

ORIGINAL RESEARCH

Using ultrasound to define inflammatory and non-inflammatory phenotypes in difficult-to-treat psoriatic arthritis

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ABSTRACT

Objective To investigate the prevalence of difficult-to-treat psoriatic arthritis (D2T-PsA) and classify patients with persistent inflammatory PsA (PIPsA) and non-inflammatory PsA (NIPsA) based on a combination of clinical and musculoskeletal ultrasound (MSUS) evidence of inflammation.

Methods A multicentre cross-sectional study was conducted on PsA patients treated with biological disease-modifying anti-rheumatic drugs/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs). D2T-PsA status was characterised by an inadequate response to ≥ 2 classes of b/tsDMARDs and the persistence of active disease, defined as a DAPSA > 14 .

Results Out of 517 PsA patients on b/tsDMARDs, 53 (10.3%) met the criteria for D2T-PsA with 30 (57%) classified as PIPsA and 23 (43%) classified as NIPsA. The PIPsA phenotype had higher swollen joint count (2.5 (IQR 1.0–7.0) vs 0.0 (IQR 0.0–1.0), $p < 0.001$), dactylitis (20% vs 0%, $p = 0.030$) and nail psoriasis (40% vs 13%, $p = 0.027$). Conversely, NIPsA patients had significantly greater Δ PtGA-PhGA (4.0 (IQR 2.5–5.0) vs 0.0 (IQR 0.0–1.5), $p < 0.001$), higher tender points (16.0 (IQR 0.0–18.0) vs 0.0 (IQR 0.0–8.0), $p = 0.009$), a higher SPARCC enthesitis index (5.0 (IQR 2.0–8.0) vs 2.0 (IQR 0.0–5.0), $p = 0.023$). The MSUS showed higher ultrasound activity (3.81 ± 2.0 vs 0.91 ± 0.5 , $p < 0.001$) and greater structural damage (4.12 ± 1.0 vs 2.38 ± 2.1 , $p < 0.001$), with both activity and damage scores being higher in PIPsA patients.

Conclusion The classification into PIPsA and NIPsA based on easily detectable clinical features can support a tailored therapeutic management of patients with D2T-PsA.

INTRODUCTION

Despite the substantial expansion of the therapeutic landscape in psoriatic arthritis (PsA) over the past two decades with three major classes of biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), achieving remission remains limited.¹ For example, less than 50% of PsA patients achieve minimal

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite an expanding therapeutic landscape in psoriatic arthritis (PsA), achieving treatment targets remains challenging. In a substantial subset of patients, a mismatch between objective signs of inflammation and patient-reported symptoms complicates disease assessment. To address this issue, two clinical phenotypes have recently been proposed: persistent inflammatory PsA (PIPsA) and non-inflammatory PsA (NIPsA).

WHAT THIS STUDY ADDS

⇒ This study highlights the clinical relevance of the PIPsA and NIPsA phenotypes in difficult-to-treat PsA, distinguishing between inflammatory and non-inflammatory mechanisms. PIPsA is characterised by swollen joints, dactylitis and nail psoriasis, whereas NIPsA is associated with a higher number of tender points, painful entheses detected by the Spondyloarthritis Research Consortium of Canada and greater patient–physician discordance in disease activity assessment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Differentiating PIPsA from NIPsA could facilitate more personalised and efficient treatment strategies, reduce unnecessary therapeutic interventions and ultimately enhance the design of more homogeneous patient cohorts for future clinical trials.

disease activity,^{2,3} while a considerable proportion only show partial responses or completely fail to respond to therapy.⁴ This often necessitates multiple therapeutic adjustments, including b/tsDMARD cycling with a further reduction in the likelihood of achieving remission or sustained low disease activity.⁵ The multidomain nature of PsA, characterised by the simultaneous involvement of multiple articular domains—some of which are difficult to identify, such as enthesitis and

axial disease^{6,7}—alongside the high prevalence of comorbidities such as obesity, osteoarthritis (OA) and fibromyalgia (FM), further complicates disease management.^{8,9} This includes the interference of such comorbidities with therapeutic responses or therapeutic strategies.^{7,10–12}

In light of these challenges, and mirroring developments of the difficult-to-treat (D2T) concept in rheumatoid arthritis (RA), increasing attention is being focused on this challenging phenotype in PsA.^{13,14} Efforts have also been made to distinguish D2T PsA from ‘treatment-resistant’ PsA driven primarily by comorbidities, a condition referred to as ‘complex-to-manage’ PsA (C2M-PsA).^{8,14} Several authors have proposed analogous criteria for identifying potential cohorts of D2T-PsA with criteria typically encompassing patients with persistently active disease despite the failure of ≥ 2 bDMARDs or tsDMARDs with different mechanisms of action, following the failure or contraindication of at least one conventional synthetic DMARD (csDMARD).^{8,15} However, a universally accepted consensus on these definitions has yet to be established and strategies to disentangle inflammatory from non-inflammatory mechanisms potentially contributing to high composite disease activity scores have only been preliminarily reported.¹⁶

In D2T-RA and refractory RA, musculoskeletal ultrasound (MSUS) scanning of apparently swollen joints differentiates between two clinical phenotypes with high disease activity scores: one group with objective inflammation on imaging and a second group with chronic pain and FM.^{17,18} Recently, we proposed that, similarly to RA, two distinct groups exist in PsA in subjects with high composite disease activity scores: a persistent inflammatory PsA (PIPsA) phenotype, characterised by imaging evidence for ongoing inflammation and a second non-inflammatory PsA (NIPsA) phenotype,¹⁶ where post-inflammation damage, OA, FM, chronic pain and lack of objective imaging evidence of inflammation underscored high disease activity scores. Although not yet formally proven in clinical practice, this distinction could be useful in managing D2T-PsA patients who have experienced multiple treatment failures, with the hope that it may reduce unnecessary therapeutic cycling. Accordingly, the present study aims to identify the clinical characteristics of the PIPsA and NIPsA phenotypes in a cohort of D2T patients, using a combination of clinical and imaging criteria to confirm the presence or absence of inflammation.

METHODS

Study design and participants

This multicentre, cross-sectional observational study was conducted from March to December 2024 at two Italian centres: the Rheumatology Clinic of Santa Maria della Misericordia Hospital (Udine) and the Rheumatology Unit of Cardarelli Hospital (Campobasso). Written informed consent was obtained from all participants for study participation. The study was ethically approved by

the institutional review boards of the University Hospital of Udine and Campobasso.

Eligible participants were required to meet the following inclusion criteria: (1) age ≥ 18 years; (2) a diagnosis of PsA and fulfilment of the CASPAR criteria;¹⁹ (3) classification as D2T-PsA, defined by failure or contraindication of ≥ 2 classes of b/tsDMARDs following the failure or contraindication of ≥ 1 csDMARD, and persistently active disease (Disease Activity Index for Psoriatic Arthritis ((DAPSA)) > 14); and (4) ongoing continuous therapy for at least 3 months prior to enrolment.

Exclusion criteria were as follows: (1) absence of a confirmed diagnosis of PsA by an expert rheumatologist specialised in chronic inflammatory arthritis, including cases with suspected but unconfirmed PsA; (2) discontinuous treatment in the 3 months prior to enrolment, including temporary interruptions (ie, due to infectious events or surgical procedures) or poor adherence to therapy; (3) use of therapies at dosages not approved for PsA or use of off-label treatments; and (4) inability or unwillingness to provide informed consent.

Clinical assessment and data collection

Consecutive PsA patients meeting these criteria underwent the following rheumatologic evaluations: complete demographic data collection (ie, age, biologic sex at birth, smoking status); anthropometric measurements (height and weight); as well as medical history collection, focusing on comorbidities (ie, arterial hypertension, diabetes mellitus, cardiovascular diseases, malignancies, hyperuricaemia, metabolic syndrome,²⁰ inflammatory bowel diseases, uveitis and depression). The Charlson Comorbidity Index was calculated for each patient. Data related to psoriasis were collected, including psoriasis type and age at onset of cutaneous manifestations of psoriatic disease. The diagnosis of OA was determined by medically qualified staff of the research team, through both clinical and radiological assessments, while FM was diagnosed based on the ACR criteria.²¹

Information regarding PsA was recorded, including its extent at onset (polyarticular vs oligoarticular), age of onset, history of dactylitis, pharmacological treatments received and any treatment failures. Each patient underwent an extended rheumatological assessment, which included swollen joint counts (SJC), tender joint counts (TJC), presence/absence of dactylitis, tender enthesis count using Spondyloarthritis Research Consortium of Canada (SPARCC),²² tender points count and psoriasis extension using Psoriasis Area Severity Index. Measures of outcome such as DAPSA, Health Assessment Questionnaire, Patients Global Assessment (PtGA), Physician Global Assessment (PhGA), Visual Analogue Scale pain, Psoriatic Arthritis Impact of Disease (PsAID-12),²³ Central Sensitization Inventory (CSI)²⁴ and Patient Acceptable Symptom State (PASS)²⁵ were also collected.

Sites were defined as clinically active based on the following criteria: (1) for peripheral disease, the presence of a tender and/or swollen joint or a tender enthesis, and

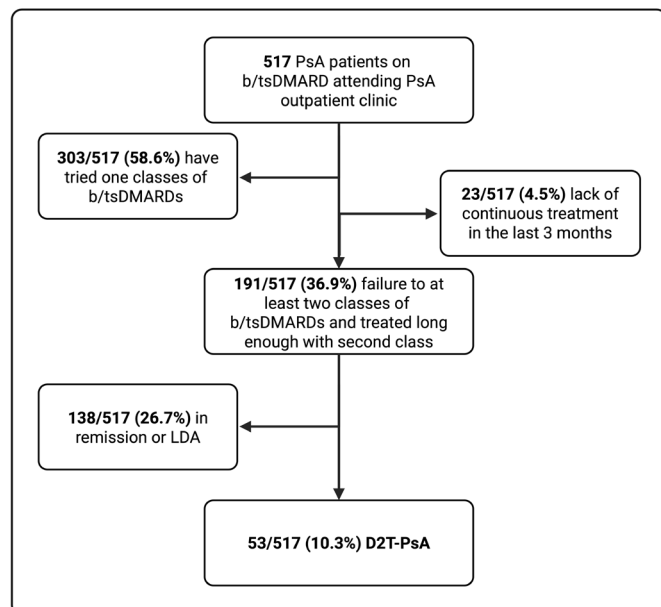


Figure 1 Flow diagram of patients enrolled in the study. b/ tsDMARDs, biologic/target synthetic disease-modifying anti-rheumatic drugs; D2T, difficult-to-treat; LDA, low disease activity; PsA, psoriatic arthritis.

(2) for axial disease, the presence of inflammatory axial symptoms accompanied by either spinal or sacroiliac tenderness.

Imaging assessment

All D2T-PsA patients underwent MSUS evaluations of 42 joints (primarily hands, wrists, knees and feet), 36 tendons (hand flexors/extensors, wrist extensors and anterior/posterior tibialis), 12 entheses (epicondyles, quadriceps tendons, patellar ligaments, Achilles tendons and plantar aponeuroses) and two bursae (Achilles bursae).^{26 27} The full MSUS protocol and the definitions used to define the elementary lesions are published in the supplementary material (online supplemental figure 1 and table 1).

An experienced MSUS physician was appointed at each participating centre to perform the scans, ensuring they were conducted blinded to the patient's clinical data. The MSUS assessments were performed using a high-end

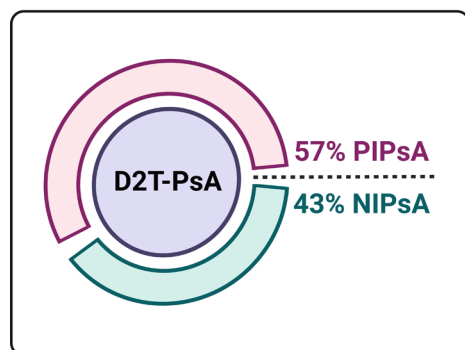


Figure 2 Prevalence of PIPsA and NIPsA in D2T-PsA. D2T, difficult-to-treat; PIPsA, persistent inflammatory psoriatic arthritis; NIPsA, non-inflammatory psoriatic arthritis.

ultrasound system (SAMSUNG RS85) equipped with multifrequency linear transducers and a high-frequency probe of at least 14 MHz.

The criteria used to define a site as MSUS-active were as follows: (1) synovitis was considered active if there was at least grade 2 on grey scale (GS) with grade 1 on power Doppler (PD), or if GS ≥ 1 was combined with PD ≥ 2 ;²⁸ (2) tenosynovitis was defined by the presence of at least GS ≥ 1 and PD ≥ 1 ;²⁹ (3) paratenonitis was identified by the combination of B-mode alteration with PD signal;²⁹ and (4) enthesitis was defined by the presence of PD signal in association with enthesal thickening and/or hypoechoic areas, consistent with the OMERACT definition.³⁰ The reliability was evaluated using kappa statistics ($\kappa \geq 0.7$) to ensure substantial agreement among sonographers. The results were compared with a 'gold-standard' scorer to validate the consistency of the scoring method.

In case of suspected axial involvement (ie, combination of axial inflammatory symptoms³¹ and spine or sacroiliac tenderness detected during physical examination), MRI of the sacroiliac joints and/or spine was performed based on clinical findings. MRI findings were considered positive according to the definitions proposed by the ASAS/OMERACT MRI Study Group.^{32 33}

Definition and stratification of patients

Based on the combination of clinical and imaging findings, D2T patients were stratified into two distinct groups, according to the classification proposed in a recently published perspective:¹⁶

- PIPsA whereby D2T patients exhibited imaging evidence of ongoing inflammation (ie, MSUS-active site) in at least one clinically active site.
- NIPsA whereby D2T patients lacked imaging evidence of ongoing inflammation at any clinically active sites.

Among D2T, those who had failed at least one drug from each class of advanced therapies (b and ts-DMARDs) due to inefficacy, intolerance or contraindications were considered to have refractory PsA.

Statistical analysis

Clinical and sonographic data were entered into Research Electronic Data Capture system.³⁴ The study employed descriptive statistics (median, IQR and percentages) to summarise patient characteristics. T-test or Mann-Whitney U tests were applied to continuous variables, as appropriate, while χ^2 or Fisher's exact tests assessed differences in categorical variables between PIPsA and NIPsA groups. Normality was assessed using the Shapiro-Wilk test. Statistical significance was determined using p values, with a threshold of <0.05 .

A multivariate (MV) logistic regression model was conducted to identify factors associated with the PIPsA phenotype, including variables statistically significant at univariable analysis. Age and sex were included in the MV model as a priori covariates, regardless of their statistical significance in the univariable analysis, due to their potential role as clinically relevant confounders.

Table 1 Characteristics of D2T-PsA patients and comparison between PIPsA and NIPsA

Median (IQR); n° (%)	D2T-PsA N=53	PIPsA N=30	NIPsA N=23	P value
Age (years)	59.0 (49.0, 65.0)	60.0 (54.0, 65.0)	57.0 (46.0, 64.0)	0.134
Female	34 (64)	19 (69)	15 (65)	1.000
Active smoker	7 (13)	4 (13)	3 (13)	0.969
BMI	26.9 (24.2, 30.5)	26.5 (24.2, 30.5)	27.0 (23.9, 30.5)	0.699
Family history of psoriatic arthritis	6 (11)	3 (10)	3 (13)	1.000
Comorbidities				
Obesity	19 (36)	10 (33)	9 (39)	0.663
Diabetes	11 (21)	5 (17)	6 (26)	0.501
Hypertension	19 (36)	13 (43)	6 (26)	0.019
Fatty liver disease	4 (7.5)	4 (13)	0 (0)	0.124
IBD	1 (1.9)	1 (3.3)	0 (0)	1.000
Depression	4 (7.5)	1 (3.3)	3 (13.0)	0.573
Malignancy	4 (7.5)	2 (6.7)	2 (8.7)	1.000
Hyperuricaemia	5 (9.4)	3 (10.0)	2 (8.7)	1.000
Cardiovascular disease	5 (9.4)	3 (10)	2 (8.7)	1.000
Dyslipidaemia	13 (25)	6 (20)	7 (30)	0.382
Charlson Comorbidity index	2.0 (1.0, 3.0)	2 (1.0, 3.0)	1 (0.0, 3.0)	0.564
Predominant pattern of psoriasis				
Vulgaris psoriasis	31 (58.4)	14 (46.7)	17 (74.0)	0.499
Pustular psoriasis	3 (5.7)	3 (10.0)	0 (0)	0.249
Guttate psoriasis	1 (1.9)	0 (0)	1 (4.3)	0.434
Nail psoriasis	15 (28.3)	12 (40.0)	3 (13)	0.027
Inverse psoriasis	3 (5.7)	1 (3.3)	2 (8.7)	0.573
PASI	0.0 (0.0, 1.0)	0 (0.0, 1.0)	0 (0.0, 1.0)	0.758
Disease duration	11 (7, 23)	13 (8, 19)	9 (7, 26)	0.328
Predominant pattern of PsA				
Axial	3 (5.7)	1 (3.4)	2 (8.7)	0.573
Peripheral	50 (94.3)	29 (96.6)	21 (91.3)	0.663
Type of peripheral involvement				
Enthesal	6 (11.3)	3 (10)	3 (13)	0.861
Oligoarticular	19 (35.8)	11 (36.6)	8 (34.7)	0.501
Polyarticular	28 (52.9)	16 (53.4)	12 (57.1)	0.715
Mechanism of action failed				
TNFi	48 (91)	27 (90)	21 (91)	1.000
IL17i	38 (72)	22 (73)	16 (70)	0.763
IL12/23i and/or IL23i	19 (36)	10 (33)	9 (39)	0.663
JAKi	10 (19)	6 (20)	4 (17)	1.000
Apremilast	10 (19)	6 (20)	4 (17)	1.000
N° of b/tsDMARDs failed	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.941
N° of b/tsDMARDs classes failed	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.861
CRP (mg/dl)	0.3 (0.2, 0.9)	0.2 (0.2, 2.0)	0.3 (0.2, 0.6)	0.329
HAQ	1.0 (0.6, 1.5)	0.7 (0.5, 1.1)	1.5 (0.6, 1.7)	0.083
VAS pain	7.5 (6.0, 8.0)	7.0 (6.0, 8.0)	8.0 (7.0, 8.0)	0.063
PhGA	5.0 (4.0, 7.0)	6.0 (5.0, 8.0)	4.0 (2.0, 5.5)	0.001
PtGA	7.0 (6.0, 8.0)	7.0 (6.0, 7.0)	7.0 (5.0, 8.0)	0.470

Continued

Table 1 Continued

Median (IQR); n° (%)	D2T-PsA N=53	PIPsA N=30	NIPsA N=23	P value
Δ PtGA-PhGA	1.0 (0.0, 4.0)	0.0 (0.0, 1.5)	4.0 (2.5, 5.0)	0.000
PASS, negative answer	45 (84.9)	25 (83.3)	20 (86.9)	0.715
DAPSA	25.0 (18.0, 38.0)	26.0 (18.0, 38.0)	25.0 (18.0, 40.0)	0.950
TJC	7.0 (2.0, 16.0)	8.0 (2.0, 14.0)	7.0 (2.0, 30.0)	0.621
SJC	1.0 (0.0, 3.0)	2.5 (1.0, 7.0)	0.0 (0.0, 1.0)	0.000
SPARCC enthesitis index	3.0 (1.0, 7.0)	2.0 (0.0, 5.0)	5.0 (2.0, 8.0)	0.023
Dactylitis (current/past)	6 (11)	6 (20)	0 (0)	0.030
Tender points	3.0 (0.0, 16.0)	0.0 (0.0, 8.0)	16.0 (0.0, 18.0)	0.009
Fibromyalgia	14 (26)	4 (13)	10 (43)	0.014
Osteoarthritis	20 (38)	9 (30)	11 (48)	0.185
CSI				0.227
0–29	13 (24.5)	6 (20.3)	7 (30)	
30–39	5 (9.4)	5 (17)	0 (0)	
40–49	17 (32)	10 (33)	7 (30)	
> 49	18 (34)	9 (30)	9 (39)	
CSI value	47.0 (38.0, 54.0)	46.0 (39.0, 53.0)	47.0 (37.0, 55.0)	0.820
PSAID 12				0.251
0–1.9	2 (3.8)	0 (0)	2 (8.6)	
2.0–3.9	5 (9.6)	2 (6.9)	3 (13)	
4.0–4.9	9 (17)	7 (24)	2 (8.7)	
> 4.9	37 (69.8)	20 (69)	16 (70)	
PSAID 12 value	5.8 (4.2, 6.8)	6.15 (4.4, 6.7)	5.2 (3.3, 7.0)	0.278

BMI, body mass index; b/tsDMARDs, biologic/ target synthetic disease modifying anti-rheumatic drugs; CRP, c-reactive protein; CSI, Central Sensitization Inventory; DAPSA, Disease Activity Index for Psoriatic Arthritis; D2T-PsA, difficult-to-treat psoriatic arthritis; HAQ, Health Assessment Questionnaire; IBD, inflammatory bowel disease; NIPsA, non-inflammatory psoriatic arthritis; PASI, Psoriasis Area Severity Index; PASS, Patient Acceptable Symptom State; PhGA, physician global assessment; PIPsA, persistent inflammatory psoriatic arthritis; PSAID-12, Psoriatic Arthritis Impact of Disease; PtGA, patient global assessment; SJC, swollen joint count; SPARCC, Spondyloarthritis Research Consortium of Canada; TJC, tender joint count; VAS pain, Visual Analogue Scale pain; Δ PtGA-PhGA, discrepancy between PtGA and PhGA.

Dactylitis was excluded to avoid complete separation effects (online supplemental figure 2).

Variable selection was based on both clinical relevance and statistical significance in the univariable analysis ($p < 0.05$), or acted as confounders ($\geq 10\%$ change in the OR of the exposure) (33).

A stepwise selection was applied, using Akaike Information Criterion as the stopping rule (online supplemental table 2).

The model followed the one-in-ten rule of thumb, ensuring at least ten events per predictor variable to minimise the risk of overfitting.³⁵

Multicollinearity was evaluated by calculating the variance inflation factor (VIF) for each variable included in the MV model. A threshold of $VIF \leq 5$ was applied to indicate acceptable levels of collinearity.

Analyses were performed using STATA 18 (StataCorp, College Station, TX, USA) and R (R Core Team, Vienna, Austria).

RESULTS

We identified 517 PsA patients receiving treatment with b/tsDMARDs, of whom 53 (10.3%) met the criteria for D2T-PsA (figure 1).

Among these, six patients (1.2% of the overall b/tsDMARD-treated cohort) had failed all available mechanisms of action and were therefore classified as having refractory PsA. The median age of D2T-PsA patients was 59.0 years (IQR: 49.0–65.0), with a predominance of females (34/53; 64%) and a median body mass index of 26.9 (IQR: 24.2–30.5). The median disease duration was 11.0 years (IQR: 7.0–23.0). Patients had been treated with a median of 3.0 b/tsDMARDs (IQR: 2.0–4.0) and had failed a median of 2.0 distinct mechanisms of action (IQR: 2.0–3.0). The most frequently failed therapeutic classes were Tumor Necrosis Factor (TNF) inhibitors (91%) and interleukin-17 inhibitors (72%). Peripheral joint involvement was present in the vast majority of

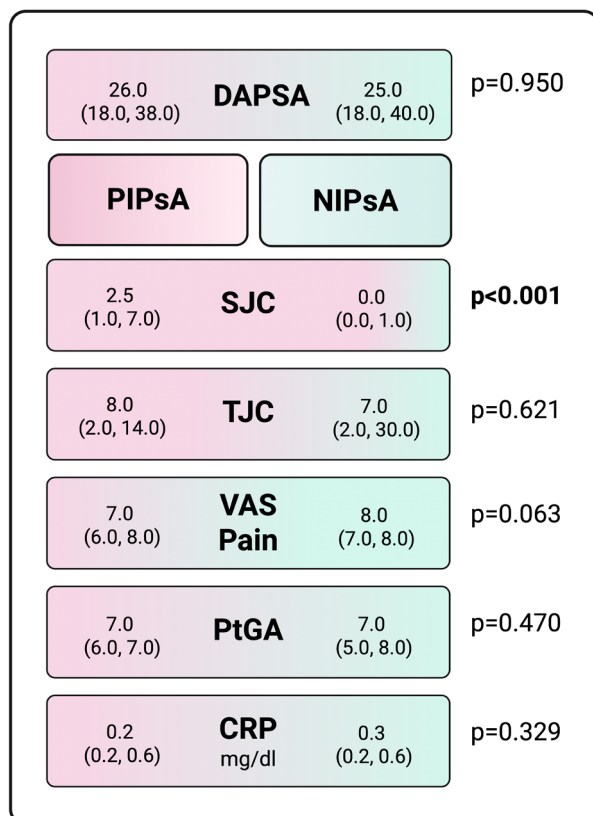


Figure 3 Comparison of DAPSA scores and components between PIPsA and NIPsA patients. CRP, c-reactive protein; DAPSA, disease activity index for psoriatic arthritis; NIPsA, non-inflammatory psoriatic arthritis; PIPsA, persistent inflammatory psoriatic arthritis; PtGA, patient global assessment; SJC, swollen joint count; TJC, tender joint count; VAS pain, Visual Analogue Scale pain.

patients (94.3%), with a polyarticular pattern observed in 52.9% of cases at the PsA onset.

Median disease activity, as assessed by the DAPSA score, was 25.0 (IQR: 18.0–38.0). Clinical evaluation revealed a median SJC of 1.0 (IQR: 0.0–3.0), a TJC of 7.0 (IQR: 2.0–16.0) and a SPARCC enthesitis index of 3.0 (IQR: 1.0–7.0). According to the PASS criteria, 84.9% of patients (45/53) were classified as having an unacceptable symptom state. Notably, FM overlap was identified in 26% of the cohort (14/53 patients).

Among the D2T, 30 out of 53 (57%) were classified as PIPsA, while 23 out of 53 (43%) presented with the NIPsA phenotype (figure 2). Baseline demographic characteristics, including age, sex, comorbidities and smoking history, were generally comparable between the two groups (table 1).

Among the PIPsA patients: 20 out of 30 (66.6%) were classified based on the presence of at least one clinically active site corresponding to a swollen joint confirmed as MSUS-active; three out of 30 (10%) were classified based on the presence of at least one clinically active site corresponding to a tender, non-swollen joint that was MSUS-active; seven out of 30 (23.4%) were classified based on the presence of at least one clinically active enthesis, with

MSUS-confirmed active enthesitis, and no signs of active inflammation in tender or swollen joints on MSUS. In three out of 53 patients, axial involvement was suspected clinically, but MRI did not reveal any signs of active inflammation. Among the NIPsA patients, five out of 23 (21.7%) had at least one swollen joint, without corresponding MSUS evidence of disease activity at that site.

Comparative clinical characterisation of persistent inflammatory psoriatic arthritis (PIPsA) and non-inflammatory psoriatic arthritis (NIPsA) phenotypes

Disease activity, as assessed by the DAPSA score, was comparable between patients with PIPsA and NIPsA phenotypes (26.0 (IQR: 18.0–38.0) vs 25.0 (IQR: 18.0–40.0); p=0.950) (figure 3). Similarly, systemic inflammation, measured by median CRP levels, did not differ significantly between groups (0.2 (IQR: 0.2–0.6) vs 0.3 (IQR: 0.2–0.6); p=0.329).

However, patients with the PIPsA phenotype demonstrated a significantly higher median SJC compared with those with NIPsA (2.5 (IQR: 1.0–7.0) vs 0.0 (IQR: 0.0–1.0); p<0.001), while the TJC remained similar between groups (8 (IQR: 2–14) vs 7 (IQR: 2–30); p=0.621). Dactylitis was observed only in the PIPsA group (6 vs 0 patients; p=0.030), and nail psoriasis as the predominant skin/nail phenotype was more common among PIPsA patients (40% vs 13%; p=0.027).

In contrast, NIPsA patients exhibited a significantly higher median number of tender points (16.0 (IQR: 0.0–18.0) vs 0.0 (IQR: 0.0–8.0); p=0.009) and a greater burden of enthesal tenderness, as indicated by higher SPARCC enthesitis index (5.0 (IQR: 2.0–8.0) vs 2.0 (IQR: 0.0–5.0); p=0.023). Patient-Reported Outcomes (PROs) tended to be higher in the NIPsA group, although differences were not statistically significant.

Conversely, the PhGA was significantly higher in PIPsA patients (6.0 (IQR: 5.0–8.0) vs 4.0 (IQR: 2.0–5.5); p=0.001). Meanwhile, NIPsA patients exhibited a markedly greater discrepancy between patient and physician assessments of disease activity (Δ PtGA–PhGA), with a median of 4.0 (IQR: 2.5–5.0) compared with 0.0 (IQR: 0.0–1.5) in PIPsA patients (p<0.001) (figure 4).

The number of mechanisms of action failed and the number of b/tsDMARDs failed did not differ significantly between the two groups. However, the NIPsA group had a higher proportion of refractory PsA (5/23, 21.7%), defined as failure of at least one drug from each b/tsDMARDs class, compared with the other group (1/30, 3.3%), but this difference did not reach statistical significance (p=0.074). NIPsA patients also demonstrated a greater overlap with FM (43% vs 13%, p=0.013) and had a higher prevalence of OA, although this difference was not statistically significant (48% vs 30%, p=0.185).

Factors associated with persistent inflammatory psoriatic arthritis (PIPsA) phenotype

The MV logistic regression analysis to identify factors associated with PIPsA was performed, including variables

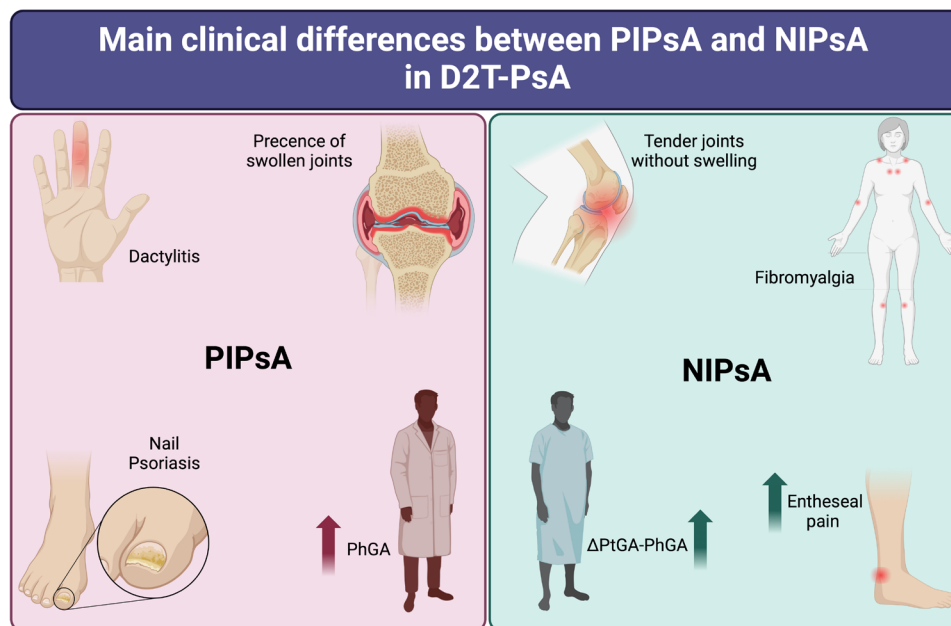


Figure 4 The comparison of clinical characteristics between PIPsA and NIPsA phenotypes in D2T-PsA reveals key differences. PIPsA phenotype is primarily characterised by joint swelling, dactylitis and nail psoriasis, along with higher PhGA levels. In contrast, the NIPsA phenotype is defined by tender, non-swollen joints, a higher number of tender points, a fibromyalgia diagnosis based on the ACR 2016 criteria, elevated SPARCC enthesitis index and a greater discrepancy between PtGA and PhGA. D2T, difficult-to-treat; NIPsA, non-inflammatory psoriatic arthritis; PhGA, physician global assessment; PIPsA, persistent inflammatory psoriatic arthritis; PsA, psoriatic arthritis; PtGA, patient global assessment.

statistically significant at univariable analysis (online supplemental table 2).

After variable selection, the final model included Δ PtGA-PhGA, nail psoriasis, SJC, tender points and the SPARCC enthesitis index. Assessment of multicollinearity confirmed that all these variables met the predefined VIF criterion (≤ 5).

Table 2 Logistic regression model adjusted for age and gender to explore associations with PIPsA

Variable	OR	CI 95%	P value
Age	1.019	0.970 to 1.076	0.458
Gender	0.486	0.049 to 3.728	0.498
Nail psoriasis	3.619	0.466 to 39.004	0.241
Δ PtGA-PhGA	0.633	0.394 to 0.927	0.031
SPARCC enthesitis index	0.888	0.608 to 1.271	0.516
SJC	2.863	1.482 to 7.226	0.008
Tender points	1.067	0.887 to 1.299	0.496

The model included sex as a categorical variable (female and male) and age as a continuous variable. Stepwise selection was performed to identify the final model. The adjusted model found a positive association between SJC and PIPsA, while Δ PtGA-PhGA was negatively associated with PIPsA. Significant values ($p < 0.05$) are indicated in bold.

NIPsA, non-inflammatory psoriatic arthritis; PhGA, physician global assessment; PIPsA, persistent inflammatory psoriatic arthritis; PtGA, patient global assessment; SPARCC, Spondyloarthritis Research Consortium of Canada; Δ PtGA-PhGA, discrepancy between PtGA and PhGA.

This analysis found that SJC was positively associated with PIPsA (OR=2.863, 95% CI 1.482 to 7.226, $p=0.008$), while Δ PtGA-PhGA was inversely associated (OR=0.633, 95% CI 0.394 to 0.927, $p=0.031$). In contrast, nail psoriasis (OR=3.619, 95% CI 0.466 to 39.009, $p=0.241$), the SPARCC enthesitis index (OR=0.888, 95% CI 0.608 to 1.271, $p=0.516$) and the tender points count (OR=1.067, 95% CI 0.887 to 1.299, $p=0.496$) were not significantly associated with PIPsA. Although nail psoriasis did not reach statistical significance, the direction and range of the CI may indicate a potential trend that warrants further investigation (table 2).

Comparative sonographic characterisation of persistent inflammatory psoriatic arthritis (PIPsA) and non-inflammatory psoriatic arthritis (NIPsA) phenotypes

The MSUS examination revealed notable differences between the PIPsA and NIPsA groups in both sonographic activity and structural damage. PIPsA patients demonstrated significantly higher MSUS activity scores (3.81 ± 2.0 vs 0.91 ± 0.5 , $p < 0.001$) and greater structural damage scores (4.12 ± 1.0 vs 2.38 ± 2.1 , $p < 0.001$).

Furthermore, PIPsA patients exhibited a significantly higher number of active synovitis (2.70 ± 2.98 vs 0.04 ± 0.21 , $p < 0.001$), active paratenonitis (0.90 ± 1.21 vs 0.04 ± 0.21 , $p = 0.001$) and active tenosynovitis (0.83 ± 1.78 vs 0.00 ± 0.00 , $p = 0.005$). Regarding active enthesitis, PIPsA patients displayed a greater number of inflamed sites compared with NIPsA, though the difference did not reach statistical significance (0.53 ± 0.68 vs 0.30 ± 0.76 , $p = 0.079$) (figure 5).

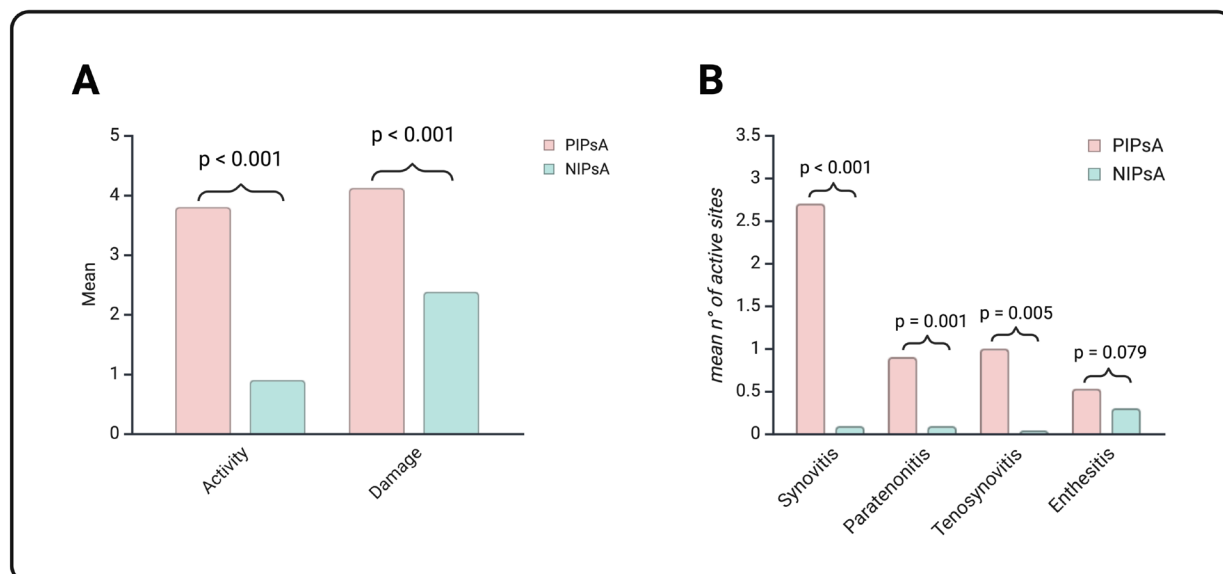


Figure 5 Sonographic characteristics of PIPsA and NIPsA. (A) Comparison of Activity and Damage scores between PIPsA and NIPsA. (B) Mean number of sonographic findings, including synovitis, paratenonitis, tenosynovitis and enthesitis, in PIPsA vs NIPsA patients. NIPsA, non-inflammatory psoriatic arthritis; PIPsA, persistent inflammatory psoriatic arthritis.

The distribution of elementary lesions between PIPsA and NIPsA is fully detailed in the supplementary material (Supplementary Table 3).

Overall, PIPsA patients show significantly higher levels of sonographic activity and structural damage compared with NIPsA patients, with notable differences in the mean number of active synovitis, tenosynovitis, paratenonitis and enthesitis.

DISCUSSION

This cross-sectional, multicentre study conducted in a real-world clinical setting confirms that D2T PsA represents a clinically relevant challenge, as demonstrated by a 10% prevalence of D2T patients in this cohort. The available literature on D2T PsA remains heterogeneous, with prevalence estimates ranging from 3% to 30%, largely due to the absence of a standardised definition.^{14 36–38} Analogous to data reported in RA, we found that more than 40% of cases with high disease activity scores had no objective evidence of joint inflammation.¹⁸

Although formal studies are still needed, these findings highlight the importance of developing strategies to better characterise inadequate treatment responses in PsA. In this context, we propose that distinguishing between PIPsA and NIPsA in D2T PsA may serve as a practical tool for clinicians. The integration of clinical and sonographic assessments of disease activity further enhances this approach, as it reflects real-world clinical practice and may help reduce unnecessary therapeutic cycling—thereby limiting the risk of adverse events associated with repeated treatment switches. Moreover, this distinction supports a more targeted approach to pain management, especially in patients with NIPsA, for whom non-inflammatory mechanisms may underlie persistent symptoms

We believe that the integration of clinical and imaging findings may be crucial for selecting patients for novel therapies, particularly in cases of apparent inadequate response to PsA treatment. This is especially relevant for indications that rely on enthesitis and musculoskeletal tenderness—both of which were strongly associated with NIPsA.

Despite the presumed differences between PIPsA and NIPsA, disease activity assessed using the DAPSA did not differ significantly between the two groups. This finding highlights the limitations of current clinimetric indices in evaluating patients who have failed multiple treatment lines. Notably, PIPsA patients exhibited several poor prognostic factors identified by EULAR, including a higher number of swollen joints and dactylitis, as well as nail involvement and greater structural damage.¹³⁹ Conversely, NIPsA patients were characterised by a discrepancy between elevated PRO values and low objective inflammatory activity. This discordance was also evident during physical examination, with widespread tender joints but often an absence of swelling. The inflated DAPSA scores in NIPsA patients likely reflect the contribution of high PRO values.

From an imaging perspective, PIPsA patients displayed a significantly higher prevalence of sonographic signs of inflammation and structural damage compared with NIPsA patients, reflecting the greater inflammatory burden and more aggressive disease course associated with this phenotype. Consistent with previous studies, these findings suggest that PIPsA patients may benefit more from treatment switching or cycling strategies. Structural damage, assessed via ultrasonography, was prominent in PIPsA patients but also notable in NIPsA patients, confirming the diagnosis of PsA and potentially explaining the persistence of joint and enthesal

tenderness in the latter group. This aligns with evidence indicating aberrant nerve proliferation in the cartilage and entheses of degenerative joints, along with increased expression of substance P, a key mediator of pain.^{40 41} A similar mechanism may occur in PsA, whereby damage resulting from arthritis or enthesitis leads to altered innervation within the enthesis or synovio-entheseal complex, contributing to refractory pain.^{10 11 42}

Conversely, the NIPsA group showed a higher proportion of refractory PsA, underscoring the need for caution when considering treatment changes in the absence of clear inflammatory signs. This finding also suggests that a distinct therapeutic approach may be warranted for this subgroup. Furthermore, NIPsA patients exhibited a higher prevalence of FM and OA, resembling patterns observed in NIRRA patients.¹⁸ These comorbidities are well-recognised negative predictors of achieving treatment targets and likely contribute to the complexity of managing this subset of D2T-PsA patients.³⁸

Several limitations should be acknowledged. First, the cross-sectional design precludes the assessment of longitudinal outcomes, emphasising the need for prospective studies to better evaluate differences in phenotype-specific treatment responses. Additionally, the lack of validated definitions for D2T-PsA and refractory PsA may affect the interpretation and clinical applicability of the findings, underscoring the need for standardised criteria to improve comparability across studies. Furthermore, the relatively small sample size of the D2T-PsA cohort—particularly after stratification into PIPsA and NIPsA subgroups—may have limited the statistical power to detect certain differences. Another limitation concerns the use of MSUS as the imaging modality for assessing peripheral inflammation. While MSUS is highly sensitive for detecting synovitis, enthesitis and subcutaneous oedema, it may not adequately capture cases where osteitis is the predominant lesion—an inflammatory feature that is particularly relevant in PsA and better detected with MRI. However, since osteitis often coexists with soft tissue inflammation such as enthesitis or synovitis, we believe this limitation is unlikely to have had a major impact on the overall characterisation of inflammatory burden in our cohort.

Finally, the presence of PD in MSUS assessment played a key role in distinguishing between PIPsA and NIPsA. However, the absence of PD does not necessarily indicate a lack of persistent active inflammation, as it may be masked by ongoing biologic therapy or remain undetected in relatively avascular areas such as the entheses.

In conclusion, this study provides a comprehensive characterisation of D2T PsA patients, highlighting the heterogeneity within this population and the need for a phenotype-driven approach to optimise management. The distinction between PIPsA and NIPsA subtypes, combined with clinical and sonographic assessments, may offer practical guidance for tailoring therapeutic strategies. Future research should validate these findings in larger prospective cohorts, explore the molecular

mechanisms underlying these phenotypes and assess the impact of phenotype-specific interventions on clinical outcomes.

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REFERENCES

- Gossec L, Kerschbaumer A, Ferreira RJO, *et al.* EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. *Ann Rheum Dis* 2024;83:706–19.
- 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.

- 3 Mease PJ, Kavanaugh A, Coates LC, *et al.* Prediction and benefits of minimal disease activity in patients with psoriatic arthritis and active skin disease in the ADEPT trial. *RMD Open* 2017;3:e000415.
- 4 Hagege B, Tan E, Gayraud M, *et al.* Remission and low disease activity in psoriatic arthritis publications: a systematic literature review with meta-analysis. *Rheumatology (Sunnyvale)* 2020;59:1818–25.
- 5 Glinthorg B, Di Giuseppe D, Wallman JK, *et al.* Uptake and effectiveness of newer biologic and targeted synthetic disease-modifying antirheumatic drugs in psoriatic arthritis: results from five Nordic biologics registries. *Ann Rheum Dis* 2023;82:820–8.
- 6 Zabotti A, Luchetti MM, Selmi CF, *et al.* An Italian Disease-Based Registry of Axial and Peripheral Spondyloarthritis: The SIRENA Study. *Front Med (Lausanne)* 2021;8:711875.
- 7 Giovannini I, Zabotti A, Ciccio C, *et al.* Axial Psoriatic Disease: Clinical and Imaging Assessment of an Underdiagnosed Condition. *J Clin Med* 2021;10:2845.
- 8 Ribeiro AL, Singla S, Chandran V, *et al.* Deciphering difficult-to-treat psoriatic arthritis (D2T-PsA): a GRAPPA perspective from an international survey of healthcare professionals. *Rheumatol Adv Pract* 2024;8:rkae074.
- 9 Witte T, Minopoulou I, Drzeniek NM, *et al.* Advances in precision medicine in imaging and therapeutic strategies for psoriatic disease. *Autoimmun Rev* 2025;24:103839.
- 10 Aydin SZ, Bridgwood C, Zabotti A, *et al.* The transition from enthesitis physiological responses in health to aberrant responses that underpin spondyloarthritis mechanisms. *Curr Opin Rheumatol* 2021;33:64–73.
- 11 Schett G, Lories RJ, D'Agostino M-A, *et al.* Enthesitis: from pathophysiology to treatment. *Nat Rev Rheumatol* 2017;13:731–41.
- 12 Gladman DD. Axial disease in psoriatic arthritis. *Curr Rheumatol Rep* 2007;9:455–60.
- 13 Marzo-Ortega H, Harrison SR, Nagy G, *et al.* Time to address the challenge of difficult to treat psoriatic arthritis: results from an international survey. *Ann Rheum Dis* 2024;83:403–4.
- 14 Singla S, Ribeiro A, Torgutalp M, *et al.* Difficult-to-treat psoriatic arthritis (D2T PsA): a scoping literature review informing a GRAPPA research project. *RMD Open* 2024;10:e003809.
- 15 Nagy G, Roodenrijs NM, Welsing PM, *et al.* EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80:31–5.
- 16 Zabotti A, Aydin SZ, David P, *et al.* Delineating inflammatory from non-inflammatory mechanisms for therapy optimization in psoriatic arthritis. *Nat Rev Rheumatol* 2025;21:237–48.
- 17 Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. *Nat Rev Rheumatol* 2021;17:17–33.
- 18 David P, Di Matteo A, Hen O, *et al.* Poly-Refractory Rheumatoid Arthritis: An Uncommon Subset of Difficult to Treat Disease With Distinct Inflammatory and Noninflammatory Phenotypes. *Arthritis Rheumatol* 2024;76:510–21.
- 19 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.
- 20 Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006;23:469–80.
- 21 Wolfe F, Clauw DJ, Fitzcharles M-A, *et al.* 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016;46:319–29.
- 22 Maksymowych WP, Mallon C, Morrow S, *et al.* Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis* 2009;68:948–53.
- 23 Gossec L, de Wit M, Kiltz U, *et al.* A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. *Ann Rheum Dis* 2014;73:1012–9.
- 24 Mayer TG, Neblett R, Cohen H, *et al.* The development and psychometric validation of the central sensitization inventory. *Pain Pract* 2012;12:276–85.
- 25 Lubrano E, Sciffignano S, Azuaga AB, *et al.* Assessment of the Patient Acceptable Symptom State (PASS) in psoriatic arthritis: association with disease activity and quality of life indices. *RMD Open* 2020;6:e001170.
- 26 Zabotti A, Piga M, Canzoni M, *et al.* Ultrasonography in psoriatic arthritis: which sites should we scan? *Ann Rheum Dis* 2018;77:1537–8.
- 27 Canzoni M, Piga M, Zabotti A, *et al.* Clinical and ultrasonographic predictors for achieving minimal disease activity in patients with psoriatic arthritis: the UPSTREAM (Ultrasound in Psoriatic arthritis TREAtment) prospective observational study protocol. *BMJ Open* 2018;8:e021942.
- 28 D'Agostino M-A, Terslev L, Aegerter P, *et al.* Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open* 2017;3:e000428.
- 29 Zabotti A, Sakellariou G, Tinazzi I, *et al.* Novel and reliable DACTylitis glObal Sonographic (DACTOS) score in psoriatic arthritis. *Ann Rheum Dis* 2020;79:1037–43.
- 30 Di Matteo A, Smerilli G, Di Donato S, *et al.* Power Doppler signal at the entheses and bone erosions are the most discriminative OMERACT ultrasound lesions for SpA: results from the DEUS (Defining Enthesitis on Ultrasound in Spondyloarthritis) multicentre study. *Ann Rheum Dis* 2024;83:847–57.
- 31 Sieper J, van der Heijde D, Landewé R, *et al.* New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis* 2009;68:784–8.
- 32 Lambert RGW, Bakker PAC, van der Heijde D, *et al.* Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis* 2016;75:1958–63.
- 33 Hermann K-GA, Baraliakos X, van der Heijde DM, *et al.* Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. *Ann Rheum Dis* 2012;71:1278–88.
- 34 Harris PA, Taylor R, Minor BL, *et al.* The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
- 35 Peduzzi P, Concato J, Kemper E, *et al.* A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49:1373–9.
- 36 Favalli EG, Biganzoli G, Cincinelli G, *et al.* Difficult-to-treat psoriatic arthritis: refining the definition using a statistical model in a real-life cohort. *Front Med (Lausanne)* 2024;11:1509082.
- 37 Lubrano E, Sciffignano S, Perrotta FM. Difficult to Treat and Refractory to Treatment in Psoriatic Arthritis. *Rheumatol Ther* 2023;10:1119–25.
- 38 Perrotta FM, Sciffignano S, Ciccio F, *et al.* Clinical Characteristics of Potential “Difficult-to-treat” Patients with Psoriatic Arthritis: A Retrospective Analysis of a Longitudinal Cohort. *Rheumatol Ther* 2022;9:1193–201.
- 39 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.
- 40 Grässel SG. The role of peripheral nerve fibers and their neurotransmitters in cartilage and bone physiology and pathophysiology. *Arthritis Res Ther* 2014;16:485.
- 41 Freemont AJ, Peacock TE, Goupille P, *et al.* Nerve ingrowth into diseased intervertebral disc in chronic back pain. *Lancet* 1997;350:178–81.
- 42 McGonagle DG, Helliwell P, Veale D. Enthesitis in Psoriatic Disease. *Dermatology (Basel)* 2012;225:100–9.