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Original article

Differences between early vs. late-onset of psoriatic arthritis: Data from the RESPONDIA and REGISPONSER registries

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ABSTRACT

Objectives: The objective was to evaluate the association between the age at onset of psoriatic arthritis (PsA) symptoms with the characteristics and burden of the disease.
Methods: This was an observational and cross-sectional study that included a subgroup of 231 patients with PsA with < 10 years of disease duration from the REGISPONSER and RESPONDIA registries. Patients were divided into two groups according to the age of PsA symptom onset (early onset: ≤ 40-years-old and late onset: ≥ 60-years-old). The characteristics and burden of the disease were compared between the two groups, and multivariate logistic regression was performed to determine the factors independently associated with late-onset PsA.
Results: Patients from the early-onset group showed a significantly lower prevalence of males [94 (62.3%) vs. 38 (86.4%)] and a higher prevalence of enthesitis [44 (24.6%) vs. 5 (9.8%)] and sacroiliitis [30 (16.8%) vs. 4 (7.7%)]. Additionally, the early-onset group showed lower scores on the BASFI [2.2 (2.2) vs. 3.3 (2.5)] and minor structural damage (BASRI) in both the spine [1.6 (2) vs. 2.9 (3)] and whole axial skeleton (total BASRI) [1.9 (2.4) vs. 3.4 (3.4)]. In contrast, no statistically significant differences were found between the groups in disease activity evaluated by the BASDAI and ASDAS. Logistic regression analysis showed that late-onset PsA was independently associated with being male (OR 4.4, 95% CI: 1.3, 16.3), greater structural damage (total BASRI) (OR 3.3, 95% CI: 1.3, 8.1), a higher frequency of arthritis in the upper limbs (OR 2.8, 95% CI: 1, 7.7), and greater loss of function (BASFI) (OR 1.3, 95% CI: 1, 1.6).
Conclusions: Patients with late-onset PsA showed different clinical characteristics and greater disease severity than those with early-onset PsA.

1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory rheumatic disease that affects the musculoskeletal system and the skin. In addition to joint involvement, it is associated with several clinical manifestations, such as enthesitis, skin and/or nail psoriasis, dactylitis, uveitis and osteitis [1]. The prevalence of PsA in the general population is 0.05–0.25% and is approximately 6–30% in patients with psoriasis (PsO) [2]. It mainly affects people between 40–50 years of age, with practically the same incidence in men and women [3]. Usually, PsO appears before arthritis (70–80% in cases), and it takes an average of 7–10 years to appear [4].

PsA is mediated by the immune system, in which genetic susceptibility and environmental factors are involved. These interactions generate several clinical phenotypes [5]; currently, Moll and Wright described five clinical subtypes of PsA that highlight the heterogeneity of the disease [6]. The development of PsA, as well as PsO, can be accompanied by several comorbidities due to the diverse mechanisms of continuous inflammation, including

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cardiovascular disease (CVD), the main cause of mortality in these patients [7].

Patients with PsA usually develop their first symptoms under the age of 50 but can be observed in older patients. There are a few studies investigating the differences between early- and late-onset PsA. These studies agree that late-onset PsA has been described as a more severe disease associated with worse functional results [8–10]; however, the difference between the groups studied is not always clear, and often overlap. To our knowledge, there are no studies that compare the early-onset group (≤ 40-years-old) with the late-onset group (≥ 60-years-old), which would avoid confusion in the ages between 40–60 years old, where the classification into the respective groups is not clear. These studies are not directly comparable because there is no accepted age cut-off to differentiate early- vs. late-onset PsA.

There are other arguments that suggest analysing clearly differentiated age groups. Late-onset PsA has been linked to an increased risk of CV disease and metabolic syndrome [11]. Changes in the immune system known as immunosenescence and accumulated epigenetic modifications could contribute to these observations [12]. Furthermore, the elderly population presents greater functional deterioration and number of comorbidities than the young population, which entails a worse quality of life and worse outcomes of PsA. In addition, older people are usually polymedicated and have an increased risk of adverse effects due to drugs, which influences the treatment decision. It has been observed that the therapeutic strategies used in early- and late-onset PsA are the same. However, it should be individualized due to the increase in comorbidities and polypharmacy in older patients [13]. The prevalence of late-onset PsA is increasing in parallel with the progressive ageing of the population, which will require a deeper understanding of the characteristics of late-onset disease. The age at onset may play a role in disease activity, progression and therapeutic decisions, as seen in other diseases, such as rheumatoid arthritis (RA) [14]. With this study, we aim to find clinically relevant differences to predict the evolution and prognosis of the disease depending on the onset of the symptoms to carry out a more exhaustive follow-up.

The objective of this study was to evaluate the association of the age at onset of PsA symptoms with the characteristics and burden of the disease.

2. Methods

2.1. Patients

This is an observational and cross-sectional study that included a subgroup of 231 patients with PsA with < 10 years of disease duration from the REGISPONSER registry (Registry of Spondyloarthritis of Spanish Rheumatology) and the RESPONDIA registry (Iberoamerican Registry of Spondyloarthropathies). Patients were divided into two groups according to the age of PsA symptom onset (early onset: ≤ 40 years and late onset: ≥ 60 years). Only patients with less than 10 years of disease duration (since the first symptom) were selected in order to maintain sample homogeneity.

REGISPONSER is a national, cross-sectional and multicentre Spanish registry that incorporated spondyloarthritis (SpA) patients who fulfilled European Spondyloarthropathy Study Group (ESSG) criteria for spondyloarthritis between March 2004 and March 2007. The study was conducted by GRESSER (Spanish Group for the Study of Spondyloarthritis of the Spanish Rheumatology Society) [15] with thirty-one participating centres. More information about the design, sampling and recruitment of patients is detailed in a previous publication [16].

All patients signed a consent form, and the project was approved centrally by the Ethics Committee ("Comisión de Ética e Investigación Sanitarias") of the Reina Sofia University Hospital from Cordoba (Spain) on 21st April 2006.

RESPONDIA is a registry launched in 2005 as an extension study of REGISPONSER in Ibero-American patients with which it shares most of the variables studied. RESPONDIA was born as an invitation from the Spanish Society of Rheumatology [17]. It was constituted by nine Latin American countries (Argentina, Brazil, Chile, Costa Rica, Ecuador, México, Perú, Uruguay and Venezuela) and two Iberian countries (Spain and Portugal). It is a multicentre, multinational, cross-sectional study conducted between 2006 and 2007, which included consecutive patients with SpA according to the criteria of the European Group for the Study of Spondyloarthropathies (ESSG) and/or the Amor criteria.

2.2. Collected variables

A case report form was used to collect the following data:

- sociodemographic data: sex, age;
- clinical characteristics and PsA features: age of onset of PsA, disease duration (years between symptom onset and the study visit), age at onset of PsO and diagnostic delay (years between symptom onset and PsA diagnosis), erythrocyte sedimentation rate (ESR), CRP, sacroiliitis, enthesitis, dactylitis, arthritis in the lower limbs, arthritis in the upper limbs and uveitis;
- patient-reported outcomes (PROs): the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [18] and the Ankylosing Spondylitis Disease Activity Score (ASDAS) [19] were collected to evaluate disease activity. Function was assessed through the Bath Ankylosing Spondylitis Functional Index (BASFI) [20], and structural damage was evaluated using the Bath Ankylosing Spondylitis Radiology Index (BASRI) for the spine and total axial skeleton (which includes the spine and sacroiliac joints) [21]. The mental (MSF12) and physical (PSF12) components of the SF12 questionnaire were also evaluated [22];
- past and current treatment: Data on previous or concomitant treatments were collected, such as the use of csDMARDs and bDMARDs.

2.3. Statistical analysis

Descriptive data are shown as the mean and standard deviation (SD) for quantitative variables and as absolute and relative frequencies for qualitative variables.

Patients were divided into two groups according to the age of PsA onset: "early onset" if symptoms started at ≤ 40 years old and "late onset" if symptoms started at ≥ 60 years old. We defined symptom onset as musculoskeletal manifestations such as arthritis, enthesitis, or dactylitis. The characteristics and burden of the disease between the two groups were compared using Student's *t*-test/Mann-Whitney *U*-test for continuous variables or using the Chi^2/Fisher test for qualitative variables. Multivariate logistic regression was performed using variables with $P < 0.15$ from the univariate analysis to determine the factors independently associated with late-onset PsA. Confounding factors and interactions were tested.

All contrasts were bilateral and considered significant when the *P*-value < 0.05. Data were collected, processed and analysed using IBM SPSS Statistics v.25 (SPSS, Inc., Chicago, IL).

Table 1
Demographic and clinical characteristics of the two populations included in the study: REGISPONSER and RESPONDIA.

	PsA patients in REGISPONSER *n* = 155	PsA patients in RESPONDIA *n* = 76
Sex (male), *n* (%)	92/155 (59.4)	35/76 (46.1)
Age (SD), years	46 (15)	46.1 (18.7)
Race (white), *n* (%)	42/42 (100)***	50/76 (65.8)***
Enthesitis, n (%)	20/155 (12.9)***	29/76 (38.2)***
Dactilytis, *n* (%)	14/155 (9)***	31/76 (40.8)***
Sacroiliitis, *n* (%)	20/155 (12.9)	14/76 (18.4)
Diagnostic delay, mean (SD)	4.4 (8.2)*	1.4 (2.2)*
Disease duration, mean (SD)	4.1 (2.7)**	3.4 (2.6)**
Uveitis, *n* (%)	2/155 (1.3)	2/74 (2.7)
Arthritis (lower limbs), *n* (%)	90/155 (58.1)***	62/76 (81.6)***
Arthritis (upper limbs), *n* (%)	79/155 (51)	35/76 (46.1)
BASDAI, mean (SD)	3.8 (2.5)	4 (2.5)
BASFI, mean (SD)	2.1 (2.2)*	3.1 (2.5)*
ASDAS, mean (SD)	2.3 (1)	2.3 (1)
PSF12, mean (SD)	38.1 (11.3)	36.9 (7.6)
MSF12, mean (SD)	47.6 (11.9)	49 (5.7)
BASRI spine, mean (SD)	1.3 (2)***	3.2 (2.5)***
BASRI total, mean (SD)	1.6 (2.4)***	3.6 (3)***
ESR mm/h, mean (SD)	18.1 (15)**	20.1 (15.4)**
CRP mg/dL, mean (SD)	8.3 (12.7)***	5.8 (9)***
csDMARDs (ever), *n* (%)	82/151 (52.9)***	60/75 (80)***
bDMARDs (ever)	19/152 (12.3)	5/76 (6.6)

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; PSF12: physical components of the SF12 questionnaire; MSF12: mental components of the SF12 questionnaire; BASRI: Bath Ankylosing Spondylitis Radiology Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; bDMARDs: biological disease-modifying antirheumatic drugs; *: *P*-value < 0.05; **: *P*-value < 0.01; ***: *P*-value < 0.001.

3. Results

A total of 231 patients with a clinical diagnosis of PsA from the REGISPONSER and RESPONDIA with less than 10 years of disease duration were included in the analysis. The description of the demographic and clinical characteristics of the two populations included in the study (REGISPONSER and RESPONDIA) is described in Table 1. Overall, patients from REGISPONSER showed a greater prevalence of white race, peripheral involvement, and a longer diagnosis delay.

In the combined population, a total of 179 (77.5%) patients were classified as having early-onset (≤ 40 years) PsA, and 52 (22.5%) were classified as having late-onset (≥ 60 years) PsA. Descriptions of different characteristics between early and late onset are presented in Table 2.

There was a significantly lower percentage of men in the early-onset group than in the late-onset group [94 (62.3%) vs. 38 (86.4%)].

A higher presence of enthesitis was found in patients with early-onset PsA [44 (24.6%) vs. 5 (9.8%)] as well as sacroiliitis [30 (16.8%) vs. 4 (7.7%)]. The diagnostic delay was greater in those whose onset of the disease was early [4 (7.7) vs. 1.5 (2.7)], as well as the duration of the disease [4.2 (2.7) vs. 2.9 (2.4)]. No statistically significant differences were found in the univariate analysis for either dactylitis, uveitis or arthritis in the lower or upper limbs.

If we take psoriasis into account as the first symptom, no differences were found between the groups.

With regard to the outcome measures, the early-onset group showed lower scores on the BASFI [2.2 (2.2) vs. 3.3 (2.5)] and higher scores on the PSF12 component [38.7 (10.5) vs. 34.6 (8.7)]. The radiographic indices measured by BASRI showed better results in those patients with early-onset disease both in the spine [1.6 (2) vs. 2.9 (3)] and in the total BASRI [1.9 (2.4) vs. 3.4 (3.4)]. No statistically significant differences were found in relation to the disease activity evaluated by the BASDAI and ASDAS or in the MSF12 questionnaires. Finally, the early-onset group had lower levels of ESR in analytical tests [17.2 (14.2) vs. 23.9 (19.1)], and no statistically significant differences were observed in terms of treatment.

Table 2
Description of different characteristics in the two groups: early and late onset.

	Early-onset *n* = 179 *n* (%) = 77.5	Late-onset *n* = 52 *n* (%) = 22.5
Sex (male), *n* (%)	94/151 (62.3)**	38/45 (86.4)**
Age (SD), years	38.7 (9.3)***	71.3 (7.5)***
Enthesitis, *n* (%)	44/179 (24.6)*	5/52 (9.8)*
Dactilytis, *n* (%)	36/179 (20.1)	9/52 (17.6)
Sacroiliitis, *n* (%)	30/179 (16.8)**	4/52 (7.7)**
Diagnostic delay, mean (SD)	4 (7.7)**	1.5 (2.7)**
Disease duration, mean (SD)	4.2 (2.7)**	2.9 (2.4)**
Uveitis, *n* (%)	4/177 (2.3)	0/52 (0)
Arthritis (lower limbs), *n* (%)	118/179 (65.9)	34/52 (64.7)
Arthritis (upper limbs), *n* (%)	82/179 (45.8)	32/52 (60.8)
PsO as first symptom, *n* (%)	123/147 (83.7)	37/41 (90.2)
BASDAI, mean (SD)	3.9 (2.5)	3.8 (2.4)
BASFI, mean (SD)	2.2 (2.2)**	3.3 (2.5)**
ASDAS, mean (SD)	2.3 (1.1)	2.3 (0.9)
PSF12, mean (SD)	38.7 (10.5)**	34.6 (8.7)**
MSF12, mean (SD)	47.7 (10.6)	49.3 (9.2)
BASRI spine, mean (SD)	1.6 (2)*	2.9 (3)*
BASRI total, mean (SD)	1.9 (2.4)*	3.4 (3.4)*
CRP mg/dL, mean (SD)	7 (9.7)	9.5 (17.3)
ESR mm/h, mean (SD)	17.2 (14.2)**	23.9 (19.1)**
csDMARDs (ever), *n* (%)	111/177 (62.7)	32/50 (63.3)
bDMARDs (ever), *n* (%)	21/177 (11.9)	3/51 (6)

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; PSF12: physical components of the SF12 questionnaire; MSF12: mental components of the SF12 questionnaire; BASRI: Bath Ankylosing Spondylitis Radiology Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; bDMARDs: biological disease-modifying antirheumatic drugs; *: *P*-value < 0.05; **: *P*-value < 0.01; ***: *P*-value < 0.001.

Table 3
Factors associated with late-onset psoriatic arthritis.

	OR (95% CI)
Sex (male)	4.4 (1.3–16.3)**
Diagnostic delay	0.7 (0.6–0.8)
Enthesitis	0.1 (0–0.5)
Sacroiliitis	0.06 (0–0.5)
Arthritis (upper limbs)	2.8 (1–7.7)*
BASFI	1.3 (1–1.6)**
BASRI spine	0.3 (0.1–1)
BASRI total	3.3 (1.3–8.1)**

BASFI: Bath Ankylosing Spondylitis Functional Index; BASRI: Bath Ankylosing Spondylitis Radiology Index; *: *P*-value < 0.05; **: *P*-value < 0.01; ***: *P*-value < 0.001.

The multivariate analysis evaluating the factors independently associated with late-onset PsA is presented in Table 3. Late-onset PsA was independently associated with being male (OR 4.4, 95% CI: 1.3, 16.3), greater structural damage (total BASRI) (OR 3.3, 95% CI: 1.3, 8.1), a higher frequency of arthritis in the upper limbs (OR 2.8, 95% CI: 1, 7.7), and greater loss of functionality (BASFI) (OR 1.3, 95% CI: 1, 1.6) (Table 2). In addition, it was associated with a shorter diagnostic delay (OR 0.7, 95% CI: 0.6, 0.8) and lower frequency of both enthesitis (OR 0.1, 95% CI: 0, 0.5) and sacroiliitis (OR 0.06, 95% CI: 0, 0.5). Interactions between gender-diagnosis delay, gender-sacroiliitis and gender-BASFI were tested, but no significant results were found.

4. Discussion

This study suggests different clinical characteristics and outcome measures in early-onset PsA (patients who started the

symptoms at ≤ 40-years-old) in comparison with late-onset PsA (patients who started the symptoms at ≥ 60-years-old). Overall, late-onset patients showed a predominance of males and shorter diagnostic delay but with poorer function and greater structural damage. These results are consistent with previous studies that showed worse disease outcomes and more damage in the late-onset group [8–10].

PsA generally affects men and women almost equally [3]. However, our results showed that patients with late-onset PsA were more frequently males. This difference between the frequency of both sexes varies in the different studies that have been published to date, without a clearly prevalent sex [23–25].

The diagnostic delay was shorter in the late-onset group. One reason may be that the disease is more aggressive and therefore easier to diagnose in this group.

With regard to the peripheral and extra-articular manifestations, the late-onset group showed a lower prevalence of sacroiliitis and enthesitis and a higher prevalence of arthritis in the upper limbs, which is in line with previous studies [25,26]. Similarly, in patients with axial SpA, sacroiliitis occurs less frequently in older patients (> 45 years) and RA and other types of arthritis that can occur in upper limbs in those older than 40 years. No statistically significant differences were found regarding the presence of arthritis in the lower limbs, uveitis or dactylitis.

Punzi et al. observed that PsA was more severe in elderly people (who had more joints involved, higher inflammation levels at baseline and higher outcomes after two years). They suggested that this was explained by possible immune changes associated with ageing, as suggested by the higher concentrations of IL1A and IL6 found in the synovial fluid of old-onset PsA [10]. In our study, we did not observe greater activity evaluated by the ASDAS and BASDAI in patients with old-onset PsA, but there were higher levels of ESR. However, the ESR reference range is highly variable depending on age, increasing slightly.

We observed that the late-onset PsA group had greater structural damage evaluated by BASRI total and BASRI spine and possibly therefore a greater loss of functionality according to BASFI. Considering that they were older patients [early onset: 38.7 (9.3) years old vs. late onset: 71.3 (7.5) years old], apart from having the damage due to the disease, this group had an associated osteoarthritic-type pathology and other comorbidities that can increase the loss of functionality.

We did not find statistically significant differences regarding the quality of life evaluated by MSF12, although late-onset patients had worse functionality. This may be explained by the fact that elderly individuals, despite having less mobility, also have less work overload and less activity than those who are younger. Greater physical deterioration was also found in patients with late-onset PsA evaluated by PSF12.

Although late-onset patients possibly had a greater number of comorbidities and polypharmacy problems, we did not find statistically significant differences in the use of csDMARDs or bDMARDs. Additionally, this may mean that patients with late-onset PsA are being undertreated, since we have observed a greater severity of the disease in them.

The effect of age of onset on the prognosis has been compared in other rheumatic diseases. Different studies agree that those with late RA have more radiographic progression and more disease activity [27,28]. On the other hand, in the case of lupus, those with late onset of the disease usually present an indolent course, with less use of immunosuppressants and reduced disease activity [29]. Regarding radiographic axial spondyloarthritis (r-axSpA), similar disease activity has been observed between early and late onset [30]. There is no consensus to establish an age cut-off point in PsA to define "late-onset" patients. For this reason, the studies comparing late- and early-onset PsA known to date are not comparable. To date, researchers have established four possible cut-offs: 40, 50, 60 and 65 years [5]. In this study, we differentiated early-onset patients as those younger than 40 years and late-onset patients older than 60 years to clearly distinguish between early and late onset. To our knowledge, there are no other studies comparing these two age groups.

This analysis has some weaknesses alongside its strengths. One weakness is the cross-sectional design of the study and the limited sample size, which prevents us from drawing strong conclusions. Another limitation is the arbitrary age cut-off to distinguish early-onset and late-onset PsA. However, we think that this cut-off can well differentiate two populations within the whole spectrum of PsA according to the age of onset. One strength of this study is that it expands the knowledge of the differences between early- and late-onset PsA, emphasizing the need for closer monitoring of patients with late-onset PsA due to aggressiveness of the disease and poorer outcome measures.

Finally, it should be noted that the increase in life expectancy of the population and the consequent increase in patients with late-onset PsA highlight the need for more prospective studies comparing the early- and late-onset groups due to potential differences in prognosis and treatment.

In conclusion, our study suggests that the age of onset of PsA was associated with different characteristics and severity of the disease. Patients with late-onset PsA were more frequently males who showed worse functionality and more structural damage, emphasizing the need for closer monitoring due to the more severe disease and poorer outcomes.

Disclosure of interest

The authors declare that they have no competing interest.

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