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ORIGINAL ARTICLE

Prevalence of central sensitization and neuropathic pain in patients with psoriatic arthritis: A cross-sectional study

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ABSTRACT

Objectives: This study aims to evaluate the frequency of central sensitization (CS) and neuropathic pain (NP) in psoriatic arthritis (PsA) and their association with disease activity and functional disability.

Patients and methods: Between April 2022 and August 2022, data of a total of 114 consecutive patients (78 males, 36 females; mean age: 49±11.5 years; range, 22 to 76 years) who were diagnosed with PsA according to the classification criteria for PsA criteria were prospectively analyzed. CS was assessed using the Central Sensitization Inventory (CSI), with scores ≥40 indicating its presence. Neuropathic pain was evaluated using the Douleur Neuropathique en 4 Questions (DN4), with scores ≥4 indicating its presence.

Results: The median disease duration was 4 (interquartile range: 9) years. Among 114 patients, CS was present in 43% and NP in 23.5%. Fibromyalgia syndrome (FMS) was diagnosed in 25.5%. Patients with CS or NP had higher Visual Analog Scale pain scores, patient and physician global assessments, tender joint counts, disease activity scores in PsA, and Health Assessment Questionnaire Disability Index (HAQ-DI). Central sensitization was also associated with enthesitis, nail involvement, and depression, while NP was linked to higher body mass index (BMI). Anxiety, depression, and HAQ-DI were independent risk factors for CS, while BMI and FMS were correlated with NP.

Conclusion: Our study results suggest that CS and NP are prevalent in PsA and are associated with worse disease outcomes. Recognizing and addressing these conditions may enhance the management of patients with refractory symptoms and unmet treatment goals.

Keywords: Central sensitization, fibromyalgia syndrome, neuropathic pain, psoriatic arthritis.

Psoriatic arthritis (PsA) is a chronic heterogeneous inflammatory disease with articular and extraarticular manifestations. Chronic inflammation with inflammatory arthropathies such as PsA can trigger both peripheral and central sensitization (CS) through central modifications of pain pathways. CS is characterized by a disproportionate response to pain stimuli and abnormal pain management mechanisms involving the central nervous system (CNS). Nociceptive and neuropathic mechanisms are involved at both the peripheral and central levels of pain. Proinflammatory cytokines and vasoactive peptides produced by immune cells act directly on the nociceptive neurons of the spinal cord's dorsal horn, contributing to peripheral sensitization and CS.[1] The International Association for the Study of Pain (IASP) defines CS as a type of nociplastic pain which presents as an "increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input".[2] Mayer et al.[3] developed the Central Sensitization Inventory (CSI) to evaluate CS practically in clinical use. Scores of 40 and above were considered indicative of CS. According to this classification,[4] studies have demonstrated that 15 to 40% of patients with PsA and other rheumatic diseases, chronic pain, and inflammatory conditions may have concomitant CS syndromes.[5,6]

Abnormal pain processing in the CNS has been demonstrated consistently in neuropathic pain (NP). Symptoms of NP include abnormal sensations such as tingling, burning, electric shock, hyperalgesia, and allodynia. The PainDETECT questionnaire (PDQ) is widely used in studies to evaluate the presence of NP. Gok

et al.[7] categorized NP in axial spondyloarthritis patients using both Douleur Neuropathique en 4 Questions (DN4) and PDQ, reporting a prevalence of 31.4 to 33.5%, respectively, with a significant association with quality of life measures and Visual Analog Scale (VAS) of fatigue. A study reported probable NP in 26.6% and probable neuropathic-like pain in 21.9% of 64 PsA according to the PDQ.[8] Another study using the PDQ found that PsA patients presenting with NP features were 10 times more likely to have increased VAS pain levels.[9] On the other hand, the DN4 questionnaire has been shown to be more sensitive in assessing NP than the PDQ.[10]

Fibromyalgia syndrome (FMS) occurs in a significant proportion of patients with PsA. The reported prevalence of concomitant FMS in PsA ranges from 10 to 27%.[11] Disease activity measures with subjective outcomes are controversial in patients with FMS and do not reliably assess the actual inflammatory disease.

Despite advances in treatment for PsA, many patients still suffer from pain. The inflammation and joint damage caused by PsA can activate pain pathways in the nervous system, leading to an increased sensitivity to pain. Treatment for PsA and its associated pain can include medications to reduce inflammation, physical therapy to improve joint function, and pain management techniques such as acupuncture and cognitive behavioral therapy. In cases where CS or NP are present, treatments such as antidepressants and anticonvulsants may also help manage pain.

Using validated questionnaires such as the CSI and DN4 can help clinicians identify patients with CS and NP symptoms. Additionally, the co-occurrence of FMS in PsA patients can complicate the assessment of disease activity measures, making it important to differentiate between inflammatory disease activity and FMS symptoms.

In the present study, we aimed to investigate the prevalence of CS and NP in patients with PsA and associated measures of disease activity, anxiety and depression, FMS, and functional disability.

PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at İzmir Katip Çelebi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, between April 2022 and August 2022. Data of a total of 114 consecutive patients (78 males, 36 females; mean age: 49±11.5 years; range, 22 to 76 years) who were diagnosed with PsA according to the classification criteria for PsA criteria[12] were prospectively analyzed. Exclusion criteria included coexisting neuropathic conditions, such as entrapment neuropathies, cervical or lumbar radiculopathies, and polyneuropathies supported by any etiology. Patients who met any of the following criteria were also excluded: *(i)* were receiving centrally acting drugs (e.g., pregabalin, gabapentin), *(ii)* had alcohol/substance consumption, *(iii)* had any uncontrolled systemic diseases or malignancy, *(iv)* had diabetic peripheral neuropathy (PNP), *(v)* were pregnant, and *(vi)* were not able to understand and fill in the questionnaires. Regarding diabetic PNP, patients with diabetes were included in the study, but those with established diabetic PNP or poorly controlled diabetes were excluded. A written informed consent was obtained from each patient. The study protocol was approved by the İzmir Katip Çelebi University Faculty Medicine Ethics Committee (date: 21.04.2022, no: 0207). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical assessments, symptom history, and neuropathy screening tests were used to identify these cases. Patients underwent a one-day, cross-sectional evaluation in which an objective musculoskeletal examination was performed by an experienced rheumatologist, and a questionnaire package [includes CSI, DN4, along with other relevant questionnaires such as Health Assessment Questionnaire Disability Index (HAQ-DI) and Hospital Anxiety and Depression Scale (HADS)] was administered by a second rheumatologist who was blind to the examination results.

The data collected included demographic information, clinical characteristics, comorbidities, ongoing treatment, acute-phase reactants, and measures of disease activity, such

as the tender joint count (TJC) (0-68 joints) and swollen joint count (SJC) (0-66 joints). Enthesitis was assessed using the Leeds Enthesitis Index (LEI), and psoriasis severity was assessed with body surface area (BSA). Disease activity was assessed using the Disease Activity index for Psoriatic Arthritis (DAPSA),[13] and patients were classified as achieving minimal disease activity (MDA), if they fulfilled at least five of the seven criteria.[14] A DAPSA score of ≤4 is considered as remission, >4 and ≤14 as low disease activity, >14 and ≤28 as moderate disease activity, and >28 as high disease activity.

The presence of CS was evaluated using the CSI, which consists of parts A and B. Part A comprises 25 questions about the patient's current complaints. Higher CSI scores indicate worse symptomatology. Each question is scored 0 to 4 on a five-point Likert scale (scoring: never = 0, rarely = 1, sometimes = 2, usually = 3, and always = 4), and the total score can range from 0 to 100. In the assessment, a score above 40 was classified as positive for CS.[4] In contrast, part B was used to question whether 10 non-organic clinical conditions (such as migraine), called central sensitivity syndromes, were diagnosed in the past. This study used the validated Turkish version of the CSI questionnaire.[15]

Neuropathic pain was evaluated using DN4, a 10-item, clinician-administered questionnaire developed in France.[16] The DN4 evaluation consists of seven items related to self-reported symptoms, namely, burning, painful cold sensation, electric shock, tingling, pins and needles, numbness, and itching, as well as a clinical examination for hypoesthesia on touch, hyperesthesia against pinprick, and increased pain with brushing. In our approach, we included the physical examination components of the DN4 (e.g., brushing and touching the area of pain) while assessing NP in PsA patients. The DN4 was selected, as it includes objective evaluation, such as physical examination findings, in addition to the pain detection questionnaire and as our main goal was to distinguish between pain due to PsA disease activity and NP. Of note, PsA can involve pain in multiple areas or none at all. For patients who reported pain, we conducted a physical examination based on the 2016 American College of Rheumatology (ACR) diagnostic criteria for FMS, focusing on at least three pain areas.[17] If any of these areas tested positive, we considered the DN4 score positive for NP. We did not perform the NP assessment for patients without reported pain. A total score of ≥4 out of 10 indicated the presence of NP. The DN4 has been shown to have 83% sensitivity and 90% specificity. The validity and reliability of the Turkish version were conducted by Çelik et al.[18]

In addition, we investigated whether disease severity, anxiety and depression, and FMS are associated with CS and NP in PsA patients. The HAQ-DI was used to evaluate functional disabilities.[19] Also, it was used to assess the presence of anxiety and depression symptoms. The 14-item measure produces two subscales: HADS-Depression and HADS-Anxiety. A score greater than or equal to 11 indicates the probability of a mood disorder.[20] Furthermore, all patients were evaluated for the 2016 ACR classification criteria for FMS. Finally, the relationships between CS and its severity, clinical disease activity, and measures of functional disability were analyzed.

Statistical analysis

Statistical analysis was performed using the SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables and in number and frequency for categorical variables. Normality for all variables was tested using the Shapiro-Wilk test. The chi-square or Fisher exact test was used to compare categorical variables. The Student t-test or Mann-Whitney U test was used to compare normally and non-normally distributed continuous variables. Correlations were calculated using the Spearman correlation analysis. Binary variables were analyzed using logistic regression, which estimated the odds ratios (OR) and 95% confidence intervals (CIs). Multivariate analyses were performed to adjust for significant or clinical relevance variables. A two-sided p value of <0.05 was considered statistically significant.

Table 1. Demographic, clinical, and disease activity characteristics of the PsA patients (n=114)

Variables	n	%	Mean±SD	Median	IQR
Age (year)			49±11.5		
Sex Female	 78	 68.4			
Oligoarthritis Polyarthritis Axial involvement Distal interphalangeal involvement Arthritis mutilans	43 43 23 4 1	37.7 37.7 20.2 3.5 0.9			
Disease duration (year)				4	9
Education (≥8 year)	56	49.1			
Unemployment	50	43.9			
Marital status, married	97	85.1			
Smoker, current	41	36			
Alcohol consumption, current	20	17.5			
Body mass index (kg/m^2)			28.7±7.3		
History or current peripheral arthritis	80	70.2			
History or current enthesitis	45	39.5			
History or current dactylitis	36	31.6			
History or current uveitis	4	3.5			
Nail involvement, ever	40	35.1			
Inflammatory bowel disease, ever	3	2.6			
Spondyloarthritis family history	27	23.7			
Rheumatoid factor positive	0	114			
ACPA positive	6/90	6.7			
CRP (mg/dL)				4.4	8
ESR (mm/h)				22	23
DAPSA Remission Low disease activity Moderate disease activity High disease activity	 8 46 42 17	 7.1 40.7 37.2 15			
Methotrexate Leflunomide Sulfasalazine Glucocorticoid Biological DMARD	72 28 7 18 46	63.7 24.6 6.2 27.3 40.4			
LEI ≥1	33	28.9			
BSA				1	2
DAPSA				15.2	15.5
MDA	52	45.6			
Comorbidity ≥1	73	64			
Hypertension	36	31.6			
Diabetes mellitus	16	14			
Thyroid disease	17	14.9			
Cardiovascular disease	11	9.6			
HAQ-DI				0.63	0.97
HADS, depression (n=107)	19	17.8			
HADS, anxiety (n=107)	23	21.5			
FMS (n=110)	28	25.5			
Central sensitization	49	43			
Neuropathic pain (n=102)	24	23.5			

PsA: Psoriatic arthritis; SD: Standard deviation; IQR: Interquartile range; ACPA: Anti-citrullinated proteins antibodies; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; DAPSA: Disease activity in psoriatic arthritis; DMARD: Disease-modifying anti-rheumatic drug; LEI: Leeds Enthesitis Index; BSA: Body surface area; MDA: Minimal disease activity; HAQ-DI: Health Assessment Questionnaire Disability Index; HADS: Hospital Anxiety and Depression Scale; FMS: Fibromyalgia syndrome. According to the exclusion criteria, twelve of 114 patients could not be included in the study.

RESULTS

In this study, the median disease duration was 4 (IQR: 9) years. The mean body mass index (BMI) of the patients was 28.7±7.3 kg/m^2, and the mean DAPSA score was 15.2±15.5. Approximately half of the patients achieved the goal of remission and low-disease activity. A remission rate of 7.1%, low disease activity of 40.7%, moderate disease activity of 37.2%, and high disease activity of 15% were observed. Minimal disease activity was also achieved in 45.6% of the patients, similar to the sum of DAPSA remission and low-disease activity. The subtypes of PsA were evaluated clinically and radiologically. Axial involvement was detected in 23 (20.2%), polyarthritis in 43 (37.7%), oligoarthritis in 43 (37.7%), distal interphalangeal (DIP) joint involvement in four (3.5%), and arthritis mutilans in one (0.9%) patient.

Of the 114 patients who were receiving treatment, 72 (63.2%) were taking methotrexate, 28 (24.6%) leflunomide, seven (6.2%) sulfasalazine, and 18 (15.7%) glucocorticoids. In addition to the conventional synthetic disease-modifying anti-rheumatic drug (csDMARD), 46 patients (40.4%) were treated with a biological DMARD, 25 (21.9%) with an anti-tumor necrosis factor-alpha drug (n=5 etanercept, n=13 adalimumab, n=5 certolizumab pegol, and n=4 infliximab),

Table 2. Comparison of characteristics of PsA patients with and without central sensitization and neuropathic pain

Variables	CS with (n=49)	CS without (n=65)	*p*	NP with (n=24)	NP without (n=78)	*p*
Sex Female n (%)	40 (81.6)	38 (58.5)	**0.008**	25(92.6)	45 (60)	**0.002**
Age (year) mean±SD	51±11	47.7±11	0.473	50.1±10	48.2±11	0.611
Unemployment, n (%)	29 (60.4)	21 (32.3)	0.012	15 (65.2)	28 (35.9)	0.047
BMI (kg/m^2) mean±SD	29.7±5.1	27.9±4.4	0.685	32.3±9.6	26.9±5.9	**0.015**
PsA duration (year) median (IQR)	6 (6)	6 (11)	0.117	3 (3)	6 (10)	0.119
TJC (0-68), median (IQR)	2 (4)	0 (1)	**0.015**	1 (11)	0 (2)	**0.048**
SJC (0-66), median (IQR)	0 (0)	0 (0)	0.866	0 (0)	0 (0)	0.162
PGA, median (IQR)	50 (38)	30 (20)	**<0.001**	60 (60)	30 (25)	**<0.001**
PhGA, median (IQR)	20 (30)	15 (18)	**0.003**	30 (20)	20 (20)	**0.001**
Pain VAS, median (IQR)	50 (38)	15 (30)	**<0.001**	60 (60)	30 (50)	**<0.001**
LEI ≥1, n (%)	22 (44.9)	11 (16.9)	**0.001**	11 (40.7)	18 (24)	0.135
BSA, n (%)	1 (2)	0 (1)	**0.045**	1 (1)	0 (2)	0.557
DAPSA, median (IQR)	17.9 (11)	9.7 (11.9)	**0.003**	20.2 (13)	11.7 (11)	**0.010**
MDA, n (%)	9 (18.4)	43 (66.2)	**<0.001**	5 (18.5)	41 (54.7)	**0.001**
Nail involvement, ever, n (%)	23 (46.9)	17 (26.2)	**0.021**	12 (50)	23 (29.5)	0.064
Leflunomide users, n (%)	11 (22.4)	17 (26.2)	0.649	2 (8.3)	24 (30.8)	**0.027**
HAQ-DI, median (IQR)	1 (0.91)	0.38 (0.69)	**<0.001**	1.38 (1.3)	0.5 (0.8)	**<0.001**
HADS, anxiety (n=107), n (%)	18 (40)	5 (8.1)	**<0.001**	10 (40)	11 (15.5)	**0.015**
HADS, depression (n=107), n (%)	15 (33.3)	4 (6.5)	**<0.001**	7 (28)	9 (12.7)	0.116
FMS (n=110), n (%)	20 (42.6)	8 (12.7)	**<0.001**	13 (48.1)	10 (13.3)	**<0.001**

PsA: Psoriatic arthritis; CS: Central sensitization; NP: Neuropathic pain; SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; TJC: Tender joint count; SJC: Swollen joint count; PGA: Patient global assessment of disease activity; PhGA: Physician's global assessment of disease activity; VAS: Visual Analog Scale; LEI: Leeds Enthesitis Index; BSA: Body surface area; DAPSA: Disease activity in psoriatic arthritis; MDA: Minimal disease activity; HAQ-DI: Health Assessment Questionnaire Disability Index; HADS: Hospital Anxiety and Depression Scale; FMS: Fibromyalgia syndrome.

13 (11.4%) with secukinumab, one (0.9%) with ustekinumab, and five (4.3%) with ixekizumab. Overall, 64% of the patients had at least one comorbidity, and the most common comorbidities were hypertension, FMS, thyroid disease, and diabetes mellitus, respectively. Other disease activity measures and clinical features are summarized in Table 1.

The mean CSI score was 35.5±18.5 on a scale of 0-100, and 43% of patients scored ≥40, indicating a high probability of CS. Neuropathic pain was detected in 24 (23.5%) patients (Table 1). Evaluation of part B of the CS revealed that 26 (22.8%) patients had one disease, nine (7.9%) patients had two diseases, and six (5.3%) patients had three diseases. These included restless legs (n=4; 3.5%), FMS (n=13; 11.4%), migraine (n=10; 8.8%), irritable bowel syndrome (n=3; 2.6%), anxiety (n=14;12.2%), and depression (n=21; 18.4%). The other disease components of part B were absent in all patients (Table 2).

Furthermore, CS and NP were statistically higher in the women and the unemployed individuals. The median scores of VAS pain, the global patient assessment (PGA), and the global physician assessment (PhGA) of disease activity, TJC, DAPSA, and HAQ scores were higher in patients with CS and NP. Other CS-related factors included enthesitis, psoriasis severity, and nail involvement, while higher BMI was associated with NP (Table 3). Age, disease duration, smoking status, alcohol consumption, SJC, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), dactylitis, peripheral arthritis, and comorbidities were similar. The usage of csDMARD and biological therapy in the patients' current treatments was similar in the patient groups with and without CS and NP. Exceptionally, the current leflunomide treatment rate was higher in patients without NP. In addition, no significant difference in the prevalence of CS and NP was found in glucocorticoid users and non-users. Anxiety and FMS were higher in patients with CS and NP, and depression was higher in CS patients only (Table 3). While 20 (42.6%) patients with FMS had CS, only 11 had NP. Among patients with NP, 16 (66.7%) met the criteria for CS, while 18 (36.7%) patients with CS also had NP.

In the correlation analyses, moderate correlations between the CSI scores and other functional parameters were observed. The CSI

Table 3. Analysis of part B of the central sensitization scale

	n	%
Restless Legs syndrome	4	3.5
Chronic Fatigue syndrome	NR	
Fibromyalgia syndrome	13	11.4
Temporomandibular joint disorder	NR	
Migraine/tension-type headache	10	8.8
Irritable bowel syndrome	3	2.6
Multiple chemical sensitivity	NR	
Whiplash injury	NR	
Anxiety/panic attack	14	12.2
Depression	21	18.4

NR: Not reported.

Table 4. Correlation of central sensitization score with patient characteristic

Variables	r	*p*
Age	0.073	0.442
PGA	0.465	**<0.001**
PhGA	0.359	**<0.001**
Pain VAS	0.561	**<0.001**
TJC	0.280	**0.003**
DAPSA	0.368	**<0.001**
BSA	0.136	0.149
LEI	0.304	**0.001**
ESR (mm/h)	0.113	0.400
CRP (mg /dL)	0.025	0.789
FMS-Widespread pain index	0.391	**<0.001**
FMS-Symptom severity scale	0.561	**<0.001**
DN4 score	0.320	**<0.001**
HADS-Anxiety score	0.536	**<0.001**
HADS-Depression score	0.395	**<0.001**
HAQ-DI	0.515	**<0.001**

PGA: Patient global assessment of disease activity; PhGA: Physician's global assessment of disease activity; VAS: Visual Analog Scale; TJC: Tender joint count; DAPSA: Disease activity in psoriatic arthritis; BSA: Body surface area; LEI: Leeds Enthesitis Index; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; FMS: Fibromyalgia syndrome; DN4: Douleur Neuropathique 4 Questions; HADS: Hospital Anxiety and Depression Scale; HAQ-DI: Health Assessment Questionnaire Disability Index.

Table 5. Evaluation of central sensitization-related parameters in univariate and multivariate logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Sex (women *vs.* men)	3.158	1.316-7.578	0.010	1.979	0.550-7.112	0.296
Nail involvement, *ever*	2.498	0.136-5.492	0.023	2.460	0.811-7.458	0.112
PhGA	1.044	1.018-1.070	0.001	0.998	0.954-1.0	0.929
DAPSA	1.050	1.015-1.086	0.005	0.986	0.927-1.049	0.654
LEI ≥1, (present *vs.* absent)	4	1.695-9.440	0.002	2.303	0.710-7.474	0.165
BSA	1.077	0.929-1.248	0.324	1.021	0.824-1.267	0.847
Anxiety (present *vs.* absent)[a]	7.600	2.551-22.638	<0.001	**4.379**	**1.092-17.564**	**0.037**
Depression (present *vs.* absent)[a]	7.250	2.211-23.778	0.001	**5.307**	**1.165-24.176**	**0.031**
FMS, (present *vs.* absent)[b]	5.093	1.988-13.042	0.001	1.367	0.382-4.888	0.631
HAQ-DI	9.646	3.786-24.577	<0.001	**4.444**	**1.378-14.330**	**0.013**

OR: Odds ratio; CI: Confidence interval; PhGA: Physician's global assessment of disease activity; DAPSA: Disease activity in psoriatic arthritis; LEI: Leeds Enthesitis Index; BSA: Body surface area; FMS: Fibromyalgia syndrome; HAQ-DI: Health Assessment Questionnaire Disability Index; HADS: Hospital Anxiety and Depression Scale; a For HADS; b For ACR2016.

Table 6. Evaluation of neuropathic pain-related parameters in univariate and multivariate logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Sex (women *vs.* men)	6.875	1.507-31.362	0.013	3375	0.561-20.287	0.096
Body mass index	1.133	1.021-1.258	0.019	**1.174**	**1.016-1.357**	**0.030**
PhGA	1.048	1.018-1.079	0.002	1.019	0.955-1.089	0.567
DAPSA	1.042	1.006-1.079	0.021	0.976	0.887-1.075	0.624
Leflunomide users	0.205	0.045-0.940	0.041	0.148	0.021-1.057	0.057
Anxiety (present *vs.* absent)*	3.577	1.251-10.231	0.017	2.129	0.523-8.663	0.291
FMS (present *vs.* absent)	6.091	2.189-16.944	0.001	**4.507**	**1.004-20.234**	**0.049**
HAQ-DI	9.973	3.358-29.619	<0.001	5.641	1.069-23.833	0.055

OR: Odds ratio; CI: Confidence interval; PhGA: Physician's global assessment of disease activity; DAPSA: Disease activity in psoriatic arthritis; FMS: Fibromyalgia syndrome; HAQ-DI: Health Assessment Questionnaire Disability Index; HADS: Hospital Anxiety and Depression Scale; * For HADS.

scores positively correlated with disease activity scores, but not inflammatory marker levels (CRP, ESR), age, or BSA (Table 4).

Multivariate logistic regression analysis was performed to identify the predictors of the development of CS. Anxiety (OR=4.379, 95% CI: 1.092-17.564), depression (OR=5.006, 95% CI: 1.165-24.176), and HAQ-DI (OR=4.444, 95% CI: 1.378-14.330) were found to be the independent risk factors for the development of CS (Table 5). Among the independent variables analyzed, those considered to explain the NP features were BMI (OR=1.168, 95% CI: 1.015-1.343) and FMS (OR=4.507, 95% CI: 1.004-20.234) (Table 6).

DISCUSSION

In the present study, we investigated the prevalence of CS and NP in patients with PsA and associated measures of disease activity, anxiety and depression, FMS, and functional

disability. Our findings demonstrated that a significant proportion of PsA patients exhibited features of CS and NP, both of which correlated with poorer clinical outcomes and increased functional impairment. In particular, anxiety, depression, and HAQ-DI were independent risk factors for developing CS in PsA patients, while BMI and FMS were independently associated with NP.

In our study, CS was observed in 43% of participants, consistent with previous reports indicating that up to 40% of patients with rheumatic diseases may present with CS syndromes.[6] Furthermore, our analysis revealed that CS was independently associated with functional disability, depression, and anxiety. Although nail involvement, enthesitis, and psoriasis severity were also higher in the CS group, these factors did not remain significant in multiple regression analyses. These results align with the Adami et al.'s[6] study, which evaluated 78 PsA patients and reported a 42.9% prevalence of CS, showing a strong and independent relationship between functional disability and CS. Similarly, Bellinato et al.[5] found that CS might be associated with psoriasis, particularly in those with a high psoriasis area severity index, concomitant PsA, anxiety, depression, and severe quality-of-life impairment.

The observed correlation between disability, disease activity, and CS scores suggests that the severity of the disease may contribute to the development of CS in these patients. Our findings also indicate that PsA patients with CS are less likely to achieve treatment targets such as MDA. Previous studies have similarly reported that when CS coexists with PsA, disease activity scores and patient-reported outcomes are almost twice as severe as those in patients without CS.[21]

The initial insights into NP features in PsA were derived from the Danish Registry for Biologic Therapies in Rheumatology (DANBIO) registry, where NP was assessed using the PDQ revealing that 28% of PsA patients exhibited NP characteristics.[21] Similarly, another study reported that NP features in 25.4% of PsA patients with FMS were the sole independent variable associated with NP in logistic regression analysis.[22] Consistent with these findings, our study demonstrated that FMS was independently associated with NP. These results suggest that NP in PsA patients is likely influenced by multiple factors, with FMS playing a significant role.

Our study highlights the significant burden of NP in PsA patients, reinforcing findings from previous research. Mathieu et al.[23] evaluated patients using the DN4 questionnaire and reported an NP prevalence of 19.4%, a finding closely aligning with our results. This underscores the consistency of NP prevalence across various PsA cohorts. Additionally, we observed that patients with concurrent CS and NP exhibited higher scores in key clinical parameters, including VAS pain, DAPSA, PGA, PhGA, TJC, anxiety, and HAQ-DI, indicating a greater overall disease burden in these individuals.

A previous study utilizing the PDQ found that 26.6% of PsA patients had likely NP, with these patients showing significantly higher disease activity, functional impairment, and clinical manifestations such as dactylitis, enthesitis, and greater pain interference in daily life.[8] These findings highlight that NP in PsA is associated not only with increased inflammatory disease activity, but also with heightened psychological comorbidities, including anxiety and depression, as seen in our study.

Another PDQ-based study identified a strong correlation between NP and sleep disorders, further contributing to a decline in the quality of life in PsA patients.[24] Our study found that NP and CS were more prevalent among females and unemployed individuals. These associations may be influenced by multiple factors, including socioeconomic factors, psychological stress, and disease severity.

Our findings also indicate a significant association between BMI and NP in PsA patients, supporting previous research by Hozumi et al.,[25] who suggested that obesity-related inflammation might exacerbate neural injury. Elevated BMI in PsA has consistently been associated with increased disease severity, comorbidities, and reduced treatment response, as documented in several studies.[26,27] Given the role of adipose tissue in contributing to systemic inflammation via cytokine secretion, it is plausible that obesity-induced inflammation contributes to the exacerbation of NP symptoms.

More interestingly, a previous study reported an association between leflunomide use and increased NP,[28] while our study did not find a significant association between leflunomide use and increased NP prevalence. In contrast, Brito et al.[29] demonstrated that leflunomide could reduce mechanical allodynia in experimental models of inflammatory and NP. This discrepancy can be attributed to differences in study design, patient populations, or treatment durations. The potential analgesic effects of leflunomide in clinical settings warrant further investigation to clarify its role in managing NP in PsA.

In our study, 25% of patients had FMS, further underscoring the complexity of pain in this population. The presence of FMS complicates disease activity assessments, as subjective measures such as TJC and VAS pain scores can be confounded by widespread pain unrelated to inflammatory disease.[11] To illustrate, MDA criteria include components such as TJC, pain VAS, PGA, and tender entheseal points, all of which can be influenced by FMS. In our study, the patients with FMS had higher median scores in VAS pain, PGA, TJC, DAPSA, LEI, and HAQ-DI compared to those without FMS. This overlap highlights the need for a more nuanced approach to evaluating disease activity in PsA, incorporating objective measures such as SJC and imaging findings.

Additionally, our study identified significant associations between CS, NP, and psychological factors such as anxiety and depression. Elevated HADS scores positively correlated with both CSI and DN4 scores, consistent with evidence linking psychological distress to central pain amplification and altered pain modulation.[30,31] The bidirectional relationship between chronic pain and mental health highlights the importance of integrated care models addressing both the physical and psychological dimensions of PsA.

Nonetheless, this study has several limitations. The cross-sectional design limits the ability to establish causal relationships between CS, FMS, and NP in patients with PsA. The lack of imaging techniques, such as ultrasonography, may have hindered objective assessment of tender points and enthesitis, particularly in patients with FMS. Additionally, the relatively small sample size and the single-center design may also restrict the generalizability of the findings. Future studies with larger, more diverse populations and incorporating advanced imaging modalities are needed to validate and expand upon these results. Despite these limitations, to the best of our knowledge, this is the first study to comprehensively evaluate the coexistence of CS, FMS, and NP in PsA patients.

In conclusion, this study can provide valuable insights into the prevalence and impact of CS and NP in patients with PsA, which can inform the development of effective pain-management strategies for this population. By incorporating routine screening for CS and NP into clinical practice, clinicians can better identify PsA patients who may benefit from additional or alternative interventions beyond conventional treatments. This approach is particularly valuable in complex cases where standard treatment goals remain unmet. Future research should focus on evaluating the effectiveness of interventions targeting CS and NP, including non-pharmacological modalities, to improve both pain control and overall disease outcomes in PsA.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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