Joint Bone Spine 89 (2022) 105296

Contents lists available at ScienceDirect

Joint Bone Spine

journal homepage: www.elsevier.com

Original article

Inconsistencies of the Disease Activity Assessment Tools for Psoriatic Arthritis: Challenges to Rheumatologists

Halise Hande Gezer[a,*], Mehmet Tuncay Duruöz[a], Kemal Nas[b], Erkan Kılıç[c], Betül Sargın[d], Sevtap Acer Kasman[a], Hakan Alkan[e], Nilay Şahin[f], Gizem Cengiz[g], Nihan Cüzdan[h], İlknur Albayrak Gezer[i], Dilek Keskin[j], Cevriye Mülkoğlu[k], Hatice Reşorlu[l], İsmihan Sunar[m], Ajda Bal[n], Okan Küçükakkaş[o], Ozan Volkan Yurdakul[o], Meltem Alkan Melikoğlu[p], Merve Baykul[q], Fikriye Figen Ayhan[r], Hatice Bodur[s], Mustafa Çalış[g], Erhan Çapkın[t], Gül Devrimsel[u], Kevser Gök[v], Sami Hizmetli[w], Ayhan Kamanlı[b], Yaşar Keskin[o], Hilal Ecesoy[x], Öznur Kutluk[y], Nesrin Şen[z], Ömer Faruk Şendur[aa], İbrahim Tekeoğlu[b], Sena Tolu[ab], Murat Toprak[ac], Tiraje Tuncer[z]

[a] *Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Marmara University School of Medicine, İstanbul, Turkey*
[b] *Division of Rheumatology and Immunology, Department of Physical Medicine and Rehabilitation, Sakarya University School of Medicine, Sakarya, Turkey*
[c] *Kanuni Training and Research Hospital; Rheumatology Clinic, Trabzon, Turkey*
[d] *Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Adnan Menderes University School of Medicine, Aydın, Turkey*
[e] *Department of Physical Medicine and Rehabilitation, Pamukkale University School of Medicine, Denizli, Turkey*
[f] *Department of Physical Medicine and Rehabilitation, Balıkesir University School of Medicine, Balıkesir, Turkey*
[g] *Division of Rheumatology, Department of Physical Medicine and Rehabilitation, School of Medicine, Erciyes University, Kayseri, Turkey*
[h] *Balıkesir Atatürk City Hospital, Rheumatology Clinic, Balıkesir, Turkey*
[i] *Department of Physical Medicine and Rehabilitation, Selçuk University School of Medicine, Konya, Turkey*
[j] *Department of Physical Medicine and Rehabilitation, Kırıkkale University School of Medicine, Kırıkkale, Turkey*
[k] *Department of Physical Medicine and Rehabilitation, Ankara Training and Research Hospital, Ankara, Turkey*
[l] *Department of Physical Medicine and Rehabilitation, Çanakkale Onsekiz Mart University School of Medicine, Çanakkale, Turkey*
[m] *Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Ankara University School of Medicine, Ankara, Turkey*
[n] *Department of Physical Medicine and Rehabilitation, University of Health Sciences Ankara Dışkapı Yıldırım Beyazıt Trainig and Research Hospital, Ankara, Turkey*
[o] *Department of Physical Medicine and Rehabilitation, Bezmiâlem Foundation University, İstanbul, Turkey*
[p] *Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Atatürk University School of Medicine, Erzurum, Turkey*
[q] *Department of Physical Medicine and Rehabilitation, Sakarya University School of Medicine, Sakarya, Turkey*
[r] *Department of Physical Medicine and Rehabilitation, Atilim University Medical School, Ankara, Turkey*
[s] *Department of Physical Medicine and Rehabilitation, Yıldırım Beyazıt University School of Medicine, Ankara, Turkey*
[t] *Department of Physical Medicine and Rehabilitation, Karadeniz Technical University School of Medicine, Trabzon, Turkey*
[u] *Department of Physical Medicine and Rehabilitation, Recep Tayyip Erdoğan University School of Medicine, Rize, Turkey*
[v] *Ankara City Hospital; Rheumatology Clinic, Ankara, Turkey*
[w] *Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Cumhuriyet University School of Medicine, Sivas, Turkey*
[x] *Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Necmettin Erbakan University Meram School of Medicine, Konya, Turkey*
[y] *Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Akdeniz University School of Medicine, Antalya, Turkey*
[z] *Kartal Dr. Lütfi Kırdar Training and Research Hospital; Rheumatology Clinic, İstanbul, Turkey*
[aa] *Department of Physical Medicine and Rehabilitation, Adnan Menderes University School of Medicine, Aydın, Turkey*
[ab] *Department of Physical Medicine and Rehabilitation, Medipol University School of Medicine, İstanbul, Turkey*
[ac] *Department of Physical Medicine and Rehabilitation, Yüzüncü Yıl University School of Medicine, Van, Turkey*

ARTICLE INFO

Article history:
Accepted 6 October 2021
Available online 14 October 2021

ABSTRACT

Objective: Currently, concerning the evaluation of psoriatic arthritis (PsA), there is no agreement on a standardized composite index for disease activity that includes all relevant domains. The present study sought to assess the rates of remission (REM)/low disease activity (LDA) and disease states [minimal disease activity (MDA), very low disease activity (VLDA)] as defined by diverse activity scales (DAPSA, DAS28-ESR) in an attempt to display discrepancies across these assessment tools for peripheral PsA.

* Corresponding author at: Pendik Training and Educational Hospital, Muhsin Yazıcıoğlu Street, No 10, 34899 İstanbul, Turkey.
E-mail address: hande_snc@hotmail.com (H.H. Gezer).

https://doi.org/10.1016/j.jbspin.2021.105296

Keywords:
Remission
Disease activity
Psoriatic arthritis
Composite index

Methods: The study involved 758 patients (496 females, 262 males; mean age 47,1 years) with peripheral PsA who were registered to the Turkish League Against Rheumatism (TLAR) Network. The patients were assessed using the DAS28-ESR, DAPSA, MDA, and VLDA. The overall yield of each scale was assessed in identifying REM and LDA. The presence or absence of swollen joints was separately analysed.
Results: The median disease duration was 4 years (range 0-44 years). According to DAPSA and DAS28-ESR, REM was achieved in 6.9% and 19.5% of the patients, respectively. The rates of MDA and VLDA were 16% and 2.9%, respectively. Despite the absence of swollen joints, a significant portion of patients were not considered to be in REM (296 (39.1%) patients with DAS28-ESR, 364 (48%) with DAPSA, and 394 (52%) with VLDA).
Conclusion: Patients with peripheral PsA may be assigned to diverse disease activity levels when assessed with the DAS28-ESR, DAPSA, MDA and VLDA, which would inevitably have clinical implications. In patients with PsA a holistic approach seems to be necessary which includes other domains apart from joint involvement, such as skin involvement, enthesitis, spinal involvement, and patient-reported outcomes.

1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease presenting with various combinations of clinical manifestations, including enthesitis, dactylitis, spondylitis, and uveitis [1]. Guidelines for the treatment of PsA are available and consistently updated. The most recent is the 2019 European League Against Rheumatism (EULAR) recommendation for PsA. According to the EULAR, treatment should target achieving remission (REM) (primarily for early disease) or, at least, low disease activity (LDA) (for established disease). In the current guideline, minimal disease activity (MDA) which was present in the previous guideline has been omitted because it merely refers to a score for LDA rather than defining a treatment target [2]. In contrast, the Treat-to-Target (T2T) International Task Force consider not only REM a final treatment target but also LDA or MDA alternative treatment targets [3]. Similarly, the Turkish League Against Rheumatism (TLAR) suggested the T2T approach and MDA as a treatment target [4]. Another approach has been proposed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), which does not specifically recommend a treatment target, but the achievement of the lowest possible level of disease activity in all domains of disease [5]. Despite differences in recommendations, REM remains the primary treatment target. Remission can be identified as the resolution of disease activity, with no symptoms and progression in joint damage [6]. Disease activity is a broad term and should include all domains of the disease, i.e., synovitis, enthesitis, dactylitis, spondylitis, nail and skin involvement [7]. Unlike rheumatoid arthritis (RA), in which joint assessment, patient-reported outcomes, and acute phase reactants are sufficient to evaluate disease activity, many additional parameters affect disease activity in PsA and additionally REM in PsA is difficult to define [8].

Even the Disease Activity Score-28 (DAS-28) and Disease Activity in Psoriatic Arthritis (DAPSA), frequently used scores in PsA, do not comprehensively encompass the multiple clinical domains of PsA [9]. Subsequently, MDA and Very Low Disease Activity (VLDA) which are states of disease activity were developed based on the outcomes of the core set, containing joint involvement, enthesitis, psoriasis, functional limitation, pain, and global assessment [10,11].

Currently, concerning the evaluation of PsA, there is no agreement on a standardized composite index for disease activity that includes all relevant domains; rather a core domain set is recommended for patient assessment, which includes peripheral joint activity, skin activity, patient global, pain, physical function, quality of life, and fatigue. Even the DAPSA, the most frequently used scale in clinical practice due to its ease, does not cover all the domains of the core set [12,13]. Furthermore, there is no consensus on which activity score provides the most distinctive information about a particular disease state, given that discrepant REM/LDA rates have been reported with diverse scales [14]. Surprisingly, the authors of the present study noted during the analysis of data that some patients would not be considered in REM as defined by the DAPSA and/or DAS-28, even though they are free from active joint involvement.

The objective of the present study was to assess the rates of REM/LDA and disease states (MDA, VLDA) as defined by diverse activity scales (DAPSA, DAS-28) in an attempt to display discrepancies across these assessment tools for peripheral PsA.

2. Methods

2.1. Study design and patients

The study included PsA patients whose data were collected in the Turkish League Against Rheumatism (TLAR) Network registry. TLAR-Network data were collected using a web-based system from patients during their routine visits throughout the year 2018 (https://www.trasd-network.org). In a cross-sectional multicentre design, patients with PsA meeting the CASPAR (Classification criteria for Psoriatic Arthritis) criteria [15] were selected for analysis. A total of 1134 patients with PsA are evaluated by 37 researchers from 25 centres from diverse regions of Turkey. Patients with malignancies, pregnancy, lactation, coexisting rheumatic diseases (e.g. rheumatoid arthritis, familial Mediterranean fever, systemic lupus erythematosus...), and age less than 18 years are excluded from the registry. The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from every participant at the time when the patients were enrolled in the TRASD-Network. Ethical approval was obtained from the Ethics Committee of Sakarya University (25.01.2018/42).

As the study focused on peripheral joint involvement, eligible patients were selected, excluding either axial involvement or enthesitis alone. Thus, 758 patients with PsA were included in the analysis.

Demographic data including age, gender, marital status, level of education, disease duration, and body mass index (BMI, kg/m^2) and disease characteristics were recorded.

Laboratory measures included the erythrocyte sedimentation rate (ESR) (mm/hr) and C-reactive protein (CRP) (mg/dL) levels. ESR and CRP levels were obtained at that time of routine outpatient visits.

2.2. Patient-reported outcome measures (PROMs)

The Health Assessment Questionnaire (HAQ) [16], Psoriatic Arthritis Quality of Life (PsAQoL) [17], Hospital Anxiety and Depression Scale (HAD) [18], and Fibromyalgia Rapid Screening Tool (FiRST) [19] were administered. Patient global assessment (PtGA), pain (VAS-pain), and fatigue (VAS-F) were rated on a visual analogue scale [20,21].

2.3. Disease activity assessments

Examinations included tender joint count (TJC), swollen joint count (SJC), enthesitis, dactylitis count, and the Psoriasis Area and Severity Index (PASI) [22]. Tender and swollen joint counts were based on 66/68 joints. DAS28 was calculated by computer based on the assigned 28 joints. The presence of spondylitis was determined on X-rays or on magnetic resonance imaging scans.

The DAS28-ESR was used to score disease activity, with scores of ≤ 2.6 indicating REM, > 2.6-≤ 3.2 LDA, > 3.2-≤ 5.1 moderate disease activity, and > 5.1 high disease activity [23]. Cut-offs for disease activity for DAPSA were as follows: REM ≤ 4, LDA > 4-≤ 14, moderate > 14-≤ 28, and high > 28 [24]. Minimal disease activity was defined as achievement of at least five of seven clinical outcomes (TJC≤ 1, SJC ≤ 1, PASI ≤ 1, VAS pain ≤ 1, PtGA ≤ 1, HAQ score ≤ 0.5, and tender entheseal points ≤ 1). An MDA score of 7/7 was defined as Very Low Disease Activity (VLDA) [25].

During the visits, findings of physical examination were entered into the network system via CRF. DAS28 was automatically calculated by the system. DAPSA, MDA and VLDA assessments were separately made after data collection was completed. The overall yield of each scale was assessed in demonstrating REM and LDA. The patients were classified according to REM and LDA status as defined by each scale. The presence or absence of swollen joints was separately analysed.

2.4. Statistical analysis

Patient demographics and disease characteristics were analysed using descriptive statistics. Categorical variables were expressed as percentages, while continuous variables as mean (±) or median (inter quarter range (IQR) or minimum-maximum). The normality of the distribution of variables was evaluated using the Kolmogorov–Smirnov test. The Chi^2 tests (Fischer's exact test if expected numbers were below five) were used for qualitative data. The Student's *t*-test and Mann–Whitney *U*-test were used comparing two groups. The level of significance was set as $P < 0.05$. No imputation of missing data was performed; data were analysed on complete cases.

All data were processed using the Statistical Package for Social Sciences Software (SPSS v22.00. Armonk, IBM Corp).

3. Results

A total of 758 patients with previous or current peripheral arthritis or arthralgia were included. Of this group, 496 (65.4%) were female. The mean age was 47.1 ± 12.2 years. The median disease duration was 4 (min-max: 0-44) years and the median PASI score was 1.8 (min-max: 0-51.3). Spondylitis was present in 257 patients (33.9%), dactylitis in 71 (9.4%) and enthesitis in 183 (24.1%). The clinical characteristics of the patients are presented in Table 1.

According to DAPSA and DAS28-ESR, REM was achieved in 6.9% and 19.5% of the patients, respectively (Table 2). The rates of MDA and VLDA were 16% and 2.9%, respectively.

Table 1
Demographic and clinical characteristics of the patients.

Parameters	Patients ($n = 758$)
Demographic	
Age, years	47.1 ± 12.2
Gender, female, *n*	496 (65.4%)
Body mass index, kg/m^2	29 ± 5.1
Clinical	
Tender joint count	6.2 ± 8.6
Swollen joint count	1.5 ± 3.1
PASI score	3.3 ± 5.1
VAS Pain score	49.5 ± 25.6
VAS Global score	47.7 ± 24.7
DAS28-ESR score	3.5 ± 1.2
DAPSA score	18.9 ± 13.1
cDAPSA score	17.5 ± 12.7
BASDAI score	4.5 ± 2.1
MDA	121 (16%)
VLDA	22 (2.9%)
Erythrocyte sedimentation rate, mm/h	22.8 ± 16
C-reactive protein, mg/dL	1.4 ± 1.9

Data are presented as mean (±) or *n* (%). PASI: Psoriasis Area and Severity Index; VAS: Visual analogue scale; DAPSA: Disease Activity in Psoriatic Arthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; MDA: Minimal Disease Activity, VLDA: Very low disease activity.

Table 2
Patients' classification according to DAPSA, cDAPSA and DAS28-ESR ($n = 758$).

	DAS-28	DAPSA	cDAPSA
Remission	148 (19.5%)	52 (6.9%)	58 (7.7%)
Low Disease Activity	141 (18.6%)	256 (33.8%)	280 (36.9%)
Moderate Disease Activity	391 (51.6%)	312 (41.2%)	298 (39.3%)
High Disease Activity	78 (10.3%)	138 (18.2%)	122 (16.1%)

Data are presented as *n* (%). DAS28-ESR: Disease Activity Assessment 28-Erythrocyte sedimentation rate; DAPSA: Disease Activity in Psoriatic Arthritis: cDAPSA: Clinical Disease Activity in Psoriatic Arthritis.

3.1. Differences in REM and LDA classifications

There were 52 patients in the DAPSA-REM. Of these, only 43 patients met the DAS28-REM criteria, whereas 8 patients met the DAS28-LDA criteria. One patient was classified as having moderate disease activity according to DAS-28 because of a high ESR.

Of 52 patients assessed as DAPSA-REM, 31 patients (%59.6) were not in VLDA (Fig. 1A) due to lack of agreement with the following domains: skin ($n = 23$), pain ($n = 7$), HAQ ($n = 5$), enthesitis ($n = 5$), global assessment ($n = 4$), and tender joint ($n = 3$). Among DAPSA-REM patients, none was discarded in the VLDA because of the swollen joint domain.

Twenty-two patients had VLDA. Of these, 21 patients (%95.4) met the DAPSA-REM criteria, while one patient was considered to have DAPSA-LDA. According to the DAS-28, 19 patients met the DAS28-REM criteria, while 3 patients were on DAS28-LDA (Fig. 1A).

There were 121 patients in MDA. Of these, 61 (%50.4) were in DAPSA-LDA, while 33 (%27.2) were in DAS28-LDA (Fig. 1B). There were 195 patients in DAPSA-LDA, but not in MDA due to lack of agreement with the following domains: global assessment ($n = 189$), pain ($n = 184$), skin ($n = 130$), tender joint ($n = 111$), HAQ ($n = 81$), enthesitis ($n = 80$), swollen joint ($n = 25$).

3.2. Distributions of REM and LDA on the basis of swollen joint counts

The patients were categorized based on the presence or absence of swollen joints to assess the relationship between the swollen joint state and REM (Table 3). In the absence of swollen joint(s), a significant portion of patients were not considered in REM (39.1% with DAS28-ESR, 48% with DAPSA, and 52% with VLDA).

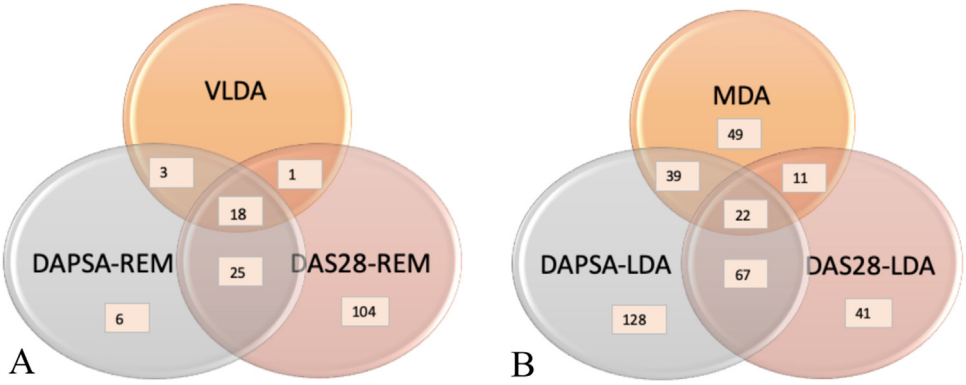

Fig. 1. Venn diagrams demonstrating discrepancies of 3 activity scales, (A) in remission, (B) in low disease activity.

Table 3
Contradictions of 3 activity scales in terms of swollen joint count (0 or ≥ 1) (n = 758).

	DAS28-ESR		DAPSA		VLDA	
	REM+	REM-	REM+	REM-	VLDA+	VLDA-
Swollen joint 0	118 (15.6)	296 (39.1)	50 (6.6)	364 (48)	20 (2.6)	394 (52)
Swollen joint ≥ 1	30 (4)	314 (41.4)	2 (0.3)	342 (45.1)	2 (0.3)	342 (45.1)
	DAS28-ESR		DAPSA		MDA	
	LDA+	LDA-	LDA+	LDA-	MDA+	MDA-
Swollen joint 0	104 (13.7)	310 (40.9)	188 (24.8)	226 (29.8)	101 (13.3)	313 (41.3)
Swollen joint ≥ 1	37 (4.9)	307 (40.5)	68 (9)	276 (36.4)	20 (2.6)	324 (42.7)

Data are presented as n (%). DAS28-ESR: Disease Activity Assessment 28- Erythrocyte sedimentation rate; DAPSA: Disease Activity in Psoriatic Arthritis; VLDA: Very Low Disease Activity; REM: Remission, MDA: Minimal Disease Activity; LDA: Low Disease Activity.

Patients who had no swollen joints did not achieve the VLDA state (n = 394) because of the following domains: global assessment (n = 355, 90.1%), pain (n = 354, 89.8%), tender joint (n = 244, 61.9%), skin (n = 242, 61.4%), HAQ (n = 179, 45.4%), and enthesitis (n = 177, 44.9%).

A similar discordance was also noted for LDA assessments in that, despite the absence of swollen joint(s), a significant portion of patients were not considered to be in LDA (40.9% with DAS28-ESR, 29.8% with DAPSA, and 41.3% with MDA) (Table 3).

Patients who had no swollen joints did not achieve the MDA state (n = 313) because of the following domains: global assessment (n = 307, 98.1%), pain (n = 304, 97.1%), skin (n = 214, 68.4%), tender joint (n = 236, 75.4%), HAQ (n = 177, 56.5%), and enthesitis (n = 175, 55.9%).

3.3. Comparisons of the DAPSA and MDA groups with no swollen joint in terms of clinical parameters

After noting that a significant portion of patients were not in REM or LDA despite the absence of swollen joint(s), we further analysed the entity of no-swollen joint in patients with and without REM or with and without MDA to better evaluate the effects of other clinical parameters on the REM and LDA states (Table 4).

The two patient groups (REM+/REM- and MDA+/MDA-) were similar in terms of age, disease duration, educational levels, and gender (P > 0.05), with the exception of female predominance in the MDA- group (68% vs. 58%, P = 0.044).

4. Discussion

This large multicentre study addressed REM and LDA in patients with peripheral PsA and compared disease activity stages with diverse activity scales. Recommendations for the treatment goals for PsA have been REM or alternatively LDA, but the universally known and validated definitions of REM and LDA are far from being satisfactory, with varying disease activity measures. In the early 2000s, Gladman et al. described REM as a resolution of active joint involvement. However, this definition has changed over time because of the heterogeneous nature of PsA, with multisystem involvement including not only peripheral (e.g., arthritis, arthralgia, enthesitis, dactylitis) but also axial, skin, and nail involvements. In the most recent description, the concept of REM has been suggested to cover the complete control of inflammation in all aspects of disease manifestations. Among multiple scales, the DAS-28 and DAPSA, frequently used activity scales for PsA, were designed for RA and reactive arthritis to primarily evaluate joint involvement [10,26,27]. In the context of arthritis, the most prominent manifestation is indeed the joint domain; however, some other domains associated with PsA may be underevaluated.

In the present study, we aimed to assess to what extent domains other than joint involvement are being underevaluated when diverse activity scales were used. Our findings demonstrate that, whatever scale is used, almost half of the patients would not be considered in REM or LDA, even though they have no swollen joint(s). In MDA and VLDA, the patient global assessment was the predominant domain to classify patients as not having REM/LDA, followed by pain, skin, tender joint. HAQ and enthesitis were the least common domains. Since the functional disability worsens with the progression of the disease, the effect of HAQ on disease activity may have been smaller. Moreover, the inclusion of functional status into clinical REM criteria for PsA is controversial because functional status is affected by many factors other than joint involvement such as age, comorbidity, and other variables [6].

In the present study, the patient population was assessed using a variety of scales. Interestingly, the VLDA rating did not equate to REM rates, owing to the former's stricter criteria. As a result, the majority of VLDA patients met the REM criteria as determined by the DAS-28 and DAPSA. A similar association also applies to MDA

Table 4
In-group comparisons of the DAPSA and MDA in terms of REM and MDA ($n = 758$).

	DAPSA		MDA	
Parameters	REM+	REM-	MDA+	MDA-
Tender joint count	0 (0)	4 (7) [c]	0 (1)	3 (6) [c]
Enthesitis, present	20 (40%)	204 (56%) [a]	33 (32.7)	191 (61%) [c]
Dactylitis, present	13 (26%)	90 (24%)	26 (25.7)	77 (24.6%)
Axial involvement, present	14 (28%)	150 (41%)	30 (29.7)	134 (42.8%) [a]
Pain VAS	10 (10)	50 (40) [c]	10 (10)	50 (40) [c]
Patient Global VAS	10 (10)	50 (40) [c]	10 (20)	50 (30) [c]
Physicians' Global VAS	0 (10)	40 (30) [c]	20 (20)	40 (20) [c]
PASI	0.9 (2.1	2 (3.7)	0.4 (1.6)	2.1 (3.7) [c]
Duration of morning stiffness, min.	10 (18)	20 (20)	20 (20	20 (20)
Fatigue	2 (3)	5 (4) [c]	3 (4)	5 (4) [c]
HAD-Anxiety	5 (6)	7 (6) [a]	6 (7)	7 (6) [b]
HAD-Depression	5 (6)	7 (6) [a]	6 (7)	7 (6) [c]
FiRST	0 (2)	2 (5) [c]	1 (3)	3 (4) [c]
PsAQoL	1 (6)	5 (11) [c]	3 (12)	7 (11) [c]
HAQ	0.05 (0.2)	0.3 (0.64) [c]	0.1 (0.35)	0.35 (0.58) [c]
BMI, kg/m^2	28.6 (6.9)	29.1 (6.4)	28.4 (7.4)	29.3 (6.4) [b]
ESR, mm/hr	14.5 (16)	19 (19)	20 (17)	18 (18)
CRP, mg/dL	0.5 (0.7)	0.7 (0.9)	0.6 (0.8)	0.7 (0.7)

Data are presented as median (IQR) and *n* (%). DAPSA: Disease Activity in Psoriatic Arthritis; MDA: Minimal Disease Activity; FiRST: Fibromyalgia Rapid Screening Tool; HAD: Hospital Anxiety and Depression; PASI: Psoriasis Area and Severity Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; PsAQoL: Psoriatic Arthritis Quality of Life; HAQ: Health Assessment Questionnaire; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

[a] $P < 0.05$.

[b] $P < 0.01$.

[c] $P < 0.001$.

and LDA, with the MDA criteria being more stringent in DAS-28 and DAPSA. In a meta-analysis in which patients were evaluated with DAPSA, DAS-28, VLDA, and MDA, the frequency of VLDA was lower than that of REM, and the frequency of MDA was lower than LDA. Unlike previous studies [28], we found lower VLDA and MDA rates, which may be due to higher global assessment and pain scores in our patients.

As noted in the current study, patients who are in REM/LDA are classified into varying activity states based on diverse scales. However, the clinical implications of this difference remain unclear and consensus regarding REM/LDA in PsA is lacking [28]. Of note, we found that some patients classified to be in REM according to the DAPSA did not meet the VLDA criteria because of several domains, skin involvement being the most residual domain, followed by pain, functional disability, enthesitis, global assessment, and tender joints. While the performance of the DAPSA and DAS-28 might be sufficient for joint involvement, it is clear that it disregards the skin, spine, enthesitis, and function. Recently, new composite scores have been developed covering joint, spine, skin involvement, quality of life, and function, such as the Psoriatic Arthritis Disease Activity Score (PASDAS), GRACE Index, and Composite Psoriatic Disease Activity Index (CPDAI) [29].

It emphasizes the importance of factors other than swollen joints where a significant number of patients has not met the REM or LDA criterion despite having no swollen joints. Furthermore, disease activity was adversely affected by anxiety, depression, fatigue, and fibromyalgia in a significant proportion of patients. These data are in agreement with previous reports addressing coexisting fibromyalgia and fatigue in relation to high disease activity in PsA [30,31]. In a prospective study assessing depressive symptoms in early inflammatory arthritis researchers concluded that depressive symptoms might play a role in patients who were considered to be in non-REM, even in the absence of joint inflammation [32]. These results indicate that some confounding factors such as fatigue, fibromyalgia can lead to overestimation of the pain or global assessment, however there is still insufficient data on their inclusion in the composite scores [33].

Contrary to our expectations, scores of dactylitis and acute phase reactants were not different between those with and without REM/LDA in the absence of swollen joints. This may be due to the small number of patients with dactylitis. On the other hand, female gender and obesity have been shown to be effective in the assessment of REM/LDA. Women are more likely to have higher disease activity scores and lower REM/LDA rates [34,35]. Our female patients also had lower REM/LDA rates independent of the presence or absence of swollen joints. In a prospective study, obese patients were less likely to achieve sustained MDA compared with those of normal-weight subjects [36]. Only MDA was negatively correlated with a higher BMI in our study.

According to a meta-analysis, the prevalence of REM ranged from 13.1 to 42.1% probably due to multiple REM definitions and varying sets of domains [28]. Among the available assessment scales, the DAS-28 and DAPSA reflect similar aspects of PsA, including joint involvement, acute phase reactants, and pain. The latter has a total score as the sum of the parameters, but with some limitations. For instance, a patient with high scores of pain or global assessments, despite the absence of active joint inflammation, may be classified as having a high disease activity. On the other hand, DAS 28 has a limitation of not involving adequate number of lower extremity joints since it was developed for RA. Another limitation is that other PsA manifestations are not covered, including symptoms related to skin, enthesitis, spine, and dactylitis. The limitations of the present assessment scales have led to the development of comprehensive PsA-specific composite activity indices, e.g., the PASDAS, GRACE, and CPDAI [28,37,38]. A brief summary of all assessment scales for PsA from other clinical studies is presented in Table 5, with domains and cut-off levels for disease activity states.

There are two major limitations to this study. First, new composite disease activity indices were not employed and DAS28-ESR were used. Alhough DAS28-CRP is more commonly used and recommended than DAS28-ESR nowadays, the TLAR network was based on DAS28-ESR. Second, our remission rates were lower than those reported in the literature probably due to higher scores on pain and global assessment. Since tender joint counts and VAS ratings are subjective parameters, they may be affected by many factors including race, educational and socioeconomic levels.

Table 5
A summary of disease activity scales for PsA and their cut-off levels for each disease activity state [23,24,29,39–41].

	Domains	Range	Remission	Low Disease Activity	Moderate Disease Activity	High Disease Activity
DAS28	Tender joints, Swollen joints, ESR/CRP, Patient Global VAS	2-10	≤ 2.6	> 2.6-≤ 3.2	> 3.2-≤ 5.1	> 5.1
DAPSA	Tender joints, Swollen joints, CRP, Pain VAS, Patient Global VAS	0-144 + CRP	≤ 4	> 4-≤ 14	> 14-≤ 28	> 28
MDA/VLDA	Tender joints (≤ 1), Swollen joints (≤ 1), PASI ≤1 or BSA≤ 3%, Enthesitis ≤ 1, Pain VAS ≤ 15, Patient Global VAS ≤ 20, HAQ ≤ 0.5		7/7 (VLDA)	≥ 5/7 (MDA)		
PASDAS	Tender joints, Swollen joints, Physician Global VAS, Patient Global VAS, SF36-PCS (Physical component score), Leeds enthesitis count, Dactylitis count, CRP (mg/L)	0-10	≤ 1.9	> 1.9-≤ 3.2	>3.2- < 5.4	≥ 5.4
GRACE Index(1-AMDF) × 10	Tender joints, Swollen joints, HAQ, Patient Global VAS, Patient Skin VAS, Patient Joint VAS, PASI, PsAQoL	0-10	≤ 1.9	> 1.9-≤ 2.3	> 2.3- < 4.7	≥ 4.7
CPDAI	Peripheral arthritis, Skin disease, Enthesitis, Dactylitis, Spinal disease	0-15	≤ 2	> 2-≤ 4	> 4- < 8	≥ 8

DAS-28: Disease Activity Assessment-28; DAPSA: Disease Activity in Psoriatic Arthritis; MDA: Minimal Disease Activity; VLDA: Very Low Disease Activity; PASDAS: Psoriatic Arthritis Disease Activity Score; AMDF: Arithmetic Mean of the Desirability Function; CPDAI: Composite Psoriatic Disease Activity Index.

In conclusion, the present study demonstrated that patients with peripheral PsA may be assigned to diverse disease activity levels when assessed with the DAS-28, DAPSA, MDA and VLDA, which would inevitably have clinical implications. Of these indices, compared with the DAS-28 and DAPSA, MDA and VLDA seem to be more meticulous assessment tools in determining REM and LDA.

In the context of arthritis, the most prominent manifestation is indeed joint involvement; however, there is some risk that other domains associated with PsA may be underevaluated. Therefore, no scale would be complete unless skin involvement, enthesitis, spinal involvement, and patient-reported outcomes including fatigue, pain, anxiety, depression, fibromyalgia, and functional disorders are considered. Novel composite scales seem to be promising in this respect.

Funding

This work was supported by the Turkish League Against Rheumatism (TLAR).

Authors' contributions

All authors contributed to the study conception, design and data collection. Material preparation and analysis were performed by HHG, MTD, KN, and İT. The first draft of the manuscript was written by HHG and MTD and all authors commented on previous versions of the manuscript. All co-authors are fully responsible for all aspects of the study and the final manuscript in line with the IJME 4 criteria.

Ethics approval

All procedures performed in studies involving human participants were performed 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. Ethical approval was taken from the Sakarya University Ethics Committee on 25.01.2018. The protocol number was 42.

Consent to participate

Informed consent was obtained from all subjects before enrollment.

Consent for publication

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Ertürk M, Alaca R, Tosun E, et al. Evaluation of the Amor and ESSG classification criteria for spondylarthropathies in a Turkish population. Rev Rhum Engl Ed 1997;64:293–300.
[2] Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700–12.
[3] Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018;77:3–17.
[4] Nas K, Kiliç E, Çevik R, et al. Management of Psoriatic Arthritis: Turkish League Against Rheumatism (TLAR) Expert Opinions. Arch Rheumatol 2018;33:108–27.
[5] Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol 2016;68:1060–71.
[6] Kavanaugh A, Fransen J. Defining remission in psoriatic arthritis. Clin Exp Rheumatol 2006;24 [S-83-7].
[7] Moverley AR, Coates LC, Helliwell PS. Aiming for remission in psoriatic arthritis. International Journal of Clinical Rheumatology 2014;9:147–53.
[8] Anderson J, Caplan L, Yazdany J, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken) 2012;64:640–7.
[9] Perrotta FM, Marchesoni A, Lubrano E. Minimal Disease Activity and Remission in Psoriatic Arthritis Patients Treated with Anti-TNF-α Drugs. J Rheumatol 2016;43:350–5.
[10] Gossec L, McGonagle D, Korotaeva T, et al. Minimal Disease Activity as a Treatment Target in Psoriatic Arthritis: A Review of the Literature. J Rheumatol 2018;45:6–13.
[11] Saber TP, Ng CT, Renard G, et al. Remission in psoriatic arthritis: is it possible and how can it be predicted? Arthritis research & therapy 2010;12 [R94-R].

[12] Helliwell P, Coates LC, FitzGerald O, et al. Disease-specific composite measures for psoriatic arthritis are highly responsive to a Janus kinase inhibitor treatment that targets multiple domains of disease. Arthritis Res Ther 2018;20:242.
[13] Orbai AM, de Wit M, Mease PJ, et al. Updating the Psoriatic Arthritis (PsA) Core Domain Set: A Report from the PsA Workshop at OMERACT 2016. J Rheumatol 2017;44:1522–8.
[14] van Mens LJJ, van de Sande MGH, van Kuijk AWR, et al. Ideal target for psoriatic arthritis? Comparison of remission and low disease activity states in a real-life cohort. Ann Rheum Dis 2018;77:251–7.
[15] Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
[16] Küçükdeveci AA, Sahin H, Ataman S, et al. Issues in cross-cultural validity: Example from the adaptation, reliability, and validity testing of a Turkish version of the Stanford Health Assessment Questionnaire. Arthritis Care & Research 2004;51:14–9.
[17] McKenna SP, Doward LC, Whalley D, et al. Development of the PsAQoL: a quality of life instrument specific to psoriatic arthritis. Ann Rheum Dis 2004;63:162–9.
[18] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
[19] Celiker R, Altan L, Rezvani A, et al. Reliability and validity of the Turkish version of the fibromyalgia rapid screening tool (FiRST). J Phys Ther Sci 2017;29:340–4.
[20] Tälli S, Etcheto A, Fautrel B, et al. Patient global assessment in psoriatic arthritis - what does it mean? An analysis of 223 patients from the Psoriatic arthritis impact of disease (PsAID) study. Joint Bone Spine 2016;83:335–40.
[21] Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407–17.
[22] Feldman SR, Fleischer Jr AB, Reboussin DM, et al. The self-administered psoriasis area and severity index is valid and reliable. J Invest Dermatol 1996;106:183–6.
[23] Acosta Felquer ML, Ferreyra Garrott L, Marin J, et al. Remission criteria and activity indices in psoriatic arthritis. Clin Rheumatol 2014;33:1323–30.
[24] Aletaha D, Alasti F, Smolen JS. Disease activity states of the DAPSA, a psoriatic arthritis specific instrument, are valid against functional status and structural progression. Ann Rheum Dis 2017;76:418–21.
[25] Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48–53.
[26] Gladman DD, Hing EN, Schentag CT, et al. Remission in psoriatic arthritis. J Rheumatol 2001;28:1045–8.
[27] Kasman SA, Gezer HH, Baklacıoğlu HŞ, et al. A standardized sonographic analysis of nails in psoriatic arthritis and healthy controls: feasibility, reliability, diagnostic performance, and demographic and clinical associations. Joint Bone Spine 2021.
[28] Hagège B, Tan E, Gayraud M, et al. Remission and low disease activity in psoriatic arthritis publications: a systematic literature review with meta-analysis. Rheumatology (Oxford) 2020;59:1818–25.
[29] Helliwell PS, Deodhar A, Gottlieb AB, et al. Composite Measures of Disease Activity in Psoriatic Arthritis: Comparative Instrument Performance Based on the Efficacy of Guselkumab in an Interventional Phase II Trial. Arthritis Care Res (Hoboken) 2020;72:1579–88.
[30] Brikman S, Furer V, Wollman J, et al. The Effect of the Presence of Fibromyalgia on Common Clinical Disease Activity Indices in Patients with Psoriatic Arthritis: A Cross-sectional Study. J Rheumatol 2016;43:1749–54.
[31] Duruöz MT, Gezer HH, Nas K, et al. The impact of fatigue on patients with psoriatic arthritis: a multi-center study of the TLAR-network. Rheumatol Int 2020;40:1803–15.
[32] Dobkin PL, Boire G. Controlled Joint Inflammation but Still No Remission? It's Time to Attend to Depressive Symptoms. J Rheumatol 2018;45:585–7.
[33] Queiro R. Remission and stringent treatment goals in psoriatic arthritis: Doctors' opinion is not enough. Joint Bone Spine 2019;86:269–70.
[34] Nas K, Capkin E, Dagli AZ, et al. Gender specific differences in patients with psoriatic arthritis. Mod Rheumatol 2017;27:345–9.
[35] Duruöz MT, Gezer HH, Nas K, et al. Gender-related differences in disease activity and clinical features in patients with peripheral psoriatic arthritis: A multicenter study. Joint Bone Spine 2021;88:105177.
[36] di Minno MN, Peluso R, Iervolino S, et al. Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. Arthritis Care Res (Hoboken) 2013;65:141–7.
[37] Mease PJ, Coates LC. Considerations for the definition of remission criteria in psoriatic arthritis. Semin Arthritis Rheum 2018;47:786–96.
[38] Helliwell PS, Kavanaugh A. Comparison of composite measures of disease activity in psoriatic arthritis using data from an interventional study with golimumab. Arthritis Care Res (Hoboken) 2014;66:749–56.
[39] Helliwell PS, FitzGerald O, Fransen J. Composite disease activity and responder indices for psoriatic arthritis: a report from the GRAPPA 2013 meeting on development of cutoffs for both disease activity states and response. J Rheumatol 2014;41:1212–7.
[40] Coates LC, Helliwell PS. Defining Low Disease Activity States in Psoriatic Arthritis using Novel Composite Disease Instruments. J Rheumatol 2016;43:371–5.
[41] Gorlier C, Orbai AM, Puyraimond-Zemmour D, et al. Comparing patient-perceived and physician-perceived remission and low disease activity in psoriatic arthritis: an analysis of 410 patients from 14 countries. Ann Rheum Dis 2019;78:201–8.