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ORIGINAL RESEARCH

Clinical Characteristics of "Severe" Peripheral Psoriatic Arthritis: A Retrospective Analysis of a Longitudinal Cohort

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ABSTRACT

Introduction: The concept of severity in a multidomain disease such as psoriatic arthritis (PsA) is still not well defined. The aim of this study was to identify the clinical characteristics of patients with severe peripheral PsA.

Methods: Retrospective analysis of a longitudinal cohort. Demographic and clinical characteristics of patients with PsA were collected at baseline and at last follow-up. We defined the severe population using the modified Composite Psoriatic Disease Activity Index (mCPDAI); which excludes ankylosing spondylitis quality of life scale). Hence, patients with a score of 3 in at least one domain were defined as having severe PsA. Clinical characteristics of patients fulfilling the definition of severe PsA were compared to those non-severe.

Results: We evaluated 177 patients with peripheral PsA (M/F: 98/76). Of these, 64 (36.1%) were identified as severe according to the mCPDAI criteria, at baseline. Eighteen patients (10.1%) at last follow-up still met the definition of severe PsA. At last follow-up visit, severe patients with PsA were only males (18/18, $P < 0.01$) and have worse outcomes in terms of disease activity, pain, function, and impact of disease. Male sex and the severity of skin involvement at baseline were factors associated with the presence of severe PsA. The agreement between the presence of severe PsA and the absence of minimal disease activity was slight [Cohen's *k*: 0.174 (0.084–0.264)].

Conclusions: Our study showed that severe patients with PsA had more disease activity, pain, and impact of disease than non-severe patients. Furthermore, we demonstrated that severity and disease activity are not interchangeable concepts.

Keywords: Psoriatic arthritis; Treatment; Outcome measures; Severity

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Key Summary Points

Psoriatic arthritis (PsA) is a chronic multidomain inflammatory disease in which several disease activity indices have been published, in order to assess disease state and response to treatment more objectively.

Less attention has been given to the concept of severity of disease which could be important to stratify patients for a better treatment.

The study identified patients with severe disease according to the modified Composite Psoriatic Disease Activity Index (mCPDAI) and showed how disease activity, pain and impact of disease are higher and remains higher during follow-up in severe patients than non-severe ones.

We also demonstrated that severity and disease activity in PsA are not interchangeable concepts.

The research opens the way for further studies in this field with the intent to identify patients with more severe disease in which treatment strategies could be implemented.

INTRODUCTION

Psoriatic arthritis (PsA) is a complex and heterogeneous inflammatory disease characterized by an association of psoriasis and arthritis that may lead to significant reduction of quality of life and to joint damage [1]. The achievement of the best possible disease control, such as disease remission or low disease activity, should be the treatment target and may be an achievable goal for patients with PsA [2, 3]. However, some recent studies reported the presence of residual disease activity in one or more domains even in patients with PsA that achieve remission or low disease activity [4, 5] and, despite significant improvements in the treatment of PsA, some patients may still remain in a high disease activity, with a percentage of patients not achieving those treatment goals ranging from 60 to 30% in long-term extensions of randomized controlled trials and observational studies [6, 7]. The complexity of this multidomain disease may also lead to reduced quality of life, joint damage, and reduced articular function, mainly in patients not achieving remission or low disease activity and thus, with a more severe disease course [8]. In this scenario, there is the clinical need to evaluate the presence of possible factors associated with a reduced treatment response, and different studies has been published on predictors for clinical outcome in PsA in order to better stratify patients with PsA [9, 10]. In this context, the presence of reduced function, female gender, and higher inflammatory burden were identified as important predictors of worse clinical outcome [9, 10]. Moreover, overweight and obesity reduce the likelihood of achieving minimal disease activity, while weight reduction can improve the probability of achieving this goal [11]. Joint damage is a good surrogate of poor physical function and is predicted by elevated tender and swollen joint counts, increased inflammatory markers, and the presence of dactylitis [9]. However, due to the heterogeneity of this complex syndrome and despite the presence of well-known prognostic factors, there are still a few studies on the severity of disease course in PsA. The concept of severity has been often associated, or confused, with disease activity, but it has also been associated with the presence of polyarticular involvement, joint function reduction, and mainly damage [12]. Generally, the concept of severity should be distinguished from the mere inflammatory activity and, at present, this is still debated. In other words, while high disease activity in a patient with PsA may be potentially totally reversible, a patient with severe PsA may not. The distinction of these two concepts in PsA is not well defined, in fact, while for other inflammatory rheumatic diseases such as systemic lupus erythematosus separate/specific indices were developed [13], for PsA there are

currently no broadly accepted criteria defining the severity of the disease, nor reports of efficacy analyses in patients with severe PsA treated with biologics or conventional (cs)-targeted synthetic (ts) disease modifying anti-rheumatic drugs (DMARDs). Moreover, of several outcome measures available to assess disease activity and burden of disease, the majority of these are not structured to evaluate the severity of the disease in PsA. Thus, since the achievement of good control of disease activity is an achievable target, there is now the clinical need to identify patients with severe disease. In fact, the concept of severity may be not totally aligned with the concept of persistent disease activity or with the concept of difficult-to-treat disease, in which patients may be refractory or intolerant to multiple treatment strategies with a difficult management of signs and symptoms [14, 15]. In this context, we do believe that disease severity may be defined as the presence of more pronounced inflammatory activity in every disease domain, together with greater functional limitation/reduced quality of life.

At present, the only outcome measure that includes in its definition the concept of severity is the Composite Psoriatic Disease Activity Index (CPDAI), in which disease activity in different domains is combined with functional and quality-of-life indices [16, 17]. In this context, the aims of this study were:

(1) To identify patients with severe PsA symptoms defined by modified (m) CPDAI in a cohort of patients with PsA with peripheral joint involvement;
(2) To evaluate the presence of clinical differences among severe and non-severe patients with PsA;
(3) To evaluate the presence of clinical factors associated with severe PsA;
(4) To evaluate the agreement of the mCPDAI compared to the absence of minimal disease activity (MDA) and the presence of disease activity score for psoriatic arthritis (DAPSA) moderate-to-high disease activity in order to verify the hypothesis that these instruments intercept two different aspects of the disease.

METHODS

Study Design and Participants

We performed a retrospective analysis of a longitudinal cohort of patients with PsA, fulfilling the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria [18]. Patients were treated according to the current standard of care, following the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the European Alliance of Associations for Rheumatology (EULAR) treatment recommendations [19, 20] recruited in our tertiary care center devoted to diagnosis and assessment of spondyloarthritis, from January 1, 2018 to January 1, 2022. Data presented were restricted to baseline clinical characteristics at the time of first visit in our unit (which may not overlap with the time of diagnosis) and to the last follow-up in our unit. Usually, patients' follow-up ranges between 3 and 6 months.

Inclusion criteria were:

(1) age $\geq$ 18 years,
(2) Peripheral psoriatic arthritis classified according to CASPAR criteria,
(3) Availability of clinical data at baseline and last visit in our unit.
(4) At least 1 year of follow-up.

For the purpose of this study, patients with axial involvement defined as having inflammatory back pain for more than 3 months according to the Assessment of SpondyloArthritis international Society (ASAS) criteria were excluded. As PsA may involve various domains, we defined PsA severity by considering multiple clinical domains. The mCPDAI (which excludes ankylosing spondylitis quality of life scale) is a composite measure defining the severity of these clinical manifestations in total and each domain. We defined the severe population using the mCPDAI domains (Fig. 1). Hence, patients with a score of 3 (the highest score) in at least one domain were defined as having severe PsA [17]. We used the mCPDAI because ankylosing spondylitis quality of life scale is not part of our routine assessment of patients.

Data Collection

A detailed medical history and physical examination were collected for all patients. Demographics and disease characteristics including gender, age, disease duration, level of education, and pattern of articular manifestations were evaluated. Laboratory parameters were also evaluated. The clinical assessment encompassed 68 tender and 66 swollen joints, enthesitis, and dactylitis. The pattern of articular involvement at disease onset was also collected as well as comorbidities and related manifestations. Enthesitis was assessed by using the Leeds Enthesitis Index (LEI) [21], and dactylitis as present/absent in each finger (digit score 0–20). Skin assessment was performed using the Psoriasis Area Severity Index (PASI) and the Dermatology Quality of Life Index (DLQI) was administered to all patients with current psoriasis as we use to do in our clinical practice. The Patient Global Assessment (PtGA), pain assessment (patient perceived pain [PtPvN]) on Visual Analogic Scale (VAS) and the physician's global evaluation of disease activity (PGA) on a VAS scale were also recorded. The MDA and DAPSA were evaluated [22]. The Patient Acceptable Symptom State (PASS) was also collected [23]. The Health Assessment Questionnaire Disability Index (HAQ-DI) and the Psoriatic Arthritis Impact of Disease (PsAID) [24] were evaluated as measures of function and quality of life. The presence of fibromyalgia was also assessed following the ACR 2010 fibromyalgia criteria [25]. Information on previous and current use of conventional synthetic and b/ts DMARDs was recorded. mCPDAI was calculated

	Not Involved (0)	Mild (1)	Moderate (2)	Severe (3)
Peripheral arthritis	No Peripheral Arthritis	≤ 4 active joints and normal function (HAQ≤0.5)	≤ 4 active joints with impaired function or > 4 active joints and normal function	> 4 joints and impaired function
Skin disease	No psoriasis	PASI ≤10 and DLQI ≤10	PASI ≤ 10 but DLQI > 10 or PASI > 10 but DLQI ≤ 10	PASI > 10 and DLQI > 10
Enthesitis	No enthesitis	≤ 3 sites and normal function (HAQ≤0.5)	≤ 3 sites with impaired function or > 3 sites with normal function	> 3 sites and impaired function
Dactylitis	No dactylitis	≤ 3 digits and normal function (HAQ≤0.5)	≤ 3 digits with impaired function or > 3 digits with normal function	> 3 digits and impaired function

Fig. 1 Modified Composite Psoriatic Disease Activity Index (mCPDAI). *HAQ-DI* Health Assessment Questionnaire Disability Index, *PASI* Psoriasis Area Severity Index, *DLQI* Dermatology Life Quality Index

for each enrolled patient. Similar methods have been presented previously [14].

Ethical Approval

The study was approved by the institutional review board of the University of Molise (protocol no. 0001-017-2021) and performed according to the Helsinki Declaration. Written informed consent to use clinical data of all participants was obtained.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics software, Version 26.0. Normally distributed variables were summarized using the mean ± standard deviation (SD), and non-normally distributed variables by the median and interquartile range (IQR). Severe patients with PsA were compared with non-severe patients with regards to baseline and last follow-up demographics and disease characteristics by descriptive statistics. Mann–Whitney test was performed accordingly. Comparisons between nominal variables were calculated using chi-square test or Fisher's exact test where appropriate. To evaluate potential clinical factors associated with the presence of severe phenotype, multivariate logistic regression analysis was performed. The agreement among mCPDAI, MDA, and DAPSA moderate-to-high disease activity was performed using Cohen's kappa. This method was used over chi-square to assess the strength of the agreement. Two-tailed *P* values were reported, where values less than 0.05 were considered statistically significant.

RESULTS

From January 2018 to January 2022, we collected data from 177 patients with PsA with peripheral involvement with the availability of all clinical data (from our dataset, which contains data on 212 patients with PsA). Male/female ratio: 98/76), mean age (range) 55 (19–73) years, median follow-up (IQR) was 2 (1–2) year. Table 1 shows the clinical characteristics of patients with PsA at baseline and at last follow-up. Of these, 64 (36.1%) were identified as severe according to the above-mentioned criteria, at baseline. Of the 64 severe patients, 42 (65.6%) were identified as severe in the peripheral arthritis domain, 11 (16.1%) dactylitis domain, eight (11.7%) skin involvement domain, and three (4.4%) by entheseal domain. At follow-up visit, only 18 (10.1%) patients with PsA still met the definition of severe PsA in almost one domain. Of these, ten (55.5%) were defined as severe PsA even at baseline.

Characteristics of Severe vs. Non-severe Patients at Baseline and at Last Follow-Up

Table 1 shows the baseline and follow-up differences between peripheral patients with PsA categorized as severe and non-severe.

At baseline, no statistically significant differences were found between the two groups in male/female ratio, disease duration, body mass index (BMI), PASI, and presence of dactylitis while severe patients with PsA have a statistically significant higher disease activity, number of tender/swollen joints, pain, reduced function, and impact of disease compared to non-severe patients. At last follow-up visit, severe patients with PsA were only males (18/18, $P < 0.01$) and have worse outcomes in terms of disease activity, pain, function, and impact of disease.

Baseline Factors Predicting the Persistency of Severe PsA at Last Follow-Up

Table 2 shows the multivariate logistic regression analysis exploring factors associated with the presence of severe PsA at last follow-up. Male sex and the severity of skin involvement assessed by PASI at baseline were the only factors associated with the presence of severe PsA at last follow-up, independently by other characteristics.

Table 1 Characteristics of PsA patients at baseline and at last follow-up

	Baseline			**Last follow-up**		
	Severe ***N*** **= 64 (36.1%)**	**Non-severe** ***N*** **= 109 (63.9%)**	***P*** **value**	**Severe** ***N*** **= 18 (10.1%)**	**Non-severe** ***N*** **= 159 (89.9%)**	***P*** **value**
M/F	32/36	68/41	0.07	18/0	80/79	< 0.01
Age (median, IQR)	57 (51–67)	53 (44–61)	0.25	61.5 (49.7–67)	54 (45–61)	0.11
Smoking, *n* (%)						
Past	12 (18.7)	14 (12.8)	0.37	1 (5.5)	25 (15.7)	0.44
Current	15 (23.4)	34 (31.2)		4 (22.2)	38 (23.9)	
BMI, median (IQR)	27 (24.1–29.8)	26.3 (23.6–30.1)	0.49	28.4 (25.8–31.1)	26.4 (23.7–29.9)	0.09
Disease duration (months), median (IQR)	60 (11–131)	29 (5–100)	0.09	28 (9–85)	41.5 (5.25–120)	0.85
PASI, median, (IQR)	2.5 (1.3–3.6)	1.8 (1–2.5)	0.08	2.1 (0.9–3.4)	0.9 (0.3–1.6)	< 0.01
PtGA (0–10), (median, IQR)	6.3 (5–8)	4 (1.75–6)	< 0.01	6 (4.7–8)	3 (1–6)	< 0.01
PtPvN (0–10), (median, IQR)	6.2 (5–8)	4.5 (1–7)	< 0.01	7 (4–8.25)	3 (1–6)	< 0.01
PGA (0–10), (median, IQR)	4 (4–6)	3 (1–5)	< 0.01	4 (3–7)	2 (1–4)	< 0.01
TJC/68, (median, IQR)	6 (3–8)	1 (0–2)	< 0.01	6 (3–8)	0 (0–2)	< 0.01
SJC/66, (median, IQR))	1 (0–3)	0 (0–1)	< 0.01	1.5 (0–3)	0 (0–0)	< 0.01
Dactylitis *n* (%)	10 (15.1)	7 (6.4)	0.11	3 (16.6)	5 (3.1)	0.03
LEI, (median, IQR)	1 (0–2)	0 (0–0)	0.02	0 (0–1)	0 (0–0)	0.12
CRP (mg/dl), (median, IQR)	0.4 (0.2–1)	0.27 (0.2–0.5)	< 0.01	0.5 (0.2–1)	0.25 (0–0.3)	< 0.01
MDA *n* (%)	2 (2.9)	14 (12.8)	< 0.01	1 (5)	70 (44.4)	< 0.01
DAPSA, median (IQR)	22 (17.4–27.5)	10.5 (4.3–15)	< 0.01	21.2 (12.6–26.5)	6.39 (2.5–14.0)	< 0.01
HAQ-DI, median (IQR)	1 (0.5–1.4)	0.5 (0.125–0.75)	< 0.01	0.62 (0.37–1)	0.5 (0–0.87)	< 0.01
PASS yes, *n* (%)	8 (11.7)	43 (39.4)	< 0.01	3 (16.6)	92 (57.8)	< 0.01
PsAID, median (IQR)	6 (4–7.2)	2 (0.9–4.1)	< 0.01	5.26 (2.15–8.2)	2 (0.8–3.2)	< 0.01
n of comorbidity (%)						
None	20 (29.4)	26 (14.6)		2 (11.1)	47 (29.6)	
1	13 (19.1)	29 (16.4)		6 (33.3)	36 (22.5)	
> 2	35 (51.4)	54 (69)		10 (55.6)	76 (57.9)	

Table 1 continued

	Baseline			Last follow-up		
	Severe $N = 64$ (36.1%)	Non-severe $N = 109$ (63.9%)	*P* value	Severe $N = 18$ (10.1%)	Non-severe $N = 159$ (89.9%)	*P* value
Treatment						
NSAIDs/steroids	19 (29.7)	35 (32.1)		0	7 (38.9)	
csDMARDs	20 (31.3)	32 (29.3)		1 (5.6)	3 (16.6)	
Anti-TNF	20 (31.3)	33 (30.2)		4 (22.2)	2 (11.1)	
Anti-IL12/23	2 (3.1)	7 (6.4)		0	0	
Anti-IL-17	11 (17.2)	24 (22)		5 (27.8)	8 (44.3)	
Anti-IL23	0	0		4 (22.2)	3 (16.6)	
JAKi	0	0		3 (16.7)	1 (5.5)	
Apremilast	4 (6.2)	7 (6.4)		1 (5.6)	4 (22.2)	

The patients were stratified into severe and non-severe by mCPDAI.
PsA psoriatic arthritis, *mCPDAI* modified Composite Psoriatic Disease Activity Index, *M* male, *F* female, *IQR* interquartile range, *BMI* body mass index, *PASI* psoriasis area severity index, *PtGA* patient global assessment, *PtPvN* patient pain, *PGA* physician global assessment, *TJC* tender joints count, *SJC* swollen joints count, *LEI* Leeds Enthesitis Index, *CRP* C reactive protein, *MDA* minimal disease activity, *DAPSA* disease activity index for psoriatic arthritis, *HAQ-DI* Health Assessment Questionnaire Disability Index, *PASS* Patient Acceptable Symptoms State, *PsAID* Psoriatic Arthritis Impact of Disease, *NSAID* non-steroidal ani-inflammatory drug, *cs* conventional synthetic, *DMARDs* disease-modifying anti-rheumatic drugs, *b* biologic, *TNF* tumor necrosis factor, *IL* interleukin, *JAKi* Janus kinases inhibitors

Agreement of the mCPDAI in Respect to Other Multidimensional and Unidimensional Indices of Disease State and Disease Activity

The agreement between the presence of severe PsA at last follow-up defined with mCPDAI and the absence of MDA is slight [Cohen's *k*: 0.174 (0.084–0.264; 95% CI)]. The agreement between the presence of severe PsA at last follow-up defined with mCPDAI and the presence of moderate to high disease activity assessed by DAPSA is slight [Cohen's *k*: 0.162 (0.005–0.32; 95% CI)]. Furthermore, we analyzed the agreement between patients with PsA that achieved MDA and DAPSA low disease activity at last follow-up starting from a condition of non-MDA or no DAPSA low disease activity at baseline and the patients that achieved a condition of non-severe PsA at last follow-up starting from a condition of severe PsA at baseline (Table 3).

DISCUSSION

To our knowledge, this is one of the first observational study assessing the clinical characteristics of potentially severe PsA [12]. Although there is no consensus on the definition of severity, this study may contribute to this intriguing topic, which is considered an unmet need in clinical practice. As PsA may show with various clinical manifestations, it could be important to define the severity of disease in each clinical domain. However, our study confirmed that the majority of patients fulfilling the definition had severe disease based on the peripheral joint involvement while, for instance, entheseal involvement was less frequently represented. Moreover, there is the clinical need to distinguish the concept of disease activity from disease severity and this study tried to address this intriguing point.

In our group, at baseline, severe patients with PsA tend to have higher disease duration

Table 2 Multivariate logistic regression analysis exploring factors associated with the presence of severe PsA at last follow-up

Severe PsA						
	Beta	**Standard error**	***P* value**	**Odds ratio**	**95% CI**	
Age	0.03	0.03	0.34	1.02	0.98	1.08
Male sex	0.73	0.61	< 0.01	1.70	1.130	2.42
Disease duration	− 0.01	0.01	0.81	0.97	0.97	1.01
BMI	0.23	0.06	0.63	1.02	0.90	1.15
PASI	0.15	0.59	0.01	1.17	1.04	1.31
Tender joints count	0.078	0.810	0.33	1.081	0.922	1.26
Swollen joints count	0.06	0.16	0.54	1.06	0.76	1.5
HAQ-DI	− 0.19	0.61	0.75	0.82	0.24	2.75
bDMARD use	− 0.2	0.72	0.34	0.88	0.54	2.23
Enthesitis (LEI ≥ 1)	0.32	0.67	0.11	1.09	0.78	16.44
Dactylitis	0.19	0.54	0.23	1.06	0.46	15.2

Hosmer–Lemeshow test chi-square: 14.4; *P*: 0.07. Cox & Snell *R* square: 0.093

PsA psoriatic arthritis, *CI* confidence interval, *BMI* body mass index, *PASI* Psoriasis Area Severity Index, *HAQ-DI* Health Assessment Questionnaire Disability Index, *bDMARD* biologic disease-modifying anti-rheumatic drug, *LEI* Leeds Enthesitis Index

(not statistically significant) and to have statistically significant higher values of PtGA, PtPvN, PGA, tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), and LEI. Furthermore, the rate of patients with dactylitis and the median PASI tend to be higher in the severe PsA but the difference was not statistically significant. Male/female ratio was also not statistically significant. However, at last follow-up, no females satisfied the criteria for severe PsA. This is quite interesting because generally, female patients with PsA tend to have higher disease activity, worse scores in the outcome measures, and reduced response and persistence to advanced biologic treatments in respect to male sex [26]. This latter result could be helpful in distinguishing the concept of severity from that of severe disease activity, which is higher in the female sex. The definition of severe PsA by mCPDAI is mainly based on the clinical evaluation of patients and on HAQ-DI. This may explain this apparent discrepancy since disease activity scores and outcome measures such as DAPSA and MDA contains "patient-driven" domains such as PtGA and pain that may influence disease activity, but the mCPDAI did not. Our results are in keeping with other studies in axial spondyloarthritis in which male sex is associated with a more severe disease course [27] and further corroborate the hypothesis that severity and disease activity are different concepts.

Generally, after a median of 2 years of follow-up and treatment, the rate of patients with severe disease dropped from 36 to 10%, which means that severity, assessed by using this instrument, could be influenced by disease activity, as well as some patients remained severe (10%) even at 2 years of advanced treatment. However, as suggested by the results summarized in Table 3, severity and disease activity are not interchangeable. In fact, the agreement between the definition of severity and the absence of MDA or low disease activity

Table 3 Concordance of MDA and DAPSA low disease activity in respect to definition of severe PsA at baseline and follow-up

Severe PsA at baseline		**Severe PsA at last follow-up (independently from baseline)**		**Patients achieving a condition of non-severe PsA at last follow-up from severe PsA at baseline**	
	Cohen' *k* agreement (95% CI)		**Cohen' *k* agreement (95% CI)**		**Cohen' *k* agreement (95% CI)**
Absence of MDA at baseline	0.24 (0.11–0.37)	Absence of MDA at last follow-up	0.17 (0.01–0.26)	Patients achieving MDA at last follow-up from no MDA at baseline	0.16 (0.01–0.30)
Absence of DAPSA low disease activity baseline	0.15 (0.01–0.36)	Absence of DAPSA low disease activity at last follow-up	0.16 (0.01–0.32)	Patients achieving DAPSA low disease activity at last follow-up from no low disease activity at baseline	0.21 (0.01–0.36)

PsA psoriatic arthritis, *MDA* minimal disease activity, *DAPSA* Disease Activity Index for Psoriatic Arthritis, *CI* confidence interval

is slight. This, in turn, supports the concept that severity is not totally aligned with disease activity and that the two indices intercept patients with different characteristics. Indeed, our results showed that mCPDAI could be considered a "surrogate" of severity; in the meantime further research on this topic will be able to validate a specific instrument for severity.

We are aware that mCPDAI as a candidate index may be weak, but to our knowledge, no formal instrument to assess severity has been published. Furthermore, mCPDAI could identify reversible severity (in fact, in our study the rate of patients satisfying the proposed criteria dropped from 36 to 10%) and, hopefully, further study will identify irreversible severity, which could be linked to joint damage, radiographic progression, and to the development of disease-related complications.

A very recent study was published on the efficacy of the anti-IL-17A ixekizumab in patients with severe peripheral PsA. In this post hoc analysis of the SPIRIT-P1, the authors adopted the same definition of severe PsA using the mCPDAI and showed an improvement in joint and skin symptoms in patients with severe disease treated with ixekizumab. Looking at the population with severe PsA, generally, the disease activity indices (in terms of TJC, SJC, LEI, and skin involvement) were worse in respect to our findings, but it is not surprising, due to the intrinsic nature of the enrolment criteria in randomized controlled trials. However, similar findings in terms of HAQ-DI, perception of pain, and disease activity by patients are present [28].

In our study, predictors of severe PsA were male sex and the extension of skin involvement. Concerning male sex, different studies showed that men assembling more peripheral and axial joint impairment have higher scores of functional disabilities, leading to a more severe disease course [29]. This could explain our findings. However, although we perform a multivariable analysis, we have to say that the number of severe patients at last follow-up was low. This in turn might lead to a careful interpretation of our results.

Recently, Queiro et al. defined the presence of severe PsA as fulfilment of at least 1 of the following criteria: treatment with DMARDs, HAQ > 0.5, polyarthritis. Interestingly, they found that over 70% of their patients with PsA can be classified as severe. However, this

definition is less stringent in respect to our definition. Moreover, in this study, several factors were associated with severe disease, including pain, localization of psoriasis, and clinical form at diagnosis, while no mention of male sex was reported [12].

Our study has some limitations. First, data on the radiographic progression were not assessed. This could be an important aspect to be addressed since more severe patients with PsA may have to show more radiographic damage and further studies are needed. Second, we stratified patients based on mCPDAI, a clinical index that was initially structured to evaluate disease activity, as stated above. Third, the study lacks data on the clinical form of the disease and information on the so-called malignant location of the disease such as a severe involvement of the hip joint, which should be taken into account when assessing the severity. Finally, overall, we reported low prevalence of enthesitis in our group (defined with the LEI, which explores only six sites) and this may have an impact on the results.

In conclusion, our study showed that severe patients with PsA had more disease activity, pain, and impact of disease than non-severe patients. They also tend to have higher disease activity, pain, and impact of disease during the course of follow-up. Furthermore, we demonstrated that severity and disease activity in PsA are not interchangeable concepts, and open the way for further studies in this field.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Ennio Lubrano and Fabio Massimo Perrotta are members of the Editorial Board of *Rheumatology and Therapy*. Ennio Lubrano and Fabio Massimo Perrotta were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Silvia Scriffignano has nothing to disclose.

Ethical Approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of the University of Molise (protocol no. 0001-017-2021) and performed according to the Helsinki declaration. Written informed consent to use clinical data of all participants was obtained.

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