conventional synthetic disease-modifying anti-rheumatic drugs, SpA: Spondyloarthritis.

Proportion of pSpA and pure pSpA across the different regions of the world

pSpA was more prevalent in Latin America (50.1% of all SpA) when using the classification criteria approach and in Asia (15.1% of all SpA) when using the diagnostic approach (Table 3). In contrast, axSpA was the most prevalent form of SpA in the MENA region using both approaches (73.4% and 69.5%, respectively). As for PsA, it was most prevalent in Latin America using both approaches (35.1% using the criteria approach and 36.1% using the diagnostic approach).

Pure pSpA was also more prevalent in Latin America (7% of all SpA in Latin America) when using the classification criteria approach, whereas it was more prevalent in the MENA region (9% of all SpA) when using the diagnostic approach (Table 4).

Discussion

This is the first post-hoc analysis to estimate the proportion of pure pSpA, i.e., pSpA without overlap with the other forms of SpA, in the whole SpA population and to characterize the profile of these patients and the burden of the disease, based on the largest observational SpA cohort, PerSpA.

The proportion of pSpA as a group varied when using the classification criteria approach (31% of SpA) or the diagnostic approach (10% of SpA). pSpA was pure in 16.8% of the pSpA cases using the first approach and 62.3% using the second one. Thus, the current analysis confirmed that pSpA often occurred combined with PsA or axSpA. *In fine*, pure pSpA constituted only 5.3% of all SpA using the classification criteria and 6.4% using the diagnostic approach. At this point, the approaches used in the current study might be criticized, including the use of two analytical approaches, and the non-strict application of classification criteria. Nevertheless, as the current study being post hoc analysis of ASAS-PerSpA (that had full set of data on the largest global cohort of SpA patients) allowed to conduct these approaches for analysis. Such analytical design (which is already performed in novel ASAS-PerSpA study), permitted to precisely define the characteristics of pSpA patients, either in the daily rheumatology practice (as per rheumatologists' diagnosis approach), and/or the homogenous group of patients that would be recruited into clinical studies (using classification criteria approach). Meanwhile, it is not unusual to find in clinical practice patients that has the "gestalt" of pSpA and can only be labelled as such; yet at another stage of their illness, other clinical features become evident to permit labeling them as another distinct entity of SpA, e.g., PsA. As such, the "non-strict application of classification criteria" may perhaps exceptionally be justified in context to conducting the present study. Moreover, the similarity of the final proportion of pure pSpA in the whole cohort of SpA using either approach supports its validity.

The difference in the proportion of pSpA using one approach or the other (31.5% versus 10.3%) may reflect the rheumatologist's perception, who would rather choose the diagnosis of PsA or axSpA as the main diagnosis when pSpA occurs in combination with one of these SpA subtypes, even if the patient fulfills the pSpA classification criteria. Thus, the rheumatologist would choose the diagnosis of pSpA as a main disease when it occurs in its pure form. In addition, these results also reflect the difference between diagnosis and classification criteria, where some patients can be diagnosed in the clinic setting as pSpA while they cannot be classified as per the criteria.

Compared with other SpA cohorts using the classification criteria approach, the proportion of pSpA in the current study was higher than the 14% proportion reported in the Comorbidities in SpA (COMOSPA) study, which included 3985 patients with SpA from 22 countries [16].

Table 2
Comparison of the socio-demographic characteristics of the patients, disease phenotype, disease burden, and treatment modalities among patients with pure peripheral spondyloarthritis, pure psoriatic arthritis, pure axial spondyloarthritis, and combined forms of spondyloarthritis according to the diagnostic approach (main form of disease as per the rheumatologist's opinion).

	Pure peripheral SpA	Pure Psoriatic Arthritis	Pure axial SpA	Combined forms of SpA
Number of patients	270	600	2046	1269
Socio-Demographic Data				
Age (continuous), years, mean (SD)	43.7 (14.7)	51.8 (13.2)	42.3 (13)	45.0 (14.1)
Gender, male, N (%)	112 (41.5)	286 (47.7)	1416 (69.2)	748 (58.9)
BMI Kg/m^2, mean (SD)	26.7 (5.7)	28.6 (6.1)	26.1 (5)	25.9 (5.4)
Educational level, N (%)				
Primary school	26 (9.6)	129 (21.6)	286 (14)	253 (19.9)
Secondary school	120 (44.4)	279 (46.7)	870 (42.6)	523 (41.2)
University	124 (45.9)	190 (31.8)	888 (43.4)	493 (38.8)
Employed, N (%)	141 (52.4)	306 (51)	1307 (64)	690 (54.5)
Smoker, N (%)	74 (27.4)	196 (32.6)	963 (47.1)	484 (38.2)
Age at SpA onset, mean (SD)	35.4 (14.6)	33.8 (14.7)	27.9 (10.6)	31.3 (13.8)
Family history of SpA, N (%)	28 (11.4)	11.0 (2.0)	447 (22.6)	156 (13.3)
Disease duration, Median [IQR]	5.9 [9.5]	15.6 [17.6]	11.8 [14.9]	11.1 [8.2]
Diagnostic delay, Median [IQR]	1.0 [4.5]	6.0 [14.5]	2.0 [7.5]	3.0 [8.5]
Disease Phenotype				
Peripheral Joint Disease, N (%)	260 (96.3)	533 (88.8)	438 (21.4)	1095 (86.3)
Synovitis, N (%)	245 (90.7)	498 (83.0)	339 (16.6)	1009 (79.5)
Enthesitis, N (%)	148 (54.8)	256 (42.7)	681 (33.3)	749 (59.0)
TJC, mean (SD)	3.6 (5.9)	5.2 (8.6)	1.1 (3.8)	3.2 (7.0)
SJC, mean (SD)	1.0 (1.8)	2.3 (5.3)	0.2 (1.7)	1.1 (3.4)
Inflammatory Back Pain, N (%)	114 (42.2)	174 (29)	1913 (93.5)	949 (74.8)
Dactylitis, N (%)	67 (24.8)	240 (40.0)	76 (3.7)	263 (20.7)
Psoriasis, N (%)	17 (6.3)	568 (94.7)	122 (6.0)	490 (38.6)
Uveitis, N (%)	42 (15.6)	17 (2.8)	432 (21.1)	199 (15.7)
Inflammatory Bowel Disease, N (%)	15 (5.6)	4 (0.7)	101 (4.9)	43 (3.4)
CRP mg/l, mean (SD)	14.1 (24.3)	12.4 (30.6)	10.1 (24.7)	14.0 (29.0)
High CRP, N (%)	138 (51.1)	257 (43.1)	812 (40.1)	555 (43.9)
HLA-B27 positive, N (%)	118 (58.7)	51.0 (17)	1285 (78.3)	538 (66.0)
Sacroiliitis on X-ray, N (%)	57 (21.1)	101 (16.8)	1542 (75.4)	700 (55.2)
Sacroiliitis on MRI, N (%)	49 (18.1)	54 (9.0)	1156 (56.5)	486 (38.3)
Disease Burden				
PGA mean (SD)	4.7(2.7)	4.8 (2.7)	4.1 (2.6)	4.5 (2.7)
BASDAI, mean (SD)	4.2 (2.4)	4.4 (2.5)	3.5 (2.3)	4.1 (2.5)
High BASDAI (binary, ≥4), N (%)	146 (54.5)	331 (55.9)	811 (39.7)	621 (48.9)
BASDAI #1, mean (SD) (Fatigue)	4.8 (2.8)	5.0 (2.8)	4.4 (2.8)	4.7 (2.8)
BASDAI #2, mean (SD) (Axial pain)	4.0 (3.3)	4.2 (3.3)	4.4 (2.9)	4.4 (3.1)
BASDAI #3, mean (SD) (Peripheral pain)	4.3 (3.1)	4.5 (3.1)	2.5 (2.9)	3.9 (3.1)
BASDAI #4, mean (SD) (Tenderness to pressure)	4.7 (3.2)	4.4 (3.1)	3.1 (3.0)	4.0 (3.1)
BASDAI #5, mean (SD) (Morning stiffness level)	3.9 (3.2)	4.2 (3.2)	3.7 (3.0)	3.9 (3.1)
BASDAI #6, mean (SD) (Morning Stiffness Duration)	2.7 (2.7)	3.0 (2.8)	2.8 (2.7)	2.9 (2.9)
ASDAS, mean (SD)	2.7 (1.1)	2.7 (1.1)	2.4 (1.1)	2.6 (1.2)
High ASDAS (binary ≥2.1), N (%)	181 (68.0)	379 (64.9)	1139 (56.6)	806 (63.9)
S-ASDAS, mean (SD)	22.1 (12.0)	22.7 (12.4)	19.3 (11.9)	14.4 (11.5)
High S-ASDAS (binary, >19)	162 (60.0)	348 (58.0)	1139 (56.6)	417 (33.1)
BASFI, mean (SD)	2.9 (2.5)	3.3 (2.7)	2.9 (2.6)	3.1 (2.8)
ASAS-HI, mean (SD)	6.8 (4.3)	7.3 (4.7)	5.9 (4.4)	7.2 (4.7)
Bamboo spine, N (%)	6 (2.2)	13 (2.2)	352 (17.2)	108 (8.5)
Loss of lumbar lordosis, N (%)	30 (11.1)	46 (7.7)	836 (40.9)	299 (23.6)
Thoracic kyphosis, N (%)	18 (6.7)	26 (4.3)	555 (27.1)	176 (13.9)
Occiput-Wall Distance >0, N (%)	15 (5.6)	27 (4.5)	624 (30.5)	241 (19.0)
FiRST (continuous), mean (SD)	2.3 (1.9)	2.6 (2.1)	2.2 (1.9)	2.5 (2.0)
FiRST score, N (%)	44 (16.3)	142 (23.7)	299 (14.6)	256 (20.2)
WPAI, mean (SD)	27.4 (17.0)	26.9 (18.2)	25.5 (18.9)	27.1 (19.1)
EQ-5D, mean (SD)	0.62 (0.23)	0.62 (0.25)	0.68 (0.22)	0.63 (0.24)
Treatment Modalities				
csDMARDs, N (%)	244 (90.4)	564 (94)	878 (42.9)	1059 (83.5)
bDMARDs, N (%)	121 (44.8)	367 (61.2)	1209 (59.1)	807 (63.6)

All percentages are presented in columns.
Comparison of the four columns simultaneously was statistically significant for all variables ($p<0.001$ in all variables except $p = 0.003$ for high CRP, $p = 0.045$ for WPAI), except BASDAI question number 2 (axial pain), $p = 0.130$, and question number 6 (Morning Stiffness Duration), $p = 0.204$).
ASAS-HI: ASAS Health Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, b-DMARDS: biological disease-modifying anti-rheumatic drugs, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, CRP: C-Reactive Protein, cs-DMARDs: conventional synthetic disease-modifying anti-rheumatic drugs, EQ-5D: EuroQOL-5 Dimension, FiRST: Fibromyalgia Rapid Screening Tool, PGA: Patient Global Assessment of well-being, S-ASDAS: Simplified ASDAS, SJC: Swollen Joint Count, SpA: Spondyloarthritis, TJC: Tender Joint Count, WPAI: Work Productivity Loss.

Importantly, in the COMOSPA study, patients who fulfilled both ASAS axial and pSpA classification criteria were exclusively classified in the axial group, whereas the criteria were used in a non-restrictive manner in the current study, as overlaps among criteria were allowed.

The proportion of pSpA relative to the whole group of SpA has also been evaluated in several cohort studies. For instance, the Belgian Be-Giant early SpA cohort [17], the Spanish Esperanza SpA cohort [18], the Dutch SpA cohort [19] and the French GAZEL cohort reported

Table 3
Proportion of peripheral spondyloarthritis (pSpA) axial SpA (axSpA), and psoriatic arthritis (PsA) in the whole SpA population across the world regions, according to the ASAS and CASPAR classification criteria approach and the diagnostic approach (rheumatologist's opinion about the main form of SpA).

World region	Number of patients	Peripheral Spondyloarthritis	Psoriatic Arthritis	Axial Spondyloarthritis
Classification Criteria Approach				
Whole Study population, N (%)	4185	1317 (31)	1020 (24)	2771 (66)
Latin America	487	244 (50.1)	171 (35.1)	280 (57.5)
Europe and North America	1603	379 (23.6)	422 (26.3)	1017 (63.4)
Asia	913	251 (27.5)	184 (20.2)	606 (66.4)
Middle East and North Africa	1182	443 (37.5)	243 (20.6)	868 (73.4)
Diagnostic Approach				
Whole Study population, N (%)	4185	433 (10)	1033 (25)	2719 (65)
Latin America	487	35 (7.2)	176 (36.1)	276 (56.7)
Europe and North America	1603	102 (6.4)	489 (30.5)	1012 (63.1)
Asia	913	138 (15.1)	165 (18.1)	610 (66.8)
Middle East and North Africa	1182	158 (13.4)	203 (17.2)	821 (69.5)

(All percentages are presented in rows; numbers may overlap between columns in the classification criteria section).

proportions of pSpA ranging from 22.8% to 28.5% of the whole SpA group, similar to the proportion we found using the classification criteria approach.

When estimating the geographical differences in pSpA proportion, based on the classification criteria approach, pSpA as a group and pure pSpA were more prevalent in Latin America and less prevalent in Europe, North America and Asia, which confirms the results of previous studies [20–22]. However, based on the diagnostic approach, the proportion of pSpA and pure pSpA was highest in Asia and the MENA region. This result could be hindered by the low number of patients in this category (433) but could also reflect differences in diagnostic habits.

In addition to the estimation of the proportion of pure pSpA, the current study also provided a depiction of its phenotype. The demographic characteristics were in the intermediate range between PsA and axSpA, but similar to the combined forms of SpA. Moreover, using the criteria and the diagnostic approach, respectively, peripheral joint disease (86%, 96%) and synovitis (76%, 91%) were obviously the most prominent features of pure pSpA, followed by a high proportion of enthesitis (57%, 55%). Dactylitis was less prevalent (17%, 25%). In addition, inflammatory back pain was reported in 52% and 42% of pure pSpA, indicating a very heterogeneous clinical pattern of this disease. Of interest, fibromyalgia was associated with pure pSpA in 23% and 16% of cases, which might raise the issue of confusing fibromyalgia patients as pSpA. Although this hypothesis might be plausible for some patients, yet, the presence of objective inflammatory signs such as high CRP (51%), positive HLA-B27 (65%, 59%), and the proportion of extra-musculoskeletal manifestations (uveitis (16%), psoriasis (17%, 6%) and IBD (3%, 6%)) are all in favor of a correct pSpA diagnosis. Moreover, the prevalence of fibromyalgia (as detected by the FiRST questionnaire) in the current study is compatible with the one reported in studies with axSpA [23,24].

Finally, the current study identified a high disease burden in pure pSpA as illustrated by worse measures of BASDAI, ASDAS, BASFI, ASAS-HI compared to pure forms of PsA and axSpA, but within a similar range of combined forms of SpA. Although high burden has been previously reported in combined forms of SpA [7], it is reported here for the first time for pure pSpA. However, this high burden contrasts with lower use of b-DMARDs (less than half of the patients) compared to pure PsA, pure axSpA, and combined forms of SpA (around 60%), a comparable finding to the COMOSPA ancillary study by Lopez-Medina et al. [16]. This contrast confirms the poorly defined nature of pSpA and the paucity of therapeutic trials in this indication [25,26], which may drive prescription hesitancy and/or difficulties in obtaining drug approvals for these patients.

The study has some limitations due to the cross-sectional design of the PerSpA study, which may introduce some recall bias regarding the disease manifestations and does not allow to evaluate cause-effect relationships. Hence, a longitudinal study design with multiple patient-reported outcomes measurements may be more suitable to draw firm results about the course of the burden of disease related to pSpA. Another limitation is the possibility of classification bias when using the classification criteria. Nevertheless, we used two parallel approaches (classification criteria and diagnostic) and would expect that the proper diagnosis and the identification of manifestations have been well judged

Table 4
Proportion of pure peripheral spondyloarthritis (pSpA) compared to pure psoriatic arthritis (PsA), pure axial SpA (axSpA) and combined form of SpA across the world regions, using the classification criteria and the diagnostic approaches.

World Region	Number of Patients	Pure peripheral SpondyloArthritis	Pure Psoriatic Arthritis	Pure axial SpondyloArthritis	Combined forms of SpondyloArthritis
Classification criteria Approach					
Whole study population, N (%)	4185	221 (5.3)	345 (8.2)	1888 (45.1)	1731 (41.4)
Latin America	**487**	35 (7.2)	54 (11.1)	135 (27.7)	263 (54.0)
Europe and North America	**1603**	60 (3.7)	165 (10.3)	778 (48.5)	600 (37.4)
Asia	**913**	53 (5.8)	58 (6.4)	433 (47.4)	369 (40.4)
Middle East and North Africa	**1182**	73 (6.2)	68 (5.8)	542 (45.9)	499 (42.2)
Diagnostic Approach					
Whole study population, N (%)	4185	270 (6.4)	600 (14.3)	2046 (48.9)	1269 (30.3)
Latin America	**487**	29 (6.0)	134 (27.5)	155 (31.8)	169 (34.7)
Europe and North America	**1603**	58 (3.6)	269 (16.8)	841 (52.5)	435 (27.1)
Asia	**913**	73 (8.0)	77 (8.4)	393 (43.0)	370 (40.5)
Middle East and North Africa	**1182**	110 (9.3)	120 (10.2)	657 (55.6)	295 (25.0)

All percentages are presented in rows.

since all patients were recruited from centers of investigators who are ASAS members with longstanding expertise in the field of SpA. A classification bias may also occur while the rheumatologists might be aware in advance that a patient fulfills the classification criteria, thus using such criteria as means of diagnosis as well. Nonetheless, the study inclusion criteria consisted specifically of the presence of axSpA, pSpA, or PsA based on the rheumatologist's diagnosis, and the fulfillment of criteria was not requested at any stage of completing the case report form.

The most important strengths of this study are the large sample of SpA patients (>4000), recruited from several countries and continents of the globe with different ethnic and genetic backgrounds, which increases the external validity and the generalizability of the results, as well as the coverage of the whole spectrum of the disease. Moreover, this is the first study to provide a detailed characterization of the proportion, phenotype, and disease burden of the poorly studied pure pSpA entity. Furthermore, the current study, allowed to conduct two approaches for analysis, by means of the readily available data of the original ASAS-PerSpA study. With that, characteristics of pSpA are fully described, either individual patients met in daily practice (as per rheumatologists' diagnosis approach), or patients fulfilling classification criteria, as would happen in clinical studies (the classification criteria approach). Also, the full spectrum of pSpA is shown (that can range from patients labelled as pSpA at one stage of their disease, and later develop features that now permit labeling them as a distinct spondyloarthritis disease entity). In that context, these analytical approaches highlighted full characterization of pSpA patients that may be met in practice.

In summary, the proportion of pSpA varies when using classification criteria or the rheumatologist's diagnosis. It occurred in a pure form (i.e., associated with neither PsA nor axSpA) less frequently than PsA and axSpA. Pure pSpA had a distinct clinical phenotype with intermediate features between pure PsA and pure axSpA but with a higher disease burden compared to both diseases and lower use of b-DMARDs. This contrast between high disease burden and low use of b-DMARDs confirms the poorly characterized nature of pure pSpA and highlights the need for a better disease definition.

Declarations

Authors' contributions

MD and CLM conducted the original ASAS-PerSpA study.

NZ and XB designed the study and wrote the study protocol for this ancillary analysis.

NZ, JR and SH conducted the statistical analysis. NZ and JR drafted the manuscript

All the authors participated in the study design and protocol, in the analysis and interpretation of the results.

All the authors made substantial contributions to work and participated in the discussion of the study results, the draft of the manuscript and revised the final submitted document for intellectual content.

All the authors approved the version to be published and agreed to be accountable for all aspects of the work.

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Ethics approval

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

Previous publication

The work was presenter as a poster (#1787) at the American College of Rheumatology ACR Convergence 2021.

Declaration of Competing Interest

The authors declare no conflict of interest related to this study.

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