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The impact of fatigue on patients with psoriatic arthritis: a multi-center study of the TLAR-network

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Abstract

Fatigue is a substantial problem in patients with psoriatic arthritis (PsA) that needs to be considered in the core set of domains. This study aimed to evaluate fatigue and its relationship with disease parameters, functional disability, anxiety, depression, quality of life, and correlation with disease activity as determined by various scales. A total of 1028 patients (677 females, 351 males) with PsA who met the CASPAR criteria were included [Turkish League Against Rheumatism (TLAR) Network multicenter study]. The demographic features and clinical conditions of the patients were recorded. Correlations between fatigue score and clinical parameters were evaluated using the Disease Activity Score 28 (DAS28), Disease Activity in Psoriatic Arthritis (DAPSA), Clinical DAPSA (cDAPSA), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Fibromyalgia Rapid Screening Tool (FiRST), minimal disease activity (MDA), and very low disease activity (VLDA). Fatigue was assessed with the Functional Assessment of Chronic Illness Therapy (FACIT-F) and a 10-point VAS (VAS-F). The mean age of the patients was 47 (SD: 12.2) years, and the mean disease duration was 6.4 (SD: 7.3) years. The mean VAS-F score was 5.1 (SD: 2.7), with fatigue being absent or mild, moderate, and severe in 12.8%, 24.6%, and 62.5% of the patients, respectively. Fatigue scores were significantly better in patients with DAS28 remission, DAPSA remission, cDAPSA remission, MDA, and VLDA ($p < 0.001$). Fatigue scores significantly increased with increasing disease activity levels on the DAS28, DAPSA, and cDAPSA ($p < 0.001$). VAS-F scores showed correlations with the scores of the BASDAI, BASFI, PsAQoL, HAD-A, FiRST, pain VAS, and PtGA. FiRST scores showed fibromyalgia in 255 (24.8%) patients. FACIT-F and VAS-F scores were significantly higher in patients with fibromyalgia ($p < 0.001$). In regression analysis, VLDA, BASDAI score, FiRST score, high education level, HAD-Anxiety, and BMI showed independent associations with fatigue. Our findings showed that fatigue was a common symptom in PsA and disease activity was the most substantial predictor, with fatigue being less in patients in remission, MDA, and VLDA. Other correlates of fatigue were female gender, educational level, anxiety, quality of life, function, pain, and fibromyalgia.

Keywords Psoriatic arthritis · Fatigue · Lassitude · Disease activity · Outcome measure

Introduction

Psoriatic arthritis (PsA) is a systemic and inflammatory disease associated with the involvement of the skin, joints, nails, and vertebrae [1]. As in many chronic diseases like rheumatoid arthritis (RA) [2], Behcet's disease [3], and systemic lupus erythematosus (SLE), fatigue is a mutual

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symptom in patients with PsA, affecting quality of life, sleep and pain [4, 5].

Fatigue is a feeling of exhaustion associated with a decrease in physical and mental capacity [6]. In affected individuals, it can be peripheral or central and is considered to be more frequently central than peripheral. Peripheral fatigue impairs strength and speed, while central fatigue is the result of the inability to initiate an intended action and physical activity [7]. The cause for fatigue is multifactorial, among which are immune and inflammatory factors, oxidative stress, bioenergy, and neuronal activity. Pro-inflammatory cytokines, including IL-1, IL-6, TNF-alpha, and IFN- alpha, are elevated in patients with fatigue [8, 9]. In a randomized controlled trial, anti-TNF treatment was shown to reduce cytokine levels, with corresponding improvements in fatigue [10].

In PsA, the severity of fatigue is moderate in half of the patients and severe in a third, with a higher prevalence in women than in men [11]. Husted et al. reported that fatigue was common in PsA, especially in female patients, and was accompanied by pain, physical impairment, and psychological distress [5]. Several studies reported correlations between fatigue and disease activity in PsA. Gorlier et al. found reduced levels of fatigue in PsA patients who were in remission, according to the Disease Activity in Psoriatic Arthritis (DAPSA) [4, 12]. As PsA is a heterogeneous disease with involvement of multiple domains, composite measures have been developed. Among them, Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA) are the most relevant criteria for targeted treatment because they contain multiple domains and provide evidence for the extent of disease control. Patients who are in MDA have higher levels of quality of life and function, with reduced disease impact [13]. Mease et al. showed that patients who achieved MDA had significantly lower fatigue scores in the FACIT-F [14].

In addition to gender and disease activity, several factors have been associated with fatigue, including pain, sleep disturbances, depression, functional disability [15] as well as cultural differences in the general population [16].

In a multicenter PsA study, fatigue was the second most common complaint following pain [17]. With increasing evidence about fatigue as an essential component of disease state, it has recently been recognized as a crucial element of evaluation scales for PsA. Non-fatigue parameters (musculoskeletal disease activity, skin disease activity, pain, patient global, quality of life, physical function, systemic inflammation) are often used to evaluate disease activity in the composite index [13]. The PsA Core Domain Set developed by the Outcome Measures in Rheumatology (OMERACT) did not initially include fatigue in the inner circle. Then, this core set was updated in 2016, with the addition of fatigue

and dactylitis, making fatigue an essential element in the evaluation of PsA [18].

This study aimed to evaluate fatigue in patients with PsA in a Turkish population and its relationship with disease parameters, including functional disability, anxiety, depression, quality of life, and sought correlations with disease activity as determined by various scales.

Patients and methods

Study design

This cross-sectional clinical study is a part of the TLAR-Network (Turkish League Against Rheumatism), a multicenter registry in Turkey, with the participation of 25 rheumatology and physical medicine and rehabilitation clinics and 37 physicians from diverse regions of Turkey. TLAR-Network data were collected using a web-based system throughout the year 2018, and the study was approved by the Ethical Committee of Sakarya University Medical School (25.01.2018-42). All participating centers and physicians were informed about the study protocol and reported approval. Written informed consent was obtained from all subjects.

Patients

The TLAR-Network involved 1134 patients with PsA who met the Classification Criteria for Psoriatic Arthritis (CASPAR) [19]. Of these, 1028 patients (677 females, 351 males) whose fatigue scores (VAS-F and FACIT-F) were available were included for the analysis.

Exclusion criteria were malignancies, chronic liver/renal diseases, pregnancy, breastfeeding, coexisting rheumatic diseases, and age less than 18 years [20, 21].

Demographic features (gender, age, educational level, and marital status), body mass index (BMI), smoking status, and duration of PsA were recorded.

Laboratory measures included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and hemogram.

Outcome measures for PsA

Patient-reported outcomes

Patient global assessment (PtGA) and pain were rated with a visual analog scale (VAS) from 0 to 100 mm [22].

Functional status was assessed using the Health Assessment Questionnaire (HAQ) and Bath Ankylosing Spondylitis Functional Index (BASFI) [23, 24].

The Psoriatic Arthritis Quality of Life Questionnaire (PsAQoL) was used to evaluate quality of life [25].

The Hospital Anxiety and Depression Scale (HAD-A and HAD-D) evaluate anxiety and depression separately within a range of 0–21 scores for each section [26].

Fibromyalgia symptoms were assessed using the Fibromyalgia Rapid Screening Tool (FiRST). The cut-off value for the FiRST was 5 [27].

Physician-reported outcomes

Measurements included tender joint count (TJC) (0–68), swollen joint count (SJC) (0–66), enthesitis, and dactylitis counts. Psoriasis was evaluated with the Psoriasis Area and Severity Index (PASI) [28].

Assessment of fatigue

A visual analog scale for fatigue (VAS-F: 0–10 cm) was used to rate general fatigue experienced during the previous week [15], with 0—< 2 cm indicating absent or mild, 2—< 5 cm moderate, and 5–10 cm severe fatigue [29].

The Functional Assessment of Chronic Illness Therapy (FACIT) was first developed for patients with chronic illnesses and was then revised as FACIT-F for patients with anemia-related fatigue. It consists of 13 items, each scored with a 5-point Likert scale (0–4 points). The total score is from 0 to 52, with higher scores indicating less fatigue [30]. Although there are no cut-off points for mild, moderate, and severe fatigue, a study on cancer-related fatigue found that FACIT-F scores of 30 or less indicated clinically significant fatigue [31].

Disease activity scales

For disease activity, peripheral involvement was evaluated using the scores of Disease Activity Score-28 (DAS28), DAPSA, and Clinical DAPSA (cDAPSA), and axial involvement was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Remission was defined as a DAS28 score of ≤ 2.6, with incremental scores indicating low disease activity (> 2.6—≤ 3.2), moderate disease activity (> 3.2—≤ 5.1), and high disease activity (> 5.1) [32].

DAPSA for PsA patients was adapted from DAREA for 66/68-joint evaluation and included patient global VAS, patient pain VAS, and CRP (mg/dL) [33]. The form used without CRP is cDAPSA [34]. Remission was defined in terms of DAPSA and cDAPSA scores of ≤ 4, with higher scores indicating low disease activity (> 4—≤ 14 for DAPSA; > 4—≤ 13 for cDAPSA), moderate disease activity (> 14—≤ 28 and > 13—≤ 27), and high disease activity (> 28 and > 27).[35].

BASDAI is a disease activity scale consisting of ten questions about fatigue, pain, and morning stiffness. Scores of greater than 4 indicate active disease [36].

Patients who were rated as having MDA and VLDA were assessed using seven domains including tender joint count ≤ 1, swollen joint count ≤ 1, enthesitis count ≤ 1, PASI ≤ 1 or body surface area (BSA) ≤ 3, PtGA ≤ 20 mm, patient pain VAS ≤ 15 mm, and health assessment questionnaire (HAQ) ≤ 0.5. MDA and VLDA were defined as achievement of 5 of the seven domain cut-offs and all seven cut-offs, respectively [37, 38].

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS v22.00. Armonk, IBM Corp). Descriptive data were expressed as means, median, standard deviation, and minimum–maximum.

To analyze the effect of data from 106 missing patients whose fatigue scores were not available, the Little's test was performed to determine whether the missing data is missing completely at random (MCAR), which yielded insignificant results (Chi-squared = 4.176, $DF = 2$, Sig = 0.124). Thus, the MCAR was verified and the effect of missing data was eliminated.

The normality of the distribution of variables was evaluated using the Kolmogorov–Smirnov test. The chi-squared tests (Fischer's exact test if expected numbers were below five) were used for qualitative data. The Student's t test and Mann–Whitney U test were used to compare two groups. Kruskal–Wallis test was used to compare more than two groups where the assumption of normality was not acceptable. The Mann–Whitney U test was performed to test the significance of pairwise differences using the Bonferroni correction to adjust for multiple comparisons. Correlations between continuous variables were assessed with the Spearman's correlation coefficient, where rho values of > 0.60, 0.40–0.60, and < 0.40 indicated strong, moderate, and weak correlations, respectively. In statistical analyses, the level of significance was considered as $p < 0.05$, but when three or more groups were compared, a Bonferroni correction was made and the adjusted critical significance level was < 0.017 for three groups and < 0.008 for four groups.

Logistic regression analysis was used to determine the strength of the effect of each factor affecting fatigue, defined as a score of ≥ 2 on VAS-F. Two regression models (Model A and B) were formed for the analyses. In Model A, all variables thought to affect fatigue were included in the regression, including gender, age, educational status, disease duration, TJC, SJC, MDA (yes/no), VLDA (yes/no), DAPSA total score, BASDAI total score, BMI, HAD-A, HAD-D, HAQ, FiRST, PsAQoL, enthesitis count, VAS pain score and CRP. Due to strong intercorrelations, the

analysis included the DAPSA total score, but not cDAPSA and DAS28 scores. In Model B, the step-wise approach was used, in which the variables that did not have a statistically significant effect were not included. Confidence intervals were calculated for 95%.

Results

Patient demographics and clinical characteristics

Of 1134 patients, 1028 whose fatigue scores were available were included for the analysis. A comparison of the patients with missing data with the study group showed that the 106 (%9.3) patients with missing data were not significantly different from the study population in terms of age and disease duration ($p > 0.05$) However, female gender was more common in this group of patients with missing data ($p < 0.001$).

The mean age of the study group was 47 (SD: 12.2) years, and the mean disease duration was 6.4 (SD: 7.3) years. The demographic and clinical characteristics of PsA patients are shown in Table 1.

Table 1 Demographic and clinical characteristics of patients with PsA ($n = 1028$)

Variables	Value
Demographics	
Female gender, n (%)	677 (65.9)
Age, years, mean (SD)	47 (12.2)
BMI, kg/m^2, mean, (SD)	28.9 (4.9)
Clinical measures, mean (SD) (min–max)	
Duration of PsA, years	6.4 (7.3) (0–44)
Duration of psoriasis, years	16.3 (12) (0–60)
TJC	5.7 (8.7) (0–56)
SJC	1.4 (3.2) (0–38)
PASI	3 (4.8) (0–51.3)
Pain VAS	48.9 (24.8) (0–100)
PtGA	47.3 (24.1) (0–100)
Laboratory measures, mean (SD)	
ESR, mm/h	21.5 (15.7)
CRP, mg/dl	1.4 (1.9)
Hb, g/l	13.2 (1.6)

n number of patients, *SD* Standard deviation, *BMI* body mass index, *PsA* psoriatic arthritis, *TJC* tender joint count, *SJC* swollen joint count, *PASI* Psoriasis Area and Severity Index, *VAS* Visual Analog Scale, *PtGA* Patient Global Assessment, *ESR* Erythrocyte sedimentation Rate, *CRP* C-reactive protein, *Hb* hemoglobin

Relationships of demographic, clinical, laboratory parameters, and disease activity with fatigue

The mean VAS-F score was 5.1 (SD: 2.7), indicating absent or mild, moderate, and severe disease in 12.8%, 24.6%, and 62.5% of the patients, respectively. The mean FACIT-F score was 32.2 (SD: 10.6). Of 1028 patients, 448 (43.6%) had scores of 30 or less on the FACIT-F, indicating clinically significant fatigue.

The mean VAS-F score for women was 5.5 (SD: 2.7), as compared with 4.2 (SD: 2.7) for men ($p < 0.001$). Both the mean VAS-F and FACIT-F scores were significantly better in men than in women ($p < 0.001$).

As to the education level, primary school graduates had higher fatigue scores than those with a university degree ($p < 0.001$). Middle- and high-school graduates did not differ from other education groups in this respect. Considering marital status, divorcees had the highest fatigue levels compared with singles and married individuals ($p < 0.001$). Current smokers experienced more fatigue than ex-smokers (FACIT-F; $p = 0.02$, VAS-F; $p = 0.09$). Patients who had morning stiffness showed higher fatigue scores than those who did not ($p < 0.001$). (Table 2).

There was a moderate-to-strong correlation between the VAS-F and FACIT-F scores ($r = -0.590$, $p < 0.001$).

Of 1028 patients, 945 had peripheral involvement, and in this patient group DAS28, cDAPSA, MDA, and VLDA were evaluated. DAPSA was analyzed in 768 patients with peripheral PsA, whose CRP levels were available. In this patient group, remission rates as defined by the DAS28, DAPSA, and cDAPSA were 22.2%, 5.3%, and 8.6%, respectively. Improvements in VAS-F and FACIT-F scores were significant in patients with remission, as defined by the DAS28, DAPSA, and cDAPSA ($p < 0.001$) (Table 3). Both VAS-F and FACIT-F scores showed significant variations across the disease activity levels according to the DAS28, DAPSA, and cDAPSA ($p < 0.001$). Although the patients who were in remission had lower levels of fatigue, 51.2% of patients with DAPSA remission had clinically significant fatigue, being moderate in 26.8%, and severe in 10%.

VAS-F showed a moderate correlation with DAS28 ($r = 0.402$, $p < 0.001$), DAPSA ($r = 0.532$, $p < 0.001$), and cDAPSA ($r = 0.565$, $p < 0.001$). FACIT-F showed weak inverse correlations with DAS28 ($r = -0.285$, $p < 0.001$) and DAPSA ($r = -0.373$, $p < 0.001$) and a moderate inverse correlation with cDAPSA ($r = -0.412$, $p < 0.001$).

The rates of MDA and VLDA were 15.3% and 2.6%, respectively. Patients who achieved MDA and VLDA had beter fatigue scores than non-MDA and non-VLDA patients ($p < 0.001$) (Table 3).

The mean BASDAI score was 4.3 (SD: 2.04), with 493 (53.7%) patients having active disease. Inactive disease state based on the BASDAI score was associated

Table 2 Levels of fatigue as assessed by VAS-F and FACIT-F scores corresponding to demographic and clinical characteristics ($n = 1028$)

Variables	n (%)	VAS-F mean (SD)	p	FACIT-F mean (SD)	p
Gender					
Male	351 (24.1)	4.2 (2.7)	< 0.001*	35.1 (9.7)	< 0.001*
Female	677 (65.9)	5.5 (2.7)		30.6 (10.7)	
Morning stiffness					
Yes	654 (63.6)	5.6 (2.7)	< 0.001*	30.3 (10.8)	< 0.001*
No	374 (36.4)	4.2 (2.6)		35.3 (9.3)	
		VAS-F median (min–max)	p	FACIT-F median (min–max)	p
Educational status			< 0.001**		< 0.001**
Primary school	504 (49)	5 (0–10)		31 (1–52)	
Middle school	143 (13.9)	5 (0–10)		34 (3–52)	
High school	227 (22.1)	5 (0–10)		33 (5–52)	
University	154 (15)	4 (0–10)		36 (9–52)	
Married status			< 0.001**		0.007**
Single	101 (9.8)	4 (0–10)		35 (5–51)	
Married	858 (83.5)	5 (0–10)		33 (1–52)	
Widow	49 (4.8)	5 (0–10)		30 (13–50)	
Divorced	20 (1.9)	8 (3–10)		26 (7–40)	
Smoking status			0.026**		0.008**
Never	595 (57.9)	5 (0–10)		33 (4–52)	
Ex-smoker	166 (16.1)	5 (0–10)		36 (5–52)	
Current smoker	267 (26)	5 (0–10)		31 (1–51)	

p value: *Mann–Whitney U test or **Kruskall–Wallis test

n Number of patients, SD standard deviation, VAS-F Visual Analog Scale-Fatigue, FACIT-F Functional Assessment of Chronic İllness Therapy-Fatigue

with significantly improved VAS-F and FACIT-F scores ($p < 0.001$).

Correlations of disease parameters and patient-reported outcomes with fatigue

The correlation coefficients for fatigue and various clinical variables are shown in Table 4. VAS-F scores showed a strong correlation with BASDAI, moderate correlations with BASFI, PsAQoL, HAD-A, FiRST scores, pain VAS and PtGA, and weak correlations with HAQ, HAD-D score, TJC, SJC, and enthesitis count. VAS-F and FACIT-F scores showed no correlations with age, onset of symptoms, BMI, PASI, CRP, ESR, and the hemoglobin level (Table 4).

According to the FiRST score, 255 patients (24.8%) had fibromyalgia. FACIT-F and VAS-F scores were significantly higher in patients with fibromyalgia ($p < 0.001$).

Predictors of fatigue

All variables thought to affect fatigue were included in the regression analysis. In Model A, VLDA (odds ratio [OR] 0.161, [95% confidence interval (CI) 0.028; 0.919]), BAS-DAI (OR 1.532; 95% CI 1.150; 2.041), FiRST score (OR

1.408; 95% CI 1.088; 1.822), educational level (for middle school, OR 0.235; 95% CI 0.094; 0.590; for high school, OR 0.228; 95% CI 0.102; 0.513), and HAD-A (OR 1.135; 95% CI 1.020; 1.263) were found to be independent factors (Table 5).

In Model B, in addition to independent factors found in Model A, the following variables were found to have independent relationship with fatigue; VLDA (OR 0.185, [95% CI 0.040; 0.844]), BASDAI (OR 1.544 [95% CI 1.236; 1.929]), FİRST (OR 1.475 [95%, CI 1.167; 1.864), education (middle school) (OR 0.270 [95% CI 0.113; 0.644), education level (high school) (OR 0.272 [95% CI 0.128; 0.574), HAD-A (OR 1.154 [95% CI 1.044; 1.275), and BMI (OR 0.951 [95% CI 0.920; 0.983]) (Table 6).

Discussion

This large population-based study demonstrated the high incidence and importance of fatigue in patients with PsA. Approximately 85% of PsA patients experienced moderate-to-severe fatigue, this rate being higher than that seen in the healthy population, but similar to those reported for patients with RA [39]. Most patient-related and demographic

Table 3 Comparison of disease activity levels as defined by VAS-F and FACIT-F scores

	n (%)	VAS-F median (min–max)	p	FACIT-F median (min–max)	p	Bonferroni's correction VAS-F and FACIT-F
DAS28 (n=945)			<0.001*		<0.001*	REM vs. Low DA; p=0.002, 0.051
Remission	210 (22.2)	4 (0–10)		36 (8–52)		REM vs. Moderate DA; p<0.001, <0.001
Low disease activity	182 (19.3)	5 (0–10)		33 (8–52)		REM vs. High DA; p<0.001, <0.001
Moderate disease activity	459 (48.6)	6 (0–10)		31 (2–52)		Low DA vs. Moderate DA; p<0.001, =0.038
High disease activity	91 (9.6)	8 (1–10)		23 (1–52)		Low DA vs. High DA; p<0.001, <0.001 Moderate DA vs High DA; p<0.001, <0.001
DAPSA (n=768)			<0.001*		<0.001*	REM vs. Low DA; p<0.001, =0.019
Remission	41 (5.3)	2 (0–8)		40 (18–52)		REM vs. Moderate DA; p<0.001, <0.001
Low disease activity	273 (35.5)	4 (0–10)		35 (11–52)		REM vs. High DA; p<0.001, <0.001
Moderate disease activity	318 (41.4)	6 (0–10)		30 (5–52)		Low DA vs. Moderate DA; p<0.001, <0.001
High disease activity	136 (17.7)	8 (0–10)		26 (2–52)		Low DA vs. High DA; p<0.001, <0.001 Moderate DA vs High DA; p<0.001, <0.001
cDAPSA (n=945)			<0.001*		<0.001*	REM vs. Low DA; p<0.001, <0.001
Remission	81 (8.6)	1 (0–8)		40 (18–52)		REM vs. Moderate DA; p<0.001, <0.001
Low disease activity	394 (41.7)	4.5 (0–10)		35 (11–52)		REM vs. High DA; p<0.001, <0.001
Moderate disease activity	329 (34.8)	6 (0–10)		29 (2–52)		Low DA vs. Moderate DA; p<0.001, <0.001
High disease activity	141 (14.9)	8 (1–10)		23 (1–52)		Low DA vs. High DA; p<0.001, <0.001 Moderate DA vs High DA; p<0.001, <0.001
MDA (n=945)						
Yes	145 (15.3)	3 (0–10)	<0.001*	37 (8–52)	<0.001*	
No	800 (84.7)	5 (0–10)		31 (2–52)		
VLDA (n=945)						
Yes	25 (2.6)	1 (0–10)	<0.001*	41 (18–52)	<0.001*	
No	920 (97.4)	5 (0–10)		32 (1–52)		
BASDAI (n=917)						
Active	493 (53.7)	7 (0–10)	<0.001*	27 (1–52)	<0.001*	
Not active	424 (46.3)	4 (0–10)		36 (12–52)		

p value: *Kruskall–Wallis test

VAS-F Visual analog scale-Fatigue, *FACIT-F* Functional Assessment of Chronic İllness Therapy-Fatigue, *DAS28* Disease Activity Score 28, *DAPSA* Disease Activity Index for Psoriatic Arthritis, *cDAPSA* Clinical DAPSA, *MDA* Minimal Disease Activity, *VLDA* Very Low Disease Activity, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *REM* Remission, *DA* Disease activity

characteristics (female gender, low educational status, divorced status, current smoking) and disease-related clinical factors (pain, morning stiffness, axial and peripheral disease activity, physical disability, poor quality of life, anxiety, depression, and fibromyalgia symptoms) were associated with fatigue, while age, acute phase reactant levels, severity of psoriasis, and hemoglobin levels were not. After adjustment with a step-wise approach, VLDA, BASDAI score, educational level, anxiety, fibromyalgia, and BMI were found to be independent variables associated with fatigue.

Due to the inflammatory process, fatigue is a prevalent and disabling problem in almost all rheumatic diseases. Being is a subjective symptom, fatigue is challenging to compare among rheumatic diseases, and the use of different instruments to evaluate fatigue may further complicate the problem. In a study evaluating several rheumatic diseases with a single score, severe fatigue was mostly seen with fibromyalgia, followed by Sjogren and PsA. As ankylosing spondylitis (AS) and PsA are considered

within the classification of spondyloarthropathies, both AS and PsA are associated with lower levels of fatigue. Also, the coexistence of multiple rheumatic diseases is another factor increasing the severity of fatigue [40]. Several variables appear to predict the severity of inflammation-related fatigue in rheumatic diseases, such as disease activity, depression, pain, anxiety, and functional capacity [6]. A summary of several PsA studies evaluating fatigue is presented in Table 7.

The present study with PsA patients showed that reduced disease activity was accompanied by better fatigue scores. The most influential factor for fatigue was the disease activity, and decreased levels of fatigue was determined in 81.5% of patients with VLDA. Previous studies assessed fatigue in relation to disease activity as determined by the DAS28 and DAPSA [41]. However, recently, VLDA and especially MDA have been integrategd into the instruments to evaluate PsA activity and to be used for treatment targets [37]. The present study showed that fatigue was associated with

Table 4 Correlations between fatigue scales and patient characteristics (*n* = 1028)

Variable	Correlations, rho (*p*)	
	VAS-F	FACIT-F
Age, years	0.023 (0.467)	− 0.109 (< 0.001)
BMI, kg/m^2	0.101 (< 0.001)	− 0.111 (< 0.001)
Onset of symptoms, years	− 0.005 (0.865)	− 0.007 (0.822)
Pain VAS	0.550 (< 0.001)	− 0.395 (< 0.001)
PtGA	0.590 (< 0.001)	− 0.415 (< 0.001)
TJC	0.349 (< 0.001)	− 0.284 (< 0.001)
SJC	0.200 (< 0.001)	− 0.132 (< 0.001)
PASI	0.067 (0.032)	− 0.051 (0.105)
Enthesitis counts	0.235 (< 0.001)	− 0.220 (< 0.001)
BASDAI	0.649 (< 0.001)	− 0.508 (< 0.001)
HAQ	0.394 (< 0.001)	− 0.519 (< 0.001)
BASFI	0.422 (< 0.001)	− 0.368 (< 0.001)
PsAQoL	0.536 (< 0.001)	− 0.678 (< 0.001)
HAD-D	0.360 (< 0.001)	− 0.624 (< 0.001)
HAD-A	0.427 (< 0.001)	− 0.646 (< 0.001)
FİRST	0.494 (< 0.001)	− 0.628 (< 0.001)
CRP mg/dl	− 0.036 (0.298)	− 0.020 (0.561)
ESR,h	0.083 (0.007)	− 0.062 (0.046)
Hb, g/l	− 0.044 (0.225)	0.055 (0.132)

Rho *Spearman's coefficient

VAS-F Visual analog scale-Fatigue, *FACIT-F* Functional Assessment of Chronic İllness Therapy-Fatigue, *BMI* Body mass index, *VAS* Visual analog scale, *PtGA* Patient Global Assessment, *TJC* Tender joint count, *SJC* Swollen joint count, *PASI* Psoriasis Area and Severity Index, *BASDAI* Bath Ankylosing Disease Activity Index, *HAQ* Health Assessment Questionnaire, *BASFI* Bath Anklosing Spondylitis Functional Index, *PsAQoL* Psoriatic Arthritis Quality of Life, *HAD* (Hospital Anxiety and Depression Scale), *FİRST* Fibromyalgia Rapid Screening Tool, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *Hb* hemoglobin

remission as determined by the DAS28, DAPSA, cDAPSA as well as with MDA and VLDA.

Gorlier et al. reported similar correlations between fatigue and disease activity instruments [12]. In contrast, in a study conducted in 13 countries, in which disease activity was assessed with the DAS28, fatigue was found to be associated with skin involvement, the number of tender joints, and low educational level, but not with disease activity. In our study, although the level of education was also associated with fatigue, all disease activity instruments (DAS28, DAPSA, cDAPSA) were correlated with fatigue and patients with MDA and VLDA had significantly lower levels of fatigue. We evaluated the severity of psoriasis with PASI, and found no relationship between PASI and fatigue. In a previous study, psoriasis was scored with affected body surface area, and patients were divided into two groups as having > 5% and ≤ 5% according to affected body surface area [41].

Discrepant results may be attributable to the use of different psoriasis severity measures.

Surprisingly, although fatigue was correlated with disease activity, half of the patients continued to have fatigue even if they were in remission. Persistence of fatigue was also shown in PsA patients whose disease activity had been controlled with anti-TNF treatment [46]. Some RA patients also experienced fatigue, despite a well-controlled disease activity. A possible reason for persisting fatigue could be elevated levels of inflammatory cytokines in RA, such as IL-1, IL-6, and TNF alpha. These cytokines could pass the blood–brain barrier to activate microglia, leading to inflammation and consequently to fatigue [47]. Another reason for refractory fatigue may be central sensitization, in which case fatigue is felt without pain and inflammation [48]. Although central sensitization is common in rheumatic diseases, fibromyalgia might have the closest relationship with fatigue. Fibromyalgia is characterized by chronic widespread nonarticular pain that is thought to be secondary to central sensitization. Fibromyalgia and fatigue have been shown to be significantly more common in patients with PsA. Magrey et al. recommended that all PsA patients with symptoms of chronic and persistent pain and fatigue be assessed for fibromyalgia [49].

Fatigue was particularly associated with patient-reported complaints such as pain, morning stiffness, anxiety, decreased quality of life, and symptoms of fibromyalgia rather than with objective measures such as swollen joint count and acute phase response. Among these, independent factors were quality of life, anxiety, pain, and fibromyalgia symptoms. Our findings substantiate previous studies reporting fibromyalgia to be associated with increased levels of fatigue [50] along with anxiety, depression, and quality of life [4]. To evaluate these frequent conditions that have a close relationship with each other, patients should also be assessed carefully and multidimensionally.

In both healthy and RA populations, obesity is a common problem [51]. Although we did not classify patients as obese and non-obese, each unit increase in BMI reduced fatigue by 4.9%. This paradoxical finding may be due to inactivity. Obese patients may feel less fatigue because of inactive daily life. On the other hand, the mean age of the study group was 47 years, young enough to allow active daily life, hence a higher level of fatigue. Therefore, the relationship between BMI and fatigue may need further clarification.

Our findings are consistent with previous studies that emphasized female gender, pain, physical disability, and psychological distress as strong correlates of fatigue in PsA patients [5]. Tobin et al. found no relationship between fatigue and PASI, tender joint, and swollen joint counts, and reported that female patients were more likely to have higher levels of fatigue than male patients [45].

Table 5 Logistic regression analysis for factors associated with fatigue, Model-A

	B	SE	X^2	Exp (B)	Model A %95 CI		p
					Lower	Upper	
VLDA	− 1.828	0.889	4.223	0.161	0.028	0.919	0.040
BASDAI	0.426	0.146	8.223	1.532	1.150	2.041	0.004
FiRST	0.342	0.131	6.776	1.408	1.088	1.822	0.009
Education							
Primary school-Reference group							
Middle school	− 1.448	0.470	9.504	0.235	0.094	0.590	0.002
High school and upper	− 1.477	0.413	12.800	0.228	0.102	0.513	< 0.001
HAD-A	0.126	0.055	5.369	1.135	1.020	1.263	0.021
BMI	− 0.50	0.029	2.965	0.952	0.899	1.007	0.085
TJC	0.170	0.1	2.900	1.185	0.975	1.442	0.089
Gender (Female)	− 0.480	0.339	2.009	0.619	0.319	1.202	0.156
PsAQoL	0.048	0.050	0.934	1.049	0.952	1.157	0.334
Age	0.000	0.015	0.000	1.000	0.971	1.031	0.986
VAS pain	0.016	0.016	0.965	1.016	0.984	1.050	0.326
Duration of disease	0.002	0.022	0.005	1.002	0.959	1.046	0.941
DAPSA	− 0.117	0.080	2.153	0.889	0.760	1.040	0.142
MDA	0.001	0.447	0.000	1.001	0.417	2.404	0.997
HAQ	0.721	0.678	1.132	2.056	0.545	7.762	0.287
SJC	0.033	0.115	0.083	1.034	0.824	1.296	0.773
Enthesitis count	0.035	0.071	0.244	1.036	0.901	1.190	0.622
CRP	0.006	0.015	0.183	1.006	0.978	1.035	0.669

Nagelkerke Model A: 0.831

VLDA Very low disease activity, *BASDAI* Bath Ankylosing Disease Activity Index, *FiRST* Fibromyalgia Rapid Screening Tool, HAD (HAD-A and HAD-D) Hospital Anxiety and Depression Scale, *BMI* body mass index, *TJC* Tender joint count, *SJC* Swollen joint count, *PsAQoL* Psoriatic arthritis quality of life, *VAS* visual analog scale, *DAPSA* Disease Activity Index for Psoriatic Arthritis, *MDA* minimal disease activity, *HAQ* Health Assessment Questionnaire, *CRP* C-reactive protein

Table 6 Logistic regression analysis for factors associated with fatigue, Model-B

	B	SE	X^2	Exp (B)	Model B %95 CI		p
					Lower	Upper	
VLDA	− 1.690	0.775	4.750	0.185	0.040	0.844	0.029
BASDAI	0.434	0.114	14.601	1.544	1.236	1.929	< 0.001
FiRST	0.389	0.119	10.584	1.475	1.167	1.864	0.001
Education							
Primary school-Reference group Middle school	− 1.311	0.444	8.715	0.270	0.113	0.644	0.003
High school and upper	− 1.303	0.382	11.646	0.272	0.128	0.574	0.001
HAD-A	0.143	0.051	7.901	1.154	1.044	1.275	0.005
BMI	− 0.050	0.017	8.840	0.951	0.920	0.983	0.003

Nagelkerke Model B: 0.824

VLDA Very low disease activity, *BASDAI* Bath Ankylosing Disease Activity Index, *FiRST* Fibromyalgia Rapid Screening Tool, *HAD* (HAD-A and HAD-D) Hospital Anxiety and Depression Scale, *BMI* Body mass index

Table 7 Comparison of the PsA studies evaluating fatigue

Study/cohort	Number of participants	Fatigue instrument	Prevalence of fatigue	Parameters associated with fatigue
Husted JA, 2009, [5]	499	Modified fatigue severity scale (mFSS)	49.5% moderate fatigue 28.7% severe fatigue	Pain, female gender, functional disability, ever use of methotrexate, psychological distress
Gudu T, 2016, [41]	246	Numeric rating scale (NRS 0–10)	44.7% high level of fatigue	Female gender, current skin psoriasis, tender joint count, enthesitis, education level
Claudio C, 2017, [4]	101	FACIT-F	Median FACIT-F score: 42 (0–52)	PASI, HAQ, HAD-A, HAD-D, PDI
Skougaard M, 2019, [42]	1062	VAS-F	51% moderate to severe fatigue	Inflammation, disease duration, chronic pain
Janice A, 2010, [43]	390	Modified fatigue severity scale (mFSS)	51.5% low, 22.3% moderate, 26.2% severe fatigue	HAQ, pain, psychological distress, fibromyalgia, hypertension
Kalyoncu U, 2017, [11]	750	Fatigue VAS	Mean Fatigue VAS 46.2 (26.2)	Female gender
Minnock P, 2010, [44]	41	Numeric rating scale (NRS 0–10)	Mean Fatigue NRS 5.6 (SD:2.3)	Global health, HAQ, pain
Tobin AM, 2016, [45]	100	Numeric rating scale (NRS 0–10)	42% mild, 18% moderate, 31% severe	Female, HAD-D

PASI Psoriasis Area and Severity Index, *HAQ* Health Assessment Questionnaire, *HAD* (HAD-A and HAD-D) Hospital Anxiety and Depression Scale, *PDI* Psoriasis Disability Index

Hewlett et al. proposed a conceptual model for RA-related fatigue, with interactions across three factors, namely, disease processes (inflammation, drugs, joint injury, and disability), cognitive and behavioral factors (illness beliefs, stress, anxiety, and depression), and personal life issues (work, health, environment, and social support). In this dynamic model, fatigue, pain, and disability act together, increasing the severity of each component; hence, interventions directed at improving pain and disability may reduce fatigue [52]. Since the introduction of this conceptual model, fatigue and associated factors have been analyzed in several studies, and the need for a holistic approach became apparent. In patients with PsA, besides an extensive range of features of the skin, joints, and spinal involvement, extra-articular contribution to the disease state is very common, eventually affecting the patients' quality of life and pain. Fatigue is prevalent and is closely associated with patient-related outcomes. Therefore, control of inflammation per se may not be adequate. Preferably all components of the disease, particularly patient-related factors, should be incorporated into the holistic approach, as recommended by the EULAR. For example, pain management in patients with inflammatory arthritis and osteoarthritis should include several factors, including biological, psychological, and social factors [53]. Fatigue should be evaluated and treated appropriately in all PsA patients before it becomes a widespread symptom and complicated by other diseases and patient-related factors.

Because fatigue is a subjective symptom and feeling, assessment mainly relies on patient-reported measures.

Moreover, there is no agreement as to which tool is more convenient to evaluate fatigue in PsA. Several scales were used in previous studies to assess fatigue, including the VAS-F and Fatigue Severity Scale (FSS), Multidimensional Assessment of Fatigue (MAF), and Fatigue Impact Scale [2]. Among them, the performance of the single item VAS was found to be equal to or better than more comprehensive scales and suitable for routine use [54]. In the present study, we evaluated fatigue using two scales (VAS-F and FACIT-F) and found a close agreement between the two scales and compatibility with other parameters. However, VAS-F was more correlated with disease activity scores than FACIT-F.

There are two major limitations to this study. First, data retrieved from the registry were not complete in terms of fatigue scores and DAPSA. Some patients were not accessible for VAS-F or FACIT-F. In large registries, some data may be missing because patients complete some forms themselves. In addition to fatigue scores, DAPSA scores could not be calculated in all patients due to the lack of CRP data. A second limitation is the absence of data on comorbidities and medications of the patients. Some authors recommended that comorbidities and drugs administered to the patients be taken into consideration. Husted et al. reported hypertension as a common comorbidity among PsA patients, and patients receiving methotrexate had higher levels of fatigue [5].

Conclusion

Our findings emphasize the importance of fatigue as a measure of disease impact. Fatigue was a common accompaniment to PsA and disease activity was the most substantial predictor, with fatigue being less in patients in remission, MDA, and VLDA. Other correlates of fatigue were female gender, educational level, anxiety, quality of life, function, pain, and fibromyalgia. Due to its importance and implications, fatigue should be considered when rating the disease impact in PsA.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was taken from the Sakarya University Ethics Committee on 25.01.2018. The protocol number was 42. The protocol for the research project has been approved by the relevant Ethics Committee and conducted in accordance with the Helsinki Declaration.

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

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