Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis

A prospective cohort study

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Title: Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: a prospective cohort study

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Bullet points

- Widespread non-arthritic pain is a common concurrent disorder in patients with psoriatic arthritis, regardless of fibromyalgia.
- Widespread non-arthritic pain is associated with worse patient-reported and composite psoriatic arthritis activity measures but not with higher disease burden evaluated by clinical- and ultrasound examination.
- A condition of widespread non-arthritic pain at baseline was strongly associated with failure to fulfil the Minimal Disease Activity Criteria following immunomodulatory therapy.

ABSTRACT

Objective: To study the prognostic value of widespread pain and of musculoskeletal ultrasound (US) examination for subsequent treatment outcomes in patients with psoriatic arthritis (PsA).

Methods: An exploratory prospective cohort study enrolled PsA patients initiating biologic/conventional synthetic disease modifying anti-rheumatic drugs in routine care. Clinical-, US- and patient-reported measures were retrieved at baseline and after 4 months. Widespread non-arthritic pain (WP) was defined as Widespread Pain Index ≥4 with pain in ≥4/5 regions. PsA activity by US was defined as colour Doppler (CD) (yes/no) in selected entheses, joints or tendons. Main response criteria included American College of Rheumatology 20% (ACR20), Disease Activity in Psoriatic Arthritis 50% (DAPSA50), and

Minimal Disease Activity (MDA). The primary analyses were age-and gender adjusted logistic regression.

Results: WP was present in 24 (35%) of 69 included patients, and associated with worse patient-reported and composite baseline measures while US and other objective findings were similar to patients without WP. The odds of 4-months MDA were significantly greater for patients enrolled without WP (OR=18.43 [95% CI: 1.51-224.41], p=0.022), while WP did not impair other response measures. Patients with baseline CD activity (n=42 [61%]) had worse objective PsA burden but their chance of treatment response was comparable to those without CD.

Conclusions: More than one-third of PsA patients presented with widespread non-arthritic pain, which was associated with worse patient-reported scores and failure to achieve MDA following cs/bDMARD therapy. PsA activity by colour Doppler ultrasound had no influence on subsequent treatment response in this PsA cohort.

INTRODUCTION

Pain is a key manifestation of psoriatic arthritis (PsA), and a core outcome in trials and observational studies according to the PsA Core Outcome Set (COS) endorsed by the group of Outcome Measures in Rheumatology (OMERACT). (1) However, little focus has been on the prognostic value of pain mechanisms for treatment effectiveness. Recent studies have reported persistent pain in >50% of PsA patients in spite of conventional synthetic or biologic disease modifying therapy (cs/bDMARD) and well-controlled inflammation. (2,3) Furthermore, patients often report non-nociceptive pain features such as allodynia and hyperalgesia. These observations could indicate contributions from central sensitization. (3–5)

Central sensitization is a normal, physiological phenomenon in relation to acute tissue damage where it accounts for secondary hyperalgesia and allodynia in the proximity of the injured site. However, as shown in rheumatoid arthritis (RA) and osteoarthritis (OA),

(6,7) central sensitization can sometimes outlast inflammation and cause persistent and widespread pain. Underlying reasons for this phenomenon possibly involve inflammatory-, genetic- and psychological factors. (8,9) Central sensitization is by many perceived as a continuum. (5) The upper end is represented by fibromyalgia characterized by widespread pain, cognitive, emotional and physical disturbances. (8) Fibromyalgia exists in 16-22% of PsA patients and seems to bias the evaluation of PsA activity. (10,11) Based on the continuum theory, central sensitization may contribute to persistent pain in PsA – regardless of fibromyalgia – and influence measures of PsA activity and treatment response. Central sensitization is not easily measured in routine care, however its key symptom, widespread non-arthritic pain, can be assessed by the widespread pain index (WPI). (8)

Musculoskeletal ultrasound (US) can dynamically visualize pathophysiology in arthritic diseases, including PsA. (12,13) Hypothetically, US could prove useful in determining if widespread pain is caused by central sensitization uncoupled from inflammatory activity or by diffuse, multisite PsA activity that warrants anti-rheumatic treatment. Besides, US could be a prognostic factor for treatment outcome by identifying patients with high inflammatory load and great need for immunomodulatory therapy. A prognostic value of US has been shown in RA but is unclarified in PsA. (13–17)

Our primary aim was to explore the presence of 1) widespread, non-arthritic pain (WP) measured by the WPI and 2) inflammatory activity evaluated by colour Doppler US, in patients with PsA. Specifically, we aimed to study the relationship between these factors, and their prognostic value for 4-month cs/bDMARD response. A second aim was to study if WP represents a chronic condition or is reversed during immunomodulatory therapy. Finally, we aimed to explore the prognostic value of secondary pain- and ultrasound measure for treatment response.

METHODS

Design and period

We performed a prospective cohort study according to a published protocol elaborated in collaboration with patient-research partners from Denmark and abroad. (18) Study findings are reported according to Strengthening The Reporting of OBservational Studies in Epi-

demiology (STROBE) guidelines. (19) The study was registered at clinicaltrials.gov (NCT02572700), and approved by the Danish ethics committee (H-15009080), and Data Protection Agency (2012-58-0004). Inclusion started September 17 2015, and ended June 1 2017. No power calculation was performed due to the exploratory design, however we anticipated to include approximately 100 participants.

Inclusion criteria

We recruited PsA patients scheduled to start cs/bDMARDs (first line/add-on/switch) from rheumatology clinics in the Capital region of Denmark. To be included, patients had to sign an informed consent form, be ≥18 years old, fulfil Classification Criteria for PsA (CASPAR) (20) and present with peripheral PsA manifestations. Exclusion criteria were pregnancy, neurological disorders, and rheumatic inflammatory diseases besides PsA. Patients were non-eligible if they could not pause glucocorticoids, centrally acting drugs, and non-opioid analgesics at 21, 7 and 1 days before baseline, respectively.

Time points and variables

Baseline was defined as the time window from 14 days before until 7 days after treatment start. No washout period was required for those switching therapy. The follow-up date was 4 months after baseline. Following information was collected at the study visits.

Interview: Physician (PH or CB) collected information on socio-demography, psoriatic disease, medications, smoking, and body mass index (BMI).

Patient reported measures of central pain sensitization: The WPI (0-19) (8) is a two-sided body diagram where patients mark all painful non-joint regions (7 day recall). Hence, the WPI measures both the number and distribution of painful sites. The WPI was developed for diagnosing the widespread pain component of fibromyalgia. (8) Inspired by the use of WPI in fibromyalgia, we interpreted symptoms of central sensitization as: WPI ≥4 and pain in ≥4/5 predefined regions. (8)

The PainDETECT (21) PDQ (-1-38) was developed to identify neuropathic pain in low back pain patients but has been used to evaluate pain phenotypes across rheumatic diseases. (3,22) High PDQ scores have been associated with measures of central sensitization in fibromyalgia. (23) The PDQ score is based on patient's description of pain; somatosensory symptoms, pain radiation and temporal characteristics, and thereby reflects nociceptive (PDQ score <13), unclear (PDQ score 13-18) or neuropathic (PDQ score >18) pain.

Other questionnaires: Patients completed Dermatology Life Quality Index (DLQI), (24) Psoriatic Arthritis Impact of Disease (PsAID), (25) Health Assessment Questionnaire Disability Index (HAQ-DI), (26) Bath Ankylosing Functional (BASFI) - and Disease Activity (BASDAI) Index, (27) MOS SF-36 questionnaire, (28) Generalized Anxiety Disorder questionnaire (GAD-10) and numeric rating of fatigue (NRS fatigue), visual analogue scales (VAS) of pain and patient global. At follow-up, patients also completed a transition questionnaire regarding overall improvement (yes/no). (18)

Clinical examination: Physicians (PH or CB) performed a 18 sites Tender Point Count (TPC), a 66/68 swollen/tender joint count (SJC, TJC), the Psoriasis Area Severity Index (PASI), the Spondyloarthritis Research Consortium of Canada enthesitis index (SPARCC), and counted psoriatic nails (0-20) and dactylitis (0-20). (18)

Paraclinical measures: X-rays of hands and feet were analysed for structural PsA changes by a radiologist unaware of clinical findings. A blood test was drawn to measure C-reactive protein (CRP).

Musculoskeletal US: US was performed the same day as clinical examinations by experienced sonographers (KE or LJ) using a General Electric E9 with a linear array matrix transducer (15 MHz frequency). Grey-scale and colour Doppler examinations included 26 small and large joints (46 projections), extensor- and flexor tendons adjacent to the wrist and finger joints (32 projections), and 12 entheses. Scans were performed in longitudinal projections. For hands and feet, both dorsal and plantar projections were applied. Central/radial/ulnar projections of wrists and medial/lateral projections of the knees were performed. The US protocol is provided in File 1S.

A third US expert (JGM), unaware of clinical findings, scored the US pathologies by stored

images and clips. Both semi-quantitative (0-3) and dichotomous (0/1) scores of Grey scale and colour Doppler findings were performed. (12,29)

Prognostic factors of interest

Primary factors:

1) Widespread non-arthritic pain: Patients with baseline WPI ≥4 and pain in ≥4/5 regions were categorized as WP+, others as no-WP. (8)

2) Inflammatory activity by colour Doppler: The sum of colour Doppler scores from joints (score 0-138), entheses (score 0-30) and tendons (score 0-32) was termed a 'Global Active Ultrasound Score' (GAUS) (score 0-200). The primary prognostic US factor was GAUS≥1/GAUS=0, i.e. presence/absence of colour Doppler activity.

Secondary factors:

Central sensitization*:* Based on previous studies, we also explored central sensitization as 1) PDQ score ≥13 i.e. non-nociceptive pain features (21,23), 2) Tender Point Count (TPC) ≥8 i.e. widespread allodynia/hyperalgesia (30) and 3) a ratio of swollen/tender joints (SJ/TJ) <0.5. (31)

US pathology: We arbitrarily defined secondary US measures as a Global Subacute Ultrasonic Score (GSAUS 0-204) and a Global Chronic Ultrasonic Score (GCUS, 0-312). GSAUS was the sum of the grey scale synovitis scores of joints (0-138) and tendons (0-32), entheses thickening (yes/no) (0-10), structural entheses changes (yes/no) (0-12) and of bursitis (0-12) (yes/no). GCUS was the sum score of erosions (0-138), osteophytes (0-138) and entheses calcifications (0-36). GSAUS and GCUS were handled as binary prognostic variables using the median value as cut-off (File 1S).

Outcome measures and composite endpoints

Treatment response after 4 months was assessed according to American College of Rheumatology 20% improvement (ACR20). (32) Secondary outcomes (assessed for WP and GAUS) included Minimal Disease Activity (MDA) (33) and 50% improvement in Disease activity index for Psoriatic Arthritis (DAPSA 50%), (34) and the exploratory outcome 'Patient-Reported Improvement' (yes/no) obtained from the transition questionnaire. (18)

Changes from baseline in composite indices including DAPSA, Disease Activity Score (DAS28-CRP), (35) the modified Composite Psoriatic Disease Activity Index (mCPDAI) (36) and change in OMERACT PsA COS measures (1) (File 1S) were compared between groups. For mCPDAI, which was added to the analyses following peer review, we used a modified Leeds Enthesitis Index, where the medial femur condyle was replaced by fascia plantaris available from the protocolled SPARCC index.

Statistical analyses

A statistical analysis plan was prepared prior to data extraction (File 1S). All analyses were performed in R (version 3.3.3) by a biostatistician. Statistical significance was interpreted as p-values <0.05 (two-sided). Logistic regression analyses were performed to investigate the association between the prognostic variables and treatment response (yes/no). Odds ratios were reported as crude estimates (OR) and adjusted for gender and age (aOR). When we observed zero-event data in one study group and imbalances in patient numbers between study groups, we used a continuity correction that was inversely proportional to the relative size of the opposite of the study (37). Since asymptotic results can be unreliable when the distribution of the dichotomous data is sparse we applied the Fisher's exact test to calculate the exact probability of the possible (2×2) table, enabling us to estimate the Wald test associated variance, corresponding to the ratio of its estimate (logOR) to its standard error. (38)

Primary analyses included the intention-to-treat (ITT) population (non-responder imputation/baseline observation carried forward). Concordance statistics (the C-index), tested the models' ability to distinguish patients who will experience a response from those who will not. (39)

The following additional analyses were performed:

1)The prognostic value of WP and GAUS profiles for ACR20 response was analysed using data 'as observed' and 'per protocol' (i.e. patients with complete data who stayed in treatment).

2) ΔCOS measures at follow-up were compared for GAUS and WP categories by Student's t-test or Mann-Whitney U test, and secondly by Analysis of Covariance (ANCOVA) adjusting for baseline values.

3) The correlation between continuous WPI and GAUS, respectively, and ΔDAS28-CRP, ΔDAPSA and ΔmCPDAI were analysed by scatter diagrams with Spearman Rank Correlation coefficients. Prediction ellipses were added to give a visual impression of the distribution of data with the center representing the sample mean. Skinny ellipses are seen when the correlation between variables is high. Following peer review, correlations between change in composite indices and ΔWPI were analysed.
4) To explore if WP reflected a reversible state we analysed the agreement between WP category at baseline and follow-up using kappa statistics.[2]
5) Fulfilment of ≥11/18 tender points (per 1990-fibromyalgia criteria) was assessed for WP groups.
6) The intra/inter reliability of GAUS, GSAUS and GCUS was calculated and appeared excellent according to Intraclass Correlation Coefficients (ICC 2,1) (File 1S), exceeding the predefined 0.75 cut-off (**Table 1S**)**.**

RESULTS

Out of 123 screened patients we included 69, and 24 (35%) of these fulfilled the widespread, non-arthritic pain criterion (WP+) as illustrated in **Figure 1.**

Baseline characteristics for the WP and GAUS profiles: Compared to those without WP, patients with WP+ presented with worse pain, fatigue and health-related quality of life, and more tender joints- and entheses as shown in **Table 1.** The WP+ group had significantly higher composite disease activity scores (DAPSA, DAS28-CRP and mCPDAI), while clinician-reported, radiographic and ultrasound findings were comparable between WP groups (Table 1). Colour Doppler activity (GAUS≥1) was present in 13 (54 %) of WP+ and 29 (64 %) of no-WP patients (p=0.566). No differences in sociodemographic, BMI, DMARDs or other background characteristics existed between WP groups, except for greater use of analgesics and a tendency towards lower educational level in WP+ patients (Table 1). The 1990-fibromyalgia tender point criterion (≥11/18) was fulfilled by 7 (29%) of WP+ and 4 (9%) of no-WP patients. WP+ patients scored higher on most SPARCC sites as shown in **Figure 1S**. The most common pain sites in WP+ patients were lower extremities, lower back and the shoulder girdle (**Figure 2S**).

Compared to patients without baseline colour Doppler (GAUS=0), those with GAUS ≥1 were older and had worse objective measures including VAS physician, swollen joints, dactylitis, CRP, radiographic damage, subacute (GSAUS) and chronic (GCUS) US pathology (**Table 2**). The mCPDAI was higher in patients with GAUS ≥1 while other composite- and composite scores were not statistically different between GAUS groups, neither was the frequency of WP+ nor the type of DMARD (Table 2).
Additional baseline characteristics for WP and GAUS profiles appear in **Tables 2S and 3S.**

Achievement of ACR20 response (primary outcome): **Table 3** shows the prognostic value of WP profile and GAUS profile for subsequent treatment response**.** Rates of 4-month ACR20 response were comparable for WP+ (25%) and no-WP (27%). Hence, baseline WP profile was not a prognostic factor for ACR20 (Table 3). The C-index statistics was 0.51/0.56 in simple/adjusted models, implying that prediction is no better than chance.

ACR20 response was obtained by 19% with baseline GAUS=0 and 31% with GAUS ≥1. GAUS profile had no clear prognostic influence on ACR20 s (Table 3). The C-index was 0.59/0.58 in simple/adjusted models, i.e. slightly better prediction than by chance.

Similarly, neither baseline WP nor GAUS profile influenced ACR20 response when analysed for the "as observed" or "per protocol" populations **(Table 4S).**

Achievement of secondary outcome measures: Baseline WP profile was a strong prognostic factor for MDA at follow-up. MDA was achieved 0%/20% of WP+/no-WP patients leading to markedly higher odds for MDA among no-WP patients (Table 3). The discrepancy in MDA between WP categories was largely attributed to differences in reaching the critical level of tender joints, enthesitis and HAQ-DI (**Table 5S**).
We found no association between WP profile and DAPSA50 or Patient-reported Improvement (Table 3). Baseline GAUS was not of prognostic value for any of the secondary response measure (Table 3).

Correlation between baseline WPI and GAUS and ΔDAS28-CRP, ΔDAPSA and ΔmCPDAI: Baseline WPI (0 to 19) did not correlate significantly with ΔDAPSA, ΔmCPDAI (Figure 2) or ΔDAS28-CRP (Figure 3S). Furthermore, we found no correlation between change in these composites and in the WPI during treatment (Figure 4S).

Baseline GAUS correlated moderately with improvement in DAPSA, mCPDAI (**Figure 2**) and DAS28-CRP (**Figure 3S**).

Change- and endpoint values of COS measures according to WP and GAUS profile: Changes in the COS measures from baseline to follow-up did not differ significantly between the WP or the GAUS profiles **(Table 4)**.
In ANCOVA models, the enthesitis score (SPARCC) improved less in those presenting with WP+ than no-WP **(Table 6S).** Patients categorised as WP+ at baseline had significantly worse COS measures at follow-up including tender joints, enthesitis, pain, disability, fatigue and health-related quality, while GAUS profiles showed comparable COS endpoint measures except for more swollen joints among GAUS≥1 (**Table 7S**).

Agreement between WP category at baseline and follow-up: Fifty-five patients had WPI information at both time points. Ten out of twenty (50%), who started as WP+ changed to no-WP at follow-up, while 4 of 35 (11%) changed from no-WP to WP+. The overall agreement on WP category at baseline and follow-up was moderate (Kappa=0.41 [95% CI 0.16-0.66]).

Baseline characteristics of the secondary pain and US profiles: Patients with PDQ score ≥13 (n=38), TPC ≥8 (n=17), and SJ/TJ <0.5 (n=47) had worse patient-reported measures including higher WPI and more tender joints and entheses compared to the opposite category (**Table 8S-10S**). A PDQ score ≥13 was also associated with more inflammatory activity, including higher US scores and CRP than patients with PDQ score<13.

Baseline characteristics for the secondary US categories (GSAUS and GCUS) are shown in **Table 11S and 12S**. The median values used to define these categories were GSAUS =16 and GCUS =7. Patients in the high GSAUS and GCUS categories were older, had worse swollen joints, pain and quality of life, and for GSAUS more radiographic damage than the lower categories.

Prognostic value of secondary pain and US profiles: None of the secondary pain (PDQ, TPC or SJ/TJ categories) or US (GSAUS, GCUS) profiles had a significant prognostic value for ACR20 response (Table 3). However, analyses following peer review showed that the chance of

MDA was significantly reduced for patients with high PDQ, low SJ/TJ and especially those with TPC≥8 (Table 13S).

DISCUSSION

The prognostic value of widespread non-arthritic pain

In the present study, about one-third of PsA patients pragmatically sampled from clinical practice presented with widespread non-arthritic pain (WP+), which was associated with increased patient-reported and composite disease scores and significantly reduced chance of reaching 'minimal disease activity' (MDA) following treatment.

To our knowledge, this study is the first to show that a WP+ profile, irrespectively of fibromyalgia, is a common condition in PsA that influences the evaluation of disease activity and treatment outcomes. WP+ was not related to higher baseline PsA activity – neither by clinical- nor by ultrasound measures whereas (partially) patient-reported measures and thereby composite indices- were significantly worse in WP+ patients. The prognostic impact of WP+ differed across the applied outcome measures, which may reflect their different weighting of patient-reported domains. Our results indicate that response measures based on absolute values for low disease activity, such as the MDA, are more affected by WP+ than measures of relative improvement (ACR20, DAPSA50).

Contributions from central sensitization to generalized pain in RA and OA are well documented. (6,7,14,40) Previous studies of pain mechanisms in PsA are scarce, and include a few studies that reported lowered pain pressure thresholds in PsA versus healthy controls (41) and high frequencies of mixed/neuropathic pain features in PsA according to PDQ, similar to our findings (3). Other studies have mainly focused on the worst-end spectrum of central sensitization i.e. fibromyalgia. This disorder exists in up to 22% of PsA patients, and has by cross-sectional studies been shown to affect measures of PsA activity (10,11,42–44) and impair MDA. (11)

By use of the WPI – and the secondary pain measures – we demonstrated that the inability to achieve MDA following anti-rheumatic treatment concerns patients within a wider spectrum of central sensitization.

The lack of correlation between improvement in WPI and in the composite disease activity indices support that WP+ represents a condition of persistent central sensitization uncoupled from inflammatory activity. On the other hand, we observed that 50% of patients switched from WP+ to no-WP during treatment, and that improvement in ACR20, DAPSA50 and ΔCOS scores were comparable between WP groups. This indicates a reversibility of WP in some patients, which could be caused by e.g., 1) natural fluctuation in the severity of central sensitization manifestations as described in studies of fibromyalgia, (45) 2) an overlap between WPI sites and PsA disease loci that respond to cs/bDMARD therapy, or 3) that for some patients, central sensitization is a transient neurophysiological phenomenon driven by inflammation. (4) Accordingly, we found that neuropathic/mixed pain features (high PDQ) was associated with worse inflammatory PsA activity, as also shown in RA. (46)

Regardless of what triggers and maintains central sensitization, the condition is important to recognize in order to adequately interpret disease measures, ensure sufficient pain management, and apply appropriate treatment targets. Our results support that feasible patient-reported tools, such as the WPI, could assist the identification of pain disorders in routine care of PsA.

The prognostic value of inflammatory activity by colour Doppler

We explored the prognostic value of US measures for treatment outcomes and found that patients with colour Doppler at baseline(GAUS ≥1) had worse objective disease burden, while the patient-reported and composite baseline measures were largely similar to patients with GAUS=0. An exception was mCPDAI, which was higher in patients with GAUS ≥1. Previous cross-sectional studies have found poor/moderate consistency between clinical measures and US findings in PsA, and in contrast to our findings reported that DAPSA is superior to CPDAI in reflecting US pathology. (16,17) These findings underscore the need to further investigate the prognostic value of US in PsA.

In the present study, none of the US measures were significantly associated to subsequent treatment response, whereas studies of RA have shown US to predict response by composite outcome measures, (13–15) flares and radiographic progression. (47,48) This

could be related to the more uniform/symmetric disease presentation of RA enhancing the adequacy of standard US examinations.

Another reason why baseline US had no impact on response could be the chosen dichotomous colour Doppler variable, which is easy to interpret and has been applied in previous studies, (16,49) but does not reflect the continuum of inflammatory activity. As seen from the scatter plot, a significant relationship between baseline GAUS (0-30) and improvement in DAPSA, DAS28-CRP and mCPDAI at follow-up was evident. Thus, using continuous scores or a different categorization could perhaps increase the prognostic value of US.

Strengths and limitations

This study represents a novel approach to investigate pain- and US profiles of PsA patients and their prognostic value for treatment response. Strengths include the integration of the updated PsA COS, and the application of PsA specific disease/response measures. (1) In addition, we strived to optimize the external validity and clinical relevance of the study by 1) using a strictly observational design 2) studying prognostic factors of relevance for clinical settings, and 3) involving patient-research partners to ensure the patient's perspective.

The study has important limitations. The exploratory approach means that results must be interpreted with caution. Our definition of central sensitization (WP) as well as the applied composite ultrasound scores (GAUS, GSAUS, GCUS) were guided by previous studies, but are widely exploratory.

The 4-month response rates reported in the present study were generally low. A reason could be that most patients received csDMARD treatment, which may have low efficacy in PsA in general, (50) and perhaps especially in this cohort where 50% had tried DMARDs previously. Furthermore, the relatively high drop-out rate decreased the intention to treat response rates.

The relationship between pain profile and measures of disease activity and treatment response is likely multifactorial. To optimize treatment strategies, clinicians and patients need insight into how pain mechanisms, disease activity, socio-demographic and

psychological factors interact and contribute to the overall prognosis. The small sample size restricted our possibility to investigate confounding and mediating factors such as smoking, obesity, educational level and disease duration, which should gain focus in future studies. WP+ patients had higher scores across several SPARCC regions, including those located outside joints and tender points, which underscores the need to study the relationship between WP and enthesitis in PsA.

Measurements of the COS domains were pragmatically chosen since a recommended set of COS instruments is not yet endorsed by OMERACT. However several of the tools have some evidence for good measurement properties in PsA. (51)

In conclusion, widespread, non-arthritic pain was present in more than a third of patients in this PsA cohort. This condition was associated with worse patient-reported and composite disease measures, and inability to fulfil the minimal disease activity criteria after 4 months' treatment. Presence of US colour Doppler activity at baseline was associated with more severe PsA activity according to objective – but not patient-reported measures. US measures had no prognostic value for treatment response in this cohort

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Table 1 Baseline characteristics according to pain profile (widespread non-arthritic pain yes/no)

Demography/Medication	WP+ (n=24)	No-WP (n=45)	Difference[1] (95%CI)	*P*-value
Age, years	51.2 (9.2)	49.9 (15.2)	1.2 (-4.6 to 7.1)	0.675
Females, n (%)	15 (63)	24 (53)	1.17 (0.78 to 1.77)	0.634
Higher Education, n (%)	4 (17)	19 (42)	0.39 (0.15 to 1.03)	0.061
Body mass index, (kg/m^2)	27.3 (5.0)	26.0 (5.6)	1.3 (-1.4 to 4.0)	0.343
Months of PsA, median [IQR]	36 [2 to 124]	6 [1 to 48]	30 (-9 to 93)	0.130
Months of Pso, median [IQR]	138 [24 to 324]	120 [24 to 384]	18 (-101 to 204)	0.719
Diagnosed axial PsA, n (%)	3 (13)	7 (16)	0-80 (0.23 to 2.63)	0.999
Radiographic PsA, n (%)	6 (25)	13 (29)	0.87 (0.38 to 1.99)	0.951
csDMARD initiator, n (%)	15 (63)	33 (73)	0.85 (0.60 to 1.22)	0.511
Daily mild analgesics, n (%)	11 (46)	9 (20)	2.29 (1.11 to 4.75)	0.048
Daily NSAIDs use, n (%)	8 (33)	11 (24)	1.36 (0.64 to 2.93)	0.614
Daily opioid use, n (%)	3 (13)	0 (0)	9.63 (1.12 to 82.64)	0.039
Patient-reported measures				
WPI (0-19), median [IQR]	6.0 [4.0 to 9.3]	2.0 [0.0 to 2.0]	4.0 [2.0 to 7.5]	<0.001
VAS global (0-100)	74.7 (17.8)	50.2 (29.7)	24.5 (13.1 to 36.0)	<0.001
VAS Pain (0-100)	68.8 (19.2)	44.5 (27.6)	24.3 (11.7 to 36.9)	<0.001
PainDETECT score (-1 to 38)	18.3 (5.6)	11.3 (6.1)	7.1 (4.1 to 10.1)	<0.001
SF-36 MCS (0-100)	43.5 (14.9)	50.3 (11.0)	-6.8 (-13.1 to -0.5)	0.034
SF-36 PCS (0-100)	28.4 (9.1)	37.9 (9.2)	-9.4 (-14.0 to -4.8)	<0.001
PsAID-12 (0-10)	6.2 (1.7)	4.2 (2.2)	2.0 (1.0 to 3.1)	<0.001
DLQI (0-30), median [IQR]	1.0 [1.0 to 4.5]	1.0 [0.0 to 4.0]	0.0 (-1.0 to 1.0)	0.558
NRS Fatigue (0-10)	7.4 (1.9)	4.7 (2.9)	2.7 (1.5 to 3.9)	<0.001
GAD-10 (0-50), median [IQR]	11.0 [7.8 to 22.0]	6.0 [4.0 to 11.0]	5.0 (2.0 to 11.0)	0.003

HAQ-DI (0-3), median [IQR]	1.2 [0.9 to 1.5]	0.6 [0.3 to 1.0]	0.6 (0.3 to 0.9)	<0.001
Clinical/paraclinical measures				
VAS doctor (0-100)	48.2 (17.8)	46.4 (16.9)	1.8 (-6.9 to 10.5)	0.683
SJC (0-66), median [IQR]	3.0 [1.0 to 6.3]	4.0 [2.0 to 8.0]	-1.0 (-4.0 to 2.0)	0.352
TJC (0-68), median [IQR]	26.5 [24.5 to 37.0]	11.0 [6.0 to 20.0]	15.5 (11.0 to 21.0)	<0.001
SPARCC enthesitis (0-16)	7.5 (3.4)	4.2 (3.0)	3.3 (1.7 to 4.8)	<0.001
DAS28-CRP(0-10)	4.9 (1.0)	3.7 (1.2)	1.1 (0.6 to 1.7)	<0.001
DAPSA (0-164)	49.3 (18.1)	29.8 (18.5)	19.5 (10.2 to 28.7)	<0.001
mCPDAI (0-12)	5.9 (1.2)	4.7 (2.0)	1.2 (0.4 to 2.0)	0.003
TPC (0-18) median [IQR]	6.0 [3.0 to 12.0]	0.0 [0.0 to 3.0]	6.0 (2.0 to 10.0)	<0.001
PASI (0-72), median [IRQ]	5.4 [3.0 to 8.7]	8.0 [3.0 to 13.3]	-2.6 (-6.1 to 2.0)	0.330
Nail psoriasis, n (%)	13 (54)	25 (56)	0.98 (0.62 to 1.53)	1.000
Dactylitis, n (%)	4 (17)	16 (36)	0.47 (0.18 to 1.25)	0.163
CRP (mg/L), median [IQR]	5.0 [2.8 to 6.0]	3.0 [1.0 to 6.0]	2.0 (-0.5 to 3.5)	0.203
GAUS ≥1, n (%)	13 (54)	29 (64)	0.84 (0.55 to 1.29)	0.566
GAUS (0-203), median [IQR]	1.0 [0.0 to 4.3]	1.0 [0.0 to 5.0]	0.0 (-3.0 to 3.0)	0.686
GSAUS (0-204), median [IQR]	17.0 [11.0 to 23.5]	16.0 [8.0 to 23.0]	1.0 (-5.0 to 8.0)	0.335
GCUS (0-312), median [IQR]	8.5 [2.8 to 11.3]	7.0 [1.0 to 10.0]	1.5 (-4.0 to 5.0)	0.387

Data presented as mean (SD) unless otherwise stated. Analyses of n=69, except PASI n=56 with BSA>1. [1]Differences in means or medians, risk ratios for binary data. CI, confidence interval; csDMARD, conventional synthetic DMARDs; DAPSA, Disease activity Index for PsA; DAS28, Disease Activity Score; DLQI, Dermatology Life Quality Index; GAD Generalized Anxiety Disorder, GAUS/GSAUS/GCUS, Global acute/subacute/chronic ultrasound score; SF-36 MCS/PCS, Short Form-36 Mental/Physical Component Summary; PASI, Psoriatic Area Severity Index; Pso, psoriasis; PsAID, PsA Impact of Disease; SPARCC, SpA Research Consortium of Canada; TPC, tender point count, WPI, widespread pain index.

Table 2 Baseline characteristics according to ultrasound profiles (colour Doppler activity yes/no)

Demography/Medication	GAUS ≥1 (n=42)	GAUS = 0 (n= 27)	Difference[1](95%CI)	P-value
Age, years	53.2 (12.9)	46.0 (13.1)	7.2 (0.8 to 13.6)	0.027
Female, n (%)	21 (50)	18 (67)	0.75 (0.50 to 1.12)	0.265
Higher Education, n (%)	14 (33)	9 (33)	1.00 (0.50 to 1.98)	0.999
Body mass index (kg/m^2)	26.4 (5.1)	26.5 (5.9)	-0.1 (-2.8 to 2.6)	0.936
Months of PsA, median [IQR]	12 [1 to 81]	9 [1 to 84]	3(-48 to 25)	0.930
Months of Pso, median [IQR]	132 [37 to 381]	100 [3 to 306]	32 (-120 to 200)	0.184
Diagnosed AxPsA n (%)	5 (12)	5 (19)	0.64 (0.21 to 2.01)	0.681
Radiographic PsA, n (%)	17 (40)	2 (7)	5.46 (1.37 to 21.79)	0.003
Scheduled for csDMARD, n (%)	28 (67)	20 (74)	0.90 (0.66 to 1.23)	0.701
Daily NSAIDs use, n (%)	11 (26)	8 (30)	0.88 (0.41 to 1.91)	0.971
Daily analgesics use, n (%)	11 (26)	9 (33)	0.79 (0.38 to 1.64)	0.714
Daily opioid use, n (%)	1 (2)	2 (7)	0.32 (0.03 to 3.37)	0.556
Patient reported measures				
Widespread pain (WP+), n (%)	13 (31)	11 (41)	0.76 (0.40 to 1.44)	0.556
VAS global (0-100)	60.4 (27.4)	56.1 (30.7)	4.2 (-9.9 to 18.3)	0.554
VAS Pain (0-100)	55.5 (27.1)	49.0 (28.0)	6.5 (-7.0 to 20.1)	0.337
PDQ score (-1 -38)	14.5 (7.6)	12.6 (5.4)	1.9 (-1.4 to 5.3)	0.257
MOS SF-36 MCS (0-100)	47.9 (13.6)	48.0 (11.8)	-0.1 (-6.4 to 6.3)	0.987
MOS SF-36 PCS (0-100)	34.6 (9.7)	34.6 (10.9)	-0.0 (-5.0 to 5.0)	0.994
PsAID-12 (0-10)	5.1 (2.4)	4.7 (2.2)	0.4 (-0.7 to 1.5)	0.472
DLQI (0-30) median [IQR]	2.0 [0.3 to 4.0]	1.0 [0.0 to 2.5]	1.0 (0.0 to 2.0)	0.179
NRS Fatigue (0-100)	5.7 (3.0)	5.6 (2.8)	0.1 (-1.4 to 1.5)	0.933
GAD-10 (0-50) median [IQR]	6.5 [5.0 to 12.5]	9.0 [5.0 to 17.5]	-2.5 (-9.5 to 2.0)	0.365

HAQ-DI (0-3) median [IQR]	0.9 [0.5 to 1.3]	0.8 [0.3 to 1.0]	0.2 (-0.1 to 0.6)	0.126
Clinical/composite measures				
VAS doctor (0-100)	52.0 (15.3)	39.3 (17.3)	12.7 (4.7 to 20.6)	0.002
SJC (0-66) median [IQR]	6.0 [2.0 to 9.0]	3.0 [1.0 to 5.0]	3.0 (0.0 to 6.0)	0.012
TJC (0-68) median [IQR]	16.5 [7.3 to 26.8]	15.0 [7.5 to 29.0]	1.5 (-12.5 to 12.0)	0.892
SPARCC enthesitis (0-16)	5.5 (3.7)	5.2 (3.3)	0.3 (-1.4 to 2.0)	0.717
DAS28CRP score (0-10)	4.3 (1.2)	3.9 (1.4)	0.4 (-0.2 to 1.1)	0.174
DAPSA score (0-164)	38.4 (21.0)	33.8 (19.8)	4.6 (-5.5 to 14.7)	0.366
mCPDAI (0-12)	5.5 (2.0)	4.5 (1.5)	0.9 (0.0 to 1.8)	0.039
TPC (0-18)	1.5 [0.0 to 4.8]	4.0 [0.0 to 9.0]	-2.5 (-6.0 to 0.5)	0.174
PASI (0-72) median [IQR]	7.0 [3.1 to 12.0]	5.0 [2.8 to 11.8]	2.1 (-3.5 to 5.0)	0.499
Nail psoriasis, n (%)	21 (50)	17 (63)	0.79 (0.52 to 1.21)	0.419
Dactylitis n (%)	17 (40%)	3 (11%)	3.64 (1.18 to 11.26)	0.013
CRP level, mg/L median [IQR]	5.0 [2.0 to 9.0]	2.0 [1.0 to 4.0]	3.0 (0.0 to 4.0)	0.010
GSAUS (0-204), median [IQR]	22.0 [14.0 to 27.8]	9.0 [6.0 to 15.5]	13.0 (5.5 to 16.0)	<0.001
GCUS (0-312), median [IQR]	8.0 [3.3 to 14.8]	4.0 [1.0 to 8.5]	4.0 (0.0 to 7.0)	0.015

Data presented as mean (SD) unless otherwise stated. Analyses included n=69, except PASI (n=56 with BSA>1).[1]Differences in means or medians, risk ratios for binary data. CI, confidence interval; csDMARD, conventional synthetic disease modifying anti-rheumatic drugs; DAPSA, Disease activity Index for PsA; DAS28, Disease Activity Score; DLQI, Dermatology Life Quality Index; GAD Generalized Anxiety Disorder, GAUS/GSAUS/GCUS, Global acute/subacute/chronic ultrasound scores; HAQ-DI,Health Assessment Questionnaire disability index; SF-36 MCS/PCS, Short Form-36 Mental/Physical Component Summary; PASI, Psoriatic Area Severity Index; Pso, psoriasis; PsAID, PsA Impact of Disease; SPARCC, SpA Research Consortium of Canada; TPC, tender point count.

Table 3: Prognostic value of pain- and ultrasound (US) profiles for treatment response

Prognostic Factors	n	Responders n (%)	Simple model OR (95%CI)	P-value	Adjusted model[1] OR (95%CI)	P-value
Primary		**ACR20 response**				
WP+	24	6 (25)	[Reference level]		[Reference level]	
No-WP	45	12 (27)	1.09 (0.36 to 3.58)	0.880	1.07 (0.35 to 3.53)	0.912
GAUS =0	27	5 (19)	[Reference level]		[Reference level]	
GAUS ≥1	42	13 (31)	1.97 (0.64 to 6.90)	0.244	1.86 (0.57 to 6.84)	0.313
Primary		**Minimal Disease activity**				
WP+	24	0 (0)	[Reference level]		[Reference level]	
No-WP	45	9 (20)	18.43 (1.51 to 224.41)[1]	0.022	NE	NE
GAUS =0	27	3 (11)	[Reference level]		[Reference level]	
GAUS ≥1	42	6 (14)	1.33 (0.32 to 6.80)	0.700	1.84 (0.39 to 10.73)	0.447
Primary		**DAPSA 50%**				
WP+	24	7 (29)	[Reference level]		[Reference level]	
No-WP	45	15 (33)	1.21 (0.42 to 3.72)	0.723	1.15 (0.39 to 3.56)	0.806
GAUS =0	27	7 (26)	[Reference level]		[Reference level]	
GAUS ≥1	42	15 (36)	1.59 (0.56 to 4.83)	0.391	1.49 (0.49 to 4.83)	0.483
Primary		**Patient-reported improvement**				
WP+	24	10 (42)	[Reference level]		[Reference level]	
No-WP	45	18 (40)	0.93 (0.34 to 2.59)	0.893	0.94 (0.34 to 2.66)	0.913
GAUS =0	27	8 (30)	[Reference level]		[Reference level]	
GAUS ≥1	42	20 (48)	2.16 (0.79 to 6.25)	0.134	2.81 (0.95 to 9.16)	0.062

Secondary		ACR20 response				
PDQ ≥13	38	9 (24)	[Reference level]		[Reference level]	
PDQ <13	31	9 (29)	1.32 (0.44 to 3.92)	0.615	1.42 (0.47 to 4.33)	0.534
TPC ≥8	17	3 (18)	[Reference level]		[Reference level]	
TPC <8	52	15 (29)	1.89 (0.52 to 9.06)	0.347	1.73 (0.45 to 8.52)	0.439
SJ/TJ[2] <0.5	47	11 (28)	[Reference level]		[Reference level]	
SJ/TJ ≥0.5	21	6 (29)	1.31 (0.39 to 4.13)	0.652	1.20 (0.35 to 3.89)	0.764
GSAUS <16[3]	32	6 (19)	[Reference level]		[Reference level]	
GSAUS ≥16	37	12 (32)	2.08 (0.70 to 6.77)	0.193	2.02 (0.60 to 7.45)	0.261
GCUS <7[3]	39	9 (23)	[Reference level]		[Reference level]	
GCUS ≥7	30	9 (30)	1.43 (0.48 to 4.26)	0.517	2.07 (0.55 to 8.39)	0.285

Intention to treat analyses. [1]Logistic regression adjusted for age and gender. [2]One patients not included due to zero SJ and TJ, patients with 0 SJ and ≥2 TJ were coded as SJ/TJ <0.5 (n=7), and 0 TJ and ≥ 1 SJ as SJ/TJ ≥0.5 (n=2). [3]Median values used as cut-offs. DAPSA, Disease Activity Index for PsA; GAUS/GSAUS/GCUS, Global Acute/Subacute/Chronic Ultrasonic Score; NE, not estimable; PDQ; PainDetect Questionnaire score; TPC; Tender point count; SJ/TJ swollen/tender joints ratio; WP, widespread non-arthritic pain. [1]A continuity correction was used to calculate the OR as explained in Methods.

Table 4 Change in PsA core domains from baseline to follow-up for WP and GAUS groups

COS[1] measures	WP+ (n=24)	No-WP (n=45)	Difference (95%CI)	P-value
ΔSJC, median [IQR]	-0.5 [-5.0 to 0.0]	-1.0 [-4.0 to 0.0]	0.5 (-3.5 to 2.0)	0.863
ΔTJC, median [IQR]	-6.5 [-17.5 to 0.0]	0.0 [-8.0 to 0.0]	-6.5 (-14.0 to 1.5)	0.071
ΔSPARCC enthesitis	-0.3 (0.8)	-0.6 (0.4)	0.3 (-1.5 to 2.0)	0.742
ΔPASI, median [IQR]	0.0 [-4.9 to 0.3]	0.0 [-6.5 to 0.0]	0.0 (-3.3 to 3.0)	0.392
ΔVAS pain	-16.5 (5.9)	-6.6 (3.5)	-9.9 (-22.7 to 2.9)	0.127
ΔSF-36 BP, median[IQR]	9.0 [0.0 to 20.3]	0.0 [0.0 to 20.0]	9.0 (-6.0 to 11.0)	0.555
ΔHAQ-DI, median [IQR]	0.0 [-0.4 to 0.0]	0.0 [-0.2 to 0.0]	0.0 (-0.2 to 0.3)	0.401
ΔSF-36 PF	7.7 (3.3)	5.1 (2.2)	2.6 (-5.2 to 10.4)	0.507
ΔDLQI, median [IQR]	0.0 [-1.0 to 0.3]	0.0 [-1.0 to 0.0]	0.0 (0.0 to 0.0)	0.787
ΔPsAID	-1.1 (0.4)	-0.9 (0.3)	-0.2 (-1.3 to 0.9)	0.691
ΔPatient Global VAS	-20.3 (5.5)	-9.9 (4.0)	-10.4 (-23.8 to 3.0)	0.126
ΔNRS Fatigue	-0.9 (0.5)	-0.5 (0.3)	-0.4 (-1.6 to 0.8)	0.487
ΔSF-36 VT	6.0 (4.4)	3.1 (2.4)	2.9 (-6.3 to 12.2)	0.528
ΔCRP, median [IQR]	-2.0 [-4.0 to 0.0]	0.0 [-2.0 to 0.0]	-2.0 (-3.0 to 0.0)	0.059
COS[1] measures	**GAUS=0 (n=27)**	**GAUS ≥1 (n=42)**	**Difference (95%CI)**	**P-value**
ΔSJC, median [IQR]	0.0 [-3.0 to 0.0]	-1.5 [-4.7 to 0.0]	1.5 (-1.0 to 3.0)	0.476
ΔTJC, median [IQR]	0.0 [-7.5 to 0.0]	-5.0 [-13.2 to 0.0]	5.0 (-3.0 to 9.0)	0.236
ΔSPARCC enthesitis	0.1 (0.6)	-0.9 (0.5)	1.0 (-0.7 to 2.7)	0.250
ΔPASI, median [IQR]	0.0 [-1.5 to 0.0]	-1.7 [-6.9 to 0.0]	1.8 (0.0 to 5.5)	0.111

ΔVAS pain	-5.5 (3.5)	-13.0 (4.5)	7.5 (-4.0 to 18.9)	0.196
ΔSF-36 BP, median[IQR]	0.0 [0.0 to 15.5]	0.0 [0.0 to 20.0]	0.0 (-10.0 to 10.0)	0.786
ΔHAQ.DI, median [IQR]	0.0 [-0.1 to 0.0]	-0.1 [-0.4 to 0.0]	0.1 (0.0 to 0.3)	0.172
ΔSF-36 PF	3.3 (2.4)	7.7 (2.6)	-4.4 (-11.9 to 3.1)	0.247
ΔDLQI, median [IQR]	0.0 [0.0 to 0.5]	0.0 [-1.0 to 0.0]	0.0 (0.0 to 0.5)	0.127
ΔPsAID	-0.7 (0.3)	-1.2 (0.4)	0.5 (-0.5 to 1.5)	0.315
ΔPatient Global VAS	-10.7 (3.8)	-15.4 (4.7)	4.7 (-7.4 to 16.8)	0.441
ΔNRS Fatigue	-0.3 (0.5)	-0.8 (0.3)	0.5 (-0.7 to 1.6)	0.430
ΔSF-36 VT	3.3 (3.2)	4.6 (3.0)	-1.3 (-10.3 to 7.7)	0.773
ΔCRP, median [IQR]	0.0 [-2.0 to 0.0]	0.0 [-5.7 to 0.0]	0.0 (-1.0 to 2.5)	0.177

Data are presented as mean (SE) unless otherwise stated, analyses of ITT data. [1]OMERACT Core Outcome Set for PsA. BP, Bodily Pain; CI, confidence interval; DLQI, Dermatology Life Quality Index; HAQ-DI, Health Assessment Questionnaire Disability Index; NRS, Numeric rating scale; PASI, Psoriatic Area Severity Index; PF, Physical Func-tion; PsAID, Psoriatic Arthritis Impact of Disease score; SF-36, Medical Outcomes Study Short Form; SJC, swollen joint count; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; TJC, tender joint count; WP,widespread non-arthritic pain; VT, Vitality.

Figure 1 Flow chart

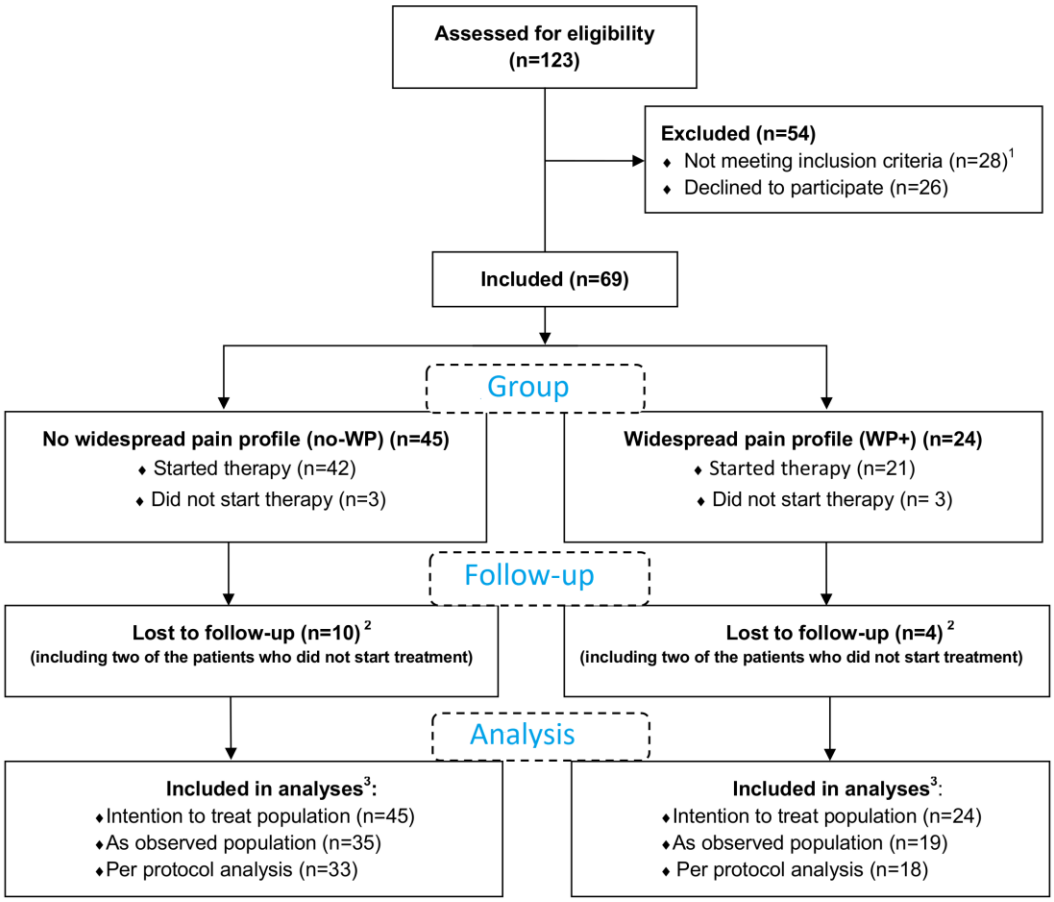

Figure 2: Correlation between baseline WPI and GAUS scores and ΔDAPSA and ΔCPDAI