Peripheral Manifestations in Spondyloarthritis and their Effect: An Ancillary Analysis of the ASAS-COMOSPA Study

Clementina López-Medina, Anna Moltó, and Maxime Dougados

ABSTRACT. ***Objective.*** To determine the factors associated with the presence of peripheral manifestations in patients with spondyloarthritis (SpA) from the Assessment in SpondyloArthritis international Society (ASAS)-COMOSPA study, and to evaluate the effect of these symptoms on treatment and patient-reported outcomes (PRO).

Methods. All patients from the ASAS-COMOSPA study were included. All patients had an SpA diagnosis according to the rheumatologist. Patients and disease characteristics associated with the presence of these peripheral manifestations (peripheral arthritis, peripheral enthesitis, or dactylitis) were analyzed by univariate and multivariate logistic regression. Patients who reported peripheral manifestations were divided into 3 categories: current, history, and no history. The effect of peripheral involvement on PRO was evaluated through the use of 1-factor ANOVA.

Results. Out of the 3984 patients included in ASAS-COMOSPA, 2562 (64.3%) reported at least 1 peripheral manifestation, with a prevalence of 51.5%, 37.8%, and 15.6% for peripheral arthritis, peripheral enthesitis, and dactylitis, respectively. Being from South America, having a history of uveitis, having a current case or history of psoriasis, and the absence of HLA-B27 were associated with higher prevalence of peripheral manifestations. Patients with peripheral involvement showed greater use of drugs, and those with "current" peripheral manifestations showed higher levels in all PRO, in contrast to those with past or no history.

Conclusion. Peripheral manifestations appear in 64% of patients with SpA. Psoriasis and the absence of HLA-B27 are associated with the development of peripheral symptoms. The presence of any peripheral symptom at the time of the visit was associated with higher scores in all PRO. (J Rheumatol First Release August 15 2019; doi:10.3899/jrheum.181331)

Key Indexing Terms:
SPONDYLOARTHRITIS PERIPHERAL MANIFESTATIONS

Spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease that mainly affects the axial skeleton and sacroiliac joints. Within the clinical picture, patients with SpA may also experience peripheral symptoms such as arthritis, enthesitis, and dactylitis, as well as extrarheumatological manifestations (psoriasis, uveitis, and inflammatory bowel disease)[1].

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The prevalence of these peripheral manifestations is rather unclear and varies depending on the subtype of SpA [e.g., ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-associated SpA, reactive arthritis, and undifferentiated SpA] and the disease stage. In addition, most studies about peripheral manifestations are focused on axial SpA (axSpA), and not on peripheral phenotypes. In 2011, the Assessment in SpondyloArthritis international Society (ASAS) group published the classification criteria for peripheral SpA[2,3]. In that study, the most frequent single peripheral manifestation was peripheral arthritis, observed in 46.6% of patients, followed by enthesitis (9.8%), and dactylitis (1.9%). One metaanalysis[4] showed that this prevalence varies depending on the disease stage; that is, the prevalence of peripheral manifestations was different between AS and nonradiographic axSpA (nr-axSpA).

The above data suggest that there is variability in the frequency of peripheral manifestations regarding the phenotype of SpA. In addition, there is a lack of knowledge about factors associated with the presence of these symptoms, and their effect on treatment and quality of life.

These preliminary remarks prompted us to conduct this

study aiming (1) to describe the prevalence (current or ever) of peripheral manifestations in patients with SpA; (2) to determine the factors associated with the presence of peripheral manifestations in these patients; and (3) to evaluate the effect of these symptoms on treatment and patient-reported outcomes (PRO).

MATERIALS AND METHODS

Study design. This is an ancillary analysis of the ASAS-COMOSPA study. ASAS-COMOSPA is an observational, cross-sectional, multicenter, and international study, with 22 participating countries from 4 continents (Africa, America, Asia, and Europe), performed under the umbrella of the ASAS society. This worldwide study was described in detail elsewhere[5].

Patients. All participants belonging to the ASAS-COMOSPA were included in this analysis (n = 3984). The inclusion criteria were adult patients fulfilling the ASAS criteria for peripheral SpA or axSpA[2]. All participants gave written informed consent and local ethics committees (North East-Newcastle/North Tyneside 2 Research Ethics committee 12/Ne/0417, the 14th/12/2012) approved the ASAS-COMOSPA study protocol.

Collected data. A case report form was used to collect the following data during face-to-face patient interviews at each center. Information about symptoms that occurred before the study visit were collected retrospectively by asking patients or checking their medical records.

Sociodemographic variables recorded included age, sex, obesity (body mass index ≥ 30 kg/m^2), smoking status, alcohol intake, education, and country of residence.

Regarding disease characteristics, data were collected on chronic inflammatory back pain (IBP; and date of onset), uveitis, personal and family history of psoriasis, HLA-B27 status, and IBD. Regarding peripheral manifestations (current or ever), peripheral arthritis was considered only in case of objective signs of synovitis demonstrated on clinical examination by a doctor or by imaging [magnetic resonance imaging (MRI), ultrasonography]. Enthesitis was considered not only at the heel level but also in other locations. History of dactylitis was collected. However, specific locations of these 3 peripheral manifestations were not collected in the case report form. Date of onset of these 3 peripheral manifestations (i.e., peripheral arthritis, peripheral enthesitis, and dactylitis) was collected.

Data were also collected regarding intake of nonsteroidal antiinflammatory drugs (NSAID), prednisone, conventional synthetic disease-modifying antirheumatic drugs (csDMARD), and biological DMARD (bDMARD). PRO collected were patient's global assessment [by numerical rate scale (NRS)], Bath Ankylosing Spondylitis Functional Index (BASFI)[6], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[7], and Work Productivity and Activity Impairment Questionnaire (WPAI)[8].

Missing data were considered negative (e.g., in case of missing data on history of dactylitis, the patient was considered as not having ever presented dactylitis).

Classification criteria. Patients included in the ASAS-COMOSPA study had to fulfill the ASAS criteria according to the rheumatologist; however, the fulfillment of these criteria was not verified before the recruitment. For this reason, the fulfillment of ASAS (peripheral SpA or axSpA) and ClASsification for Psoriatic ARthritis (CASPAR) criteria was recalculated in this analysis[9].

To evaluate ASAS criteria, we first selected patients with "current" IBP. In this group, only axial ASAS criteria could be applied[2]; thus, in these patients, we confirmed the presence of back pain for at least 3 months and age at onset below 45 years, and if they were positive, we confirmed the fulfillment of any of the 2 arms (imaging or clinical arm). In patients with radiographic or MRI sacroiliitis, only 1 SpA feature was required to fulfill the imaging arm. Patients without positive imaging but with HLA-B27–positive antigen needed at least 2 other additional SpA features to be classified as axSpA according to the clinical arm. In patients without "current" IBP, peripheral ASAS criteria could only be applied in patients with "current" peripheral manifestations (i.e., peripheral arthritis, peripheral enthesitis, or dactylitis)[10]. These patients were required to have another SpA feature if this was a specific SpA feature or at least 2 SpA features for less-specific features to be classified as peripheral SpA[2]. Finally, in patients with neither "current" IBP nor "current" peripheral manifestations, ASAS criteria for axSpA were applied in case of presence of back pain for at least 3 months and age at onset below 45 years.

Regardless of the fulfillment of ASAS criteria, all patients were evaluated for CASPAR criteria fulfillment[9]. In this criteria set, the entry criterion is the presence of inflammatory articular disease (joint, spine, or entheseal) and a score ≥ 3 points based on the presence of psoriasis, psoriatic nail dystrophy, negative test result for rheumatoid factor, dactylitis, and radiologic evidence of juxtaarticular new bone formation (each characteristic is assigned a specific number of points).

Statistical analysis. First, a description of the prevalence of the 3 peripheral manifestations, both in the entire cohort and regarding different sets of criteria, was performed.

To evaluate the time of occurrence of peripheral manifestations regarding axial disease (i.e., IBP), we evaluated date of onset of each symptom. In this way, patients were divided into 3 groups: before, concomitantly, or after axial symptoms.

Factors associated with the presence of each peripheral manifestation were studied first by univariate analysis, and thereafter by multivariate logistic regression, including in the model variables selected by the univariate analysis (when $p \leq 0.15$). Interactions, confounding factors, and collinearity were tested, and all comparisons were bilateral, considering $p \leq 0.05$ as a significant result.

Treatment modalities were compared in patients with/without each of the peripheral manifestations by using the chi-square and t test for qualitative and quantitative variables, respectively.

PRO were compared across patients with history/current/never peripheral manifestations by 1-factor ANOVA test.

All of these analyses were performed for peripheral arthritis, enthesitis, and dactylitis individually, and considering "any" peripheral manifestation (peripheral arthritis OR peripheral enthesitis OR dactylitis). Data were analyzed using the software SPSS 20.0 version.

RESULTS

Prevalence. Regarding the total worldwide COMOSPA database, 2777 (69.7%) patients fulfilled the axial ASAS criteria, 558 (14.0%) the peripheral ASAS criteria, and 894 (22.4%) the CASPAR criteria, while 431 (10.8%) patients did not fulfill any classification set. There were 322 patients (8.1%) who fulfilled both the peripheral ASAS and CASPAR criteria.

A total of 2562 patients (64.3%) reported at least 1 peripheral manifestation during their disease course. The most prevalent peripheral manifestation was peripheral arthritis (51.5%). Among patients who fulfilled both the peripheral ASAS and CASPAR criteria, this percentage increased to 98.4% (Figure 1). Peripheral enthesitis was reported in 37.8% of patients. Among those who fulfilled the peripheral ASAS criteria, this prevalence was 62.7%, and 50.5% in the CASPAR criteria group. Finally, the prevalence of dactylitis was 15.6% and was more frequent among patients who fulfilled both the peripheral ASAS and CASPAR criteria (52.8%). Among the group of patients who did not fulfill any classification set (n = 431), 57.5% reported at least 1 peripheral manifestation (44.5%, 35.3%, and 11.4% reported peripheral arthritis, peripheral enthesitis, and

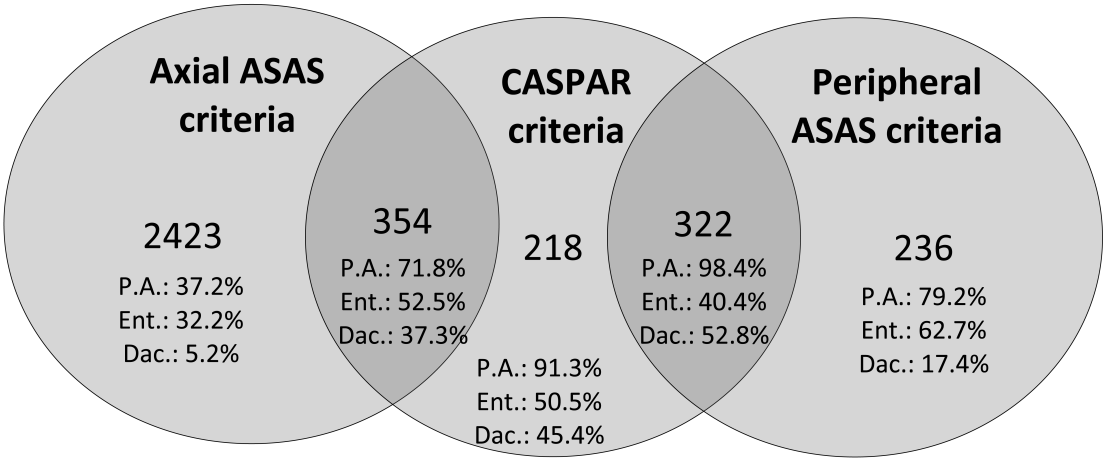

Figure 1. Venn diagram from the total of the COMOSPA database (3984 patients), representing the distribution of peripheral manifestations among the different classification sets. Note: 431 patients fulfilled neither axial ASAS, nor peripheral ASAS, nor CASPAR criteria (peripheral arthritis 44.5%, enthesitis 35.3%, dactylitis 11.4%). P.A.: peripheral arthritis; Ent.: enthesitis; Dac.: dactylitis; ASAS: Assessment in SpondyloArthritis international Society; CASPAR: ClASsification for Psoriatic ARthritis criteria.

dactylitis, respectively). The prevalence of other SpA features in each subgroup of patients is shown in Supplementary Table 1, available with the online version of this article. Among patients who reported current peripheral arthritis at the time of the study (n = 1333), the presentation was more frequently oligoarticular (40.2% showed between 1 and 3 swollen joints) than polyarticular (16% of patients showed between 4 and 10 swollen joints; Supplementary Figure 1).

Distribution of peripheral manifestations across continents (Supplementary Table 2, available with the online version of this article) showed that these are more frequent among patients from South American countries.

Among the 2562 patients (64.3%) who presented at least 1 peripheral manifestation (i.e., either peripheral arthritis, enthesitis, or dactylitis), a total of 1875 patients (47.1% from the entire cohort) also had axial involvement. Among these, 489 (26.1%) showed at least 1 peripheral manifestation before axial symptoms, 518 (27.6%) concomitantly, and 1149 (61.3%) after axial involvement. Analyzing each peripheral manifestation individually, the 3 appeared more frequently after axial symptoms onset (47.4%, 58.3%, and 60.8% for peripheral arthritis, peripheral enthesitis, and dactylitis, respectively; Supplementary Figure 2, available with the online version of this article).

Factors associated with peripheral manifestations. Peripheral manifestations (Table 1) were more frequent among older patients (≥ 43 yrs old, which corresponds to the median age of the ASAS-COMOSPA population; OR 1.68, 95% CI 1.45–1.94), females (OR 1.42, 95% CI 1.21–1.66), those from South American countries (OR 3.23, 95% CI 2.40–4.37), HLA-B27–negative patients (OR 1.32, 95% CI 1.14–1.54), those with absence of chronic IBP (OR 1.56, 95% CI 1.27–1.91), with uveitis (OR 1.32, 95% CI 1.10–1.57), with psoriasis (OR 5.45, 95% CI 3.98–7.46), with family history of psoriasis (OR 1.61, 95% CI 1.26–2.07), those who have never smoked (OR 1.34, 95% CI 1.15-1.50), and those who have never consumed alcohol (OR 1.32, 95% CI 1.14–1.53).

Peripheral arthritis, specifically (Table 2), was associated with age ≥ 43 years (OR 1.44, 95% CI 1.24–1.67), residence in South American countries (OR 1.97, 95% CI 1.51–2.58), HLA-B27–negative patients (OR 1.29, 95% CI 1.11–1.50), absence of chronic IBP (OR 1.89, 95% CI 1.55–2.33), peripheral enthesitis (OR 2.48, 95% CI 2.13–2.88), dactylitis (OR 6.56, 95% CI 4.90–8.84), psoriasis (OR 4.20, 95% CI 3.22–5.50), family history of psoriasis (OR 1.44, 95% CI 1.13–1.82), never smoking (OR 1.41, 95% CI 1.21–1.64), and never alcohol intake (OR 1.36, 95% CI 1.17–1.58).

Peripheral enthesitis (Table 3) was frequent among South American patients (OR 2.29, 95% CI 1.81–2.90), obese patients (OR 1.22, 95% CI 1.03–1.45), those with peripheral arthritis (OR 2.58, 95% CI 2.23–3.00), dactylitis (OR 2.33, 95% CI 1.91-2.84), uveitis (OR 1.50, 95% CI 1.27–1.78), and family history of psoriasis (OR 1.25, 95% CI 1.02–1.53).

Finally, dactylitis (Supplementary Table 3, available with the online version of this article) was more frequent in older patients (age ≥ 43 years; OR 1.33, 95% CI 1.08–1.63), those with high socioeducational level (OR 1.49, 95% CI 1.22–1.84), HLA-B27–negative patients (OR 1.48, 95% CI 1.19–1.84), absence of chronic IBP (OR 1.81, 95% CI 1.45–2.27) peripheral arthritis (OR 6.95, 95% CI 5.16–9.36), peripheral enthesitis (OR 2.51, 95% CI 2.05–3.06), psoriasis (OR 2.08, 95% CI 1.64–2.64), family history of psoriasis (OR 1.60, 95% CI 1.25–2.03), and non-smokers (OR 1.44, 95% CI 1.18–1.76).

Effect on treatment and PRO. Evaluation of the effect of peripheral manifestations on treatment (Table 4) yielded that the presence of any of the 3 peripheral manifestations was

Table 1. Multivariate logistic regression showing factors associated with the presence of any peripheral manifestation.

Characteristics	Any Peripheral Manifestation, n = 2562 (%)	No Peripheral Manifestation, n = 1422 (%)	OR (95% CI)[1]	p
Age ≥ 43 yrs	1415 (55.2)	535 (37.6)	1.68 (1.45–1.94)	< 0.001
Sex (female)	1016 (39.7)	378 (26.6)	1.42 (1.21–1.66)	< 0.001
Socioeducational level (university)	1075 (42.0)	608 (42.8)		
South American	295 (11.5)	57 (4.0)	3.23 (2.40–4.37)	< 0.001
Obese (BMI ≥ 30)	554 (21.6)	209 (14.7)		
HLA-B27–negative	1297 (50.6)	470 (33.1)	1.32 (1.14–1.54)	< 0.001
Absence of chronic IBP	592 (23.1)	167 (11.7)	1.56 (1.27–1.91)	< 0.001
Uveitis	510 (19.9)	259 (18.2)	1.32 (1.10–1.57)	0.003
Psoriasis	584 (22.8)	50 (3.5)	5.45 (3.98–7.46)	< 0.001
Family history of psoriasis	443 (17.3)	101 (7.1)	1.61 (1.26–2.07)	< 0.001
IBD	148 (5.8)	60 (4.2)		
Never smoking	1448 (56.5)	690 (48.5)	1.34 (1.15–1.50)	< 0.001
Never alcohol intake	1289 (50.3)	630 (44.3)	1.32 (1.14–1.53)	< 0.001

Hosmer-Lemeshow test: chi-square = 9.165; p = 0.329. [1] OR (95% CI) for statistically significative variables that remain in the final model. Percentages indicate no. patients with the covariate from the total no. patients in each column. BMI: body mass index; IBD: inflammatory bowel disease; IBP: inflammatory back pain.

Table 2. Multivariate logistic regression showing factors associated with current or ever peripheral arthritis.

Characteristics	Peripheral Arthritis, n = 2051 (%)	No Peripheral Arthritis, n = 1933 (%)	OR (95% CI)[1]	p
Age ≥ 43 yrs	1163 (56.7)	787 (40.7)	1.44 (1.24–1.67)	< 0.001
Sex (female)	821 (40.0)	573 (29.6)		
Socioeducational level (university)	867 (42.3)	816 (42.2)		
South American	249 (12.1)	103 (5.3)	1.97 (1.51–2.58)	< 0.001
Obese (BMI ≥ 30)	446 (21.7)	317 (16.4)		
HLA-B27–negative	1100 (53.6)	667 (34.5)	1.29 (1.11–1.50)	0.001
Absence of chronic IBP	545 (26.6)	214 (11.1)	1.89 (1.55–2.33)	< 0.001
Peripheral enthesitis	1021 (49.8)	485 (25.1)	2.48 (2.13–2.88)	< 0.001
Dactylitis	563 (27.5)	55 (2.8)	6.56 (4.90–8.84)	< 0.001
Uveitis	381 (18.6)	388 (20.1)		
Psoriasis	545 (26.6)	89 (4.6)	4.20 (3.22–5.50)	< 0.001
Family history of psoriasis	390 (19.0)	154 (8.0)	1.44 (1.13–1.82)	0.003
IBD	120 (5.9)	88 (4.6)		
Never smoking	1191 (58.1)	947 (49.0)	1.41 (1.21–1.64)	< 0.001
Never alcohol intake	1046 (51.0)	873 (45.2)	1.36 (1.17–1.58)	< 0.001

Hosmer-Lemeshow test: chi-square = 10.575; p = 0.227. [1] OR (95% CI) for statistically significative variables that remain in the final model. Percentages indicate no. patients with the covariate from the total no. patients in each column. BMI: body mass index; IBD: inflammatory bowel disease; IBP: inflammatory back pain.

associated (p < 0.001) with a greater use of drugs such as NSAID [2326 (90.8%) vs 1222 (85.9%)], csDMARD [1825 (71.2%) vs 546 (38.4%)], bDMARD [1236 (48.2%) vs 506 (35.6%)], and corticosteroids [1223 (47.7%) vs 300 (21.1%)], compared to patients without history of these symptoms. The same results were obtained when we analyzed the effect of each peripheral manifestation individually (Supplementary Table 4, available with the online version of this article).

PRO were compared in patients divided into 3 groups depending on the presence of the peripheral manifestation at the time of the study: "current" (before the study), "past history," or "never" (not at all). These factors showed statistically significant higher numbers in patients with "current" peripheral arthritis compared to patients classified as "past history" or "never," respectively (Supplementary Figure 3, available with the online version of this article): patient's global NRS (4.6 vs 3.3 vs 3.9), BASDAI (4.5 vs 2.9 vs 3.4), BASFI (38.2 vs 24.9 vs 26.6), work impairment (34.7 vs 21.0 vs 26.6), and activity impairment (39.4 vs 24.9 vs 29.5; both from the WPAI questionnaire). Similar results were obtained for peripheral enthesitis and dactylitis (Supplementary Figures 4 and 5).

DISCUSSION

To our knowledge, this is one of the first studies to attempt to evaluate peripheral manifestations not only in axSpA but also in the whole group of SpA. Our study shows that more than 64.3% of patients with SpA, regardless of the initial

Table 3. Multivariate logistic regression showing factors associated with current or ever peripheral enthesitis.

Characteristics	Peripheral Enthesitis, n = 1506 (%)	No Peripheral Enthesitis, n = 2478 (%)	[1]OR (95% CI)	p
Age ≥ 43 yrs	805 (53.5)	1145 (46.2)		
Sex (female)	582 (38.6)	812 (32.8)		
Socioeducational level (university)	654 (43.4)	1029 (41.5)		
South American	210 (13.9)	142 (5.7)	2.29 (1.81–2.90)	< 0.001
Obese (BMI ≥ 30)	331 (22.0)	432 (17.4)	1.22 (1.03–1.45)	0.023
HLA-B27–negative	690 (45.8)	1077 (43.5)		
Absence of chronic IBP	277 (18.4)	482 (19.5)	0.65 (0.54–0.78)	< 0.001
Peripheral arthritis	1168 (77.6)	1211 (48.9)	2.58 (2.23–3.00)	< 0.001
Dactylitis	378 (25.1)	240 (9.7)	2.33 (1.91–2.84)	< 0.001
Uveitis	348 (23.1)	421 (17.0)	1.50 (1.27–1.78)	< 0.001
Psoriasis	273 (18.1)	361 (14.6)	1.31 (1.07–1.61)	0.010
Family history of psoriasis	255 (16.9)	289 (11.7)	1.25 (1.02–1.53)	0.031
IBD	92 (6.1)	116 (4.7)		
Never smoking	830 (55.1)	1380 (52.8)		
Never alcohol intake	765 (50.8)	1154 (46.6)		

Hosmer-Lemeshow test: chi-square = 9.166; p = 0.241. [1] OR (95% CI) for statistically significative variables that remain in the final model. Percentages indicate no. patients with the covariate from the total no. patients in each column. BMI: body mass index; IBD: inflammatory bowel disease; IBP: inflammatory back pain.

Table 4. Effect of any peripheral manifestation on the treatment.

	Total = 3984	Any Peripheral Manifestation		
		Yes = 2562, n (%)	No = 1422, n (%)	p[1]
NSAID				
N (%) patients since the onset of SpA symptoms	3548 (89.0)	2326 (90.8)	1222 (85.9)	< 0.001
DMARD intake, past or present, n (%)				
csDMARD	2371 (59.5)	1825 (71.2)	546 (38.4)	< 0.001
bDMARD	1742 (43.7)	1236 (48.2)	506 (35.6)	< 0.001
Corticosteroids				
% of patients using corticosteroids	1523 (38.2)	1223 (47.7)	300 (21.1)	< 0.001
Current prednisone intake, mg, mean (SD)	1.01 (4.18)	1.35 (4.82)	0.39 (2.53)	< 0.001
Estimated total intake, mg, mean (SD)	1741 (6901)	2388 (8047)	576 (3827)	< 0.001

[1] Chi-square and t test for qualitative and quantitative variables, respectively. Percentages indicate no. patients with the covariate from the total no. patients in each column. NSAID: nonsteroidal antiinflammatory drugs; SpA: spondyloarthritis; DMARD: disease-modifying antirheumatic drugs; csDMARD: conventional synthetic DMARD; bDMARD: biological DMARD.

presentation, report at least 1 peripheral manifestation at some point during the course of the disease. This study confirms the high prevalence of peripheral rheumatological manifestations in the history of patients presenting axial symptoms, emphasizing the importance of checking for those clinical features to facilitate the diagnosis of SpA. Moreover, the high probability of the occurrence of these peripheral manifestations over time after the occurrence of axial symptoms emphasizes also the importance of a systematic iterative check of these clinical features during the monitoring of these patients.

The most frequent peripheral manifestation in our study was peripheral arthritis (51.5%). This manifestation was found to be more prevalent among patients fulfilling concomitantly the CASPAR criteria for psoriatic arthritis. These results are in line with those reported in studies focused on peripheral SpA and PsA, where peripheral arthritis was reported in about 46% and 51% of patients, respectively[2,11]. Cases of peripheral arthritis were more frequently oligoarticular than polyarticular; only 16% of patients showed polyarticular involvement (most likely patients with the psoriatic subtype). These data confirm the suitability of including peripheral arthritis as a SpA feature in the Amor, European Spondylarthropathy Study Group, and ASAS criteria[2,12,13], allowing us to cover the whole spectrum of the SpA, in contrast to the New York criteria[14].

In our study, considering patients who fulfill only the axial ASAS criteria, the percentage of peripheral arthritis decreased to 37.2%, slightly higher than that reported in axSpA (20–30%)[4,11]. This can be explained by the great heterogeneity of COMOSPA participants, which include South American patients, who are more likely to develop

peripheral manifestations. The second most prevalent peripheral manifestation was enthesitis (37.8%), followed by dactylitis (15.6%). In axSpA, these manifestations appeared more frequently after axial symptom onset; that is, patients with axial forms can develop peripheral manifestations at any time during the followup.

Peripheral manifestations were more frequent among older patients. This is because the cumulative probability of appearance of these symptoms is higher in older patients. These symptoms are also more frequent among patients from South American countries, which confirms previous studies reporting a greater prevalence of peripheral arthritis and enthesitis in Latin Americans compared with European patients[15]. This finding can be explained by the lower prevalence of the HLA-B27 antigen in Latin populations[16], which is classically associated with axSpA, particularly AS[17]. Psoriasis and family history of psoriasis are also 2 independent factors associated with the development of these symptoms. These results are expected because 96% of patients with PsA have peripheral joints affected and only 50% have axial involvement[18].

In our study, peripheral arthritis and dactylitis were less prevalent among HLA-B27–positive patients, patients with chronic IBP, and smokers. It is well known that smoking can be associated with radiographic severity in axSpA[19,20]; however, the relationship between smoking and peripheral manifestation is not well known. Our results are in line with a recent work that demonstrated a lower prevalence of arthritis among current smokers in comparison to patients who have never smoked[21]. On the other hand, peripheral enthesitis was more prevalent among patients with chronic IBP and was not associated with either HLA-B27 or tobacco. This study also confirms results from the ESPeranza cohort in Spain, in which dactylitis was found to be associated with peripheral arthritis, enthesitis, and psoriasis[22]. Finally, we have shown that the presence of any of the 3 peripheral manifestations (arthritis, enthesitis, or dactylitis) is associated with the development of other peripheral symptoms.

The evaluation of the effect of peripheral manifestations on treatment showed that the presence of any of the 3 peripheral manifestations was associated with a greater use of any drug. As expected, corticosteroids and csDMARD were more frequent among patients with arthritis, peripheral enthesitis, or dactylitis. Interestingly, bDMARD were also more frequently used among patients with these peripheral symptoms as compared to those without peripheral manifestations.

Regarding PRO, the presence of any peripheral manifestation at the time of the study visit resulted in higher levels on all questionnaires compared to those patients with a history or who had never had these symptoms.

Our study had some limitations but also several strengths. A limitation was the cross-sectional design of the study, which hampered our ability to collect information about symptoms that occurred before the study visit, and to determine whether the appearance of peripheral manifestations are causes or consequences of other clinical characteristics. However, the availability of the timing of each manifestation provided us the possibility to determine the natural course of the disease in each patient. The second limitation was that no systematic assessment and scoring of peripheral manifestations was performed (e.g., 44 swollen joint count, Maastricht AS Enthesitis Score). Finally, the proportion of patients with axSpA is larger than the other 2 groups, which could lead to an underestimation of peripheral symptoms. However, this proportion is in line with clinical practice, in which patients with axSpA are more prevalent than those with peripheral SpA.

The main strengths of our study are the large sample of patients with SpA, covering the whole spectrum, and that to our knowledge, it is the first to evaluate peripheral manifestations not only in axSpA but also in the whole group of SpA in a worldwide population.

Because the majority of studies evaluating peripheral manifestations have been conducted in patients with axSpA, other studies focused in peripheral SpA patients are required. This will enable us to better determine the relationship between these clinical manifestations and psoriasis and also to better analyze this clinical presentation and treatment possibilities.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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