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ORIGINAL ARTICLE

# Depression is the most significant independent predictor of fatigue in patients with primary Sjögren's syndrome

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***ABSTRACT***

**Objectives:** The study aimed to evaluate the level of fatigue and the relationship between mood, pain, fibromyalgia, insomnia, disease activity, and dryness with fatigue in primary Sjögren's syndrome (PSS) patients.

**Patients and methods:** In this case-control study, the participants were recruited between January 2021 and July 2021. Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F), pain DETECT questionnaire, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Insomnia Severity Index (ISI) were administered to 50 PSS patients (48 females, 2 males; mean age: 48.9±10.8 years; range, 29 to 71 years) and 60 healthy controls (HCs; 57 females, 3 males; mean age: 49.8±8.4 years; range, 32 to 72 years). In addition, EULAR Sjögren's syndrome disease activity index (ESSPRI), EULAR Sjögren's Syndrome Patient Reported Index (ESSDAI), pain thresholds, Schirmer tests, and whole unstimulated salivary flow rate measurements were determined in PSS patients. Independent predictors of fatigue (fatigue subscale scores <30.5) were investigated by logistic regression analysis.

**Results:** The frequency of fatigue in PSS patients and HCs was 54.0% and 8.3%, respectively. The rates of mood disturbance (BDI ≥11) in PSS patients with and without fatigue were 70.4% and 13.1%, respectively. BDI (Rho=-0.804), BAI (Rho=-0.586), ISI (Rho=-0.483), and ESSDAI (Rho=-0.345) were negatively correlated with the fatigue subscale score. Depression [Odds ratio (OR): 1.214, confidence interval (CI): 1.007-1.463], fibromyalgia (OR: 21.674, CI: 1.470-319.469), disease activity (OR: 1.440; CI: 1.005-2.065), and insomnia (OR: 1.223, CI: 1.003-1.4922) were identified as independent predictors of fatigue in PSS patients. It was determined that BD alone could predict fatigue by 84% in PSS patients.

**Conclusion:** Depression can be a prominent predictor of fatigue in PSS patients. There is a need for studies evaluating the effect of antidepressant treatment approaches on fatigue accompanied by mood disturbance in PSS patients.

***Keywords:*** Depression, fatigue, fibromyalgia, Sjögren's syndrome.

Primary Sjögren's syndrome (PSS) is a chronic inflammatory autoimmune disease of unknown etiology, characterized by diminished salivary gland function. Apart from glandular involvement in PSS, fatigue, which is the most common extraglandular finding, can be seen in more than half of PSS patients.[1] Studies in the literature on predictors of fatigue in PSS provide evidence that emotional state, fibromyalgia, pain, sleep disturbance, and dryness are associated with fatigue.[2-6] The associations of disease activity and inflammation with fatigue in PSS patients are somewhat complex. Evidence to date shows a limited association between disease activity

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and fatigue in PSS patients, and in addition, B cell-acting drugs, such as rituximab, also have limited beneficial effects on fatigue.[7-10] The fact that proinflammatory cytokines were found to be lower in PSS patients with fatigue is also proof of the complexity of the relationship between inflammation and fatigue.[1] Since variables such as fibromyalgia, pain, and emotional state may be interrelated and some other variables have a complex relationship with fatigue, it is very difficult to have information about the predictor of fatigue in PSS that is the independent or strongest predictor without evaluating the effect of all predictors simultaneously. There is a lack of studies in the literature in which all possible predictors related to fatigue in PSS were evaluated and the independent effects of predictors on fatigue were investigated. Due to the lack of information on the etiology and pathophysiology of fatigue in PSS, there are currently no established guidelines that can guide clinicians on how to fight against fatigue in PSS.

In this study, we aimed to compare the level of fatigue, as well as the level of the predictors of fatigue, including mood, pain, fibromyalgia, and insomnia, in PSS patients and healthy individuals and evaluate the association of fatigue with all predictors of fatigue and PSS-related parameters, such as disease activity and dryness.

## PATIENTS AND METHODS

In the case-control study, the participants were recruited between January 2021 and July 2021. Patients diagnosed with PSS according to the 2016 The American College of Rheumatology (ACR)/The European Alliance of Associations for Rheumatology (EULAR) classification criteria and who were being followed up by the Rheumatology Outpatient Clinic of the University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital Hospital were included in the study as the patient group, and relatives of the hospital employees matched by age and sex with the PSS patients were included as healthy controls (HCs).[11] Adults over the age of 18 were included in the study. The exclusion criteria were as follows: being pregnant, having cancer, multiple sclerosis, adrenal insufficiency, chronic obstructive pulmonary disease, heart failure, chronic kidney failure, hypothyroidism, and a hemoglobin level <11 mg/dL in females and <12 mg/dL in males. Consequently, 50 PSS patients (48 females, 2 males; mean age: 48.9±10.8 years; range, 29 to 71 years) and 60 HCs (57 females, 3 males; mean age: 49.8±8.4 years; range, 29 to 71 years) were included in the study.

A detailed physical examination of all participants was performed, and previous laboratory test results of them were checked from the electronic archive. The time elapsed after diagnosis, minor salivary gland pathology results, and ANA, anti-SSA, and anti-SSB autoantibody results of PSS patients were recorded from the archived patient charts.

The fatigue level of the participants was evaluated with the Turkish and licensed form of the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) questionnaire.[12,13] This questionnaire evaluates fatigue under five subscales consisting of physical well-being (PWB), social/familial well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and the fatigue subscale (FS). The answers given to the questions are not at all (0), a little bit (1), somewhat (2), quite a bit (3), and very much (4). The total FACIT score is obtained by summing the total scores of all subscales; the higher the score, the lower the fatigue level.

The pain DETECT questionnaire (PDQ) is a questionnaire that aims to question the severity and character of pain in individuals and to determine the presence of neuropathic pain component.[14] In this questionnaire, participants rate seven sensory symptoms that may be present in the pain area, including paresthesia, mechanical allodynia, spontaneous pain attacks, thermal hyperalgesia, numbness, and pressure hyperalgesia, on a scale of 0 to 5 (0=nothing, 5=severe). A PDQ score >18 points indicates the presence of a neuropathic pain component with a high probability (>90%). The Turkish version of the PDQ was used in this study.[15]

In this study, the Turkish version of the Beck Depression Inventory (BDI) was used to evaluate the depression level of the participants.[16,17] In BDI, the depression level of the participants is based

on 21 questions that allow grading the severity of depression between 0 and 3 points for each question. A total score of ≥11 indicates a range from mild mood disorder to extreme depression. The Turkish version of the Beck Anxiety Inventory (BAI) was used to assess the anxiety status of the participants.[18,19] In this questionnaire, the level of anxiety is evaluated over 21 questions that can be answered between 0 and 3 (0=none, 1=mild, 2=moderate, 3=severe). A total score of ≥22 indicates clinically significant anxiety, including moderate and severe anxiety.

The Turkish version of the Insomnia Severity Index (ISI) was used to evaluate the insomnia level of the participants.[20,21] With this inventory, the participants were asked to answer their insomnia levels under seven items according to a 5-point Likert scale. These items are *(i)* the level of difficulty falling asleep and staying asleep, *(ii)* waking up too early, *(iii)* dissatisfaction with insomnia, *(iv)* awareness by others of the negative effects of sleep disturbance on daily life, and *(v)* the influence level due to existing sleep disorders. A total ISI score >14 points includes moderate and severe insomnia, indicating clinically significant insomnia. FACIT-F, BAI, and ISI do not have validation studies in the native language.

In this study, a manual dolorimeter (Baseline® Dolorimeters, NY, USA) was used to evaluate pain thresholds (PTs). The PT was evaluated by the same investigator by measuring it from the midpoint of the trapezius muscle on both sides. Pounds were used as the pressure unit when measuring the PT with the dolorimeter, and pressure was applied by the investigator at a constant rate of 1 Newton/sec until the patient expressed pain. Each measurement was carried out three times, and the mean of the three measurements was recorded as PT.

The presence of fibromyalgia was investigated according to the Analgesic, Anesthetic, and ACTTION (Addiction Clinical Trial Translations Innovations Opportunities and Networks)-APS (American Pain Society) Pain Taxonomy criteria.[22] According to this criteria, nine painful body sites were defined (head, left arm, right arm, chest, abdomen, upper back and spine, lower back and spine including buttocks, left leg, and right leg). Those with at least three months of duration, at least six painful body sites, and accompanying sleep disorder or fatigue were classified as those with fibromyalgia.

Schirmer I and whole unstimulated salivary flow rate (WUSFR) tests were used to evaluate the severity of dryness in PSS patients. In the Schirmer I test, the wetting amount of the filter paper in millimeters in 5 min was measured from both the right and left eyes. The amount of saliva in the WUSFR test was determined by PSS patients collecting their saliva for 15 min

**Table 1.** Characteristics and laboratory results in patients with PSS

| | PSS patients (n=50) | | | |
|---|---|---|---|---|
| | n | % | Mean±SD | Median |
| Age (year) | | | 48.9±10.8 | 47 |
| Disease duration (year) | | | 3.5±1.4 | 4.0 |
| Schirmer (mm) | | | | |
| Right | | | 9.4±7.7 | 7.5 |
| Left | | | 9.7±7.5 | 8.0 |
| WUSFR (mL) | | | 0.9±1.0 | 0.8 |
| ESSDAI | | | 3.9±1.8 | 4.0 |
| ESSPRI mean | | | 6.6±1.7 | 7.0 |
| ESSPRI fatigue | | | 6.9±2.1 | 8.0 |
| Laboratory | | | | |
| GFR (mL/m) | | | 98.2±16.0 | 100.0 |
| CK (U/L) | | | 73.4±23.0 | 72.0 |
| Hemoglobin (gr/dL) | | | 12.6±1.4 | 12.5 |
| Lymphocyte ($10^3$/mL) | | | 2.0±0.8 | 1.8 |
| Neutrophil ($10^3$/mL) | | | 3.4±1.3 | 3.2 |
| Thrombocyte (mcL) | | | 280.6±65.7 | 275.0 |
| ESR (mm/h) | | | 29.7±17.3 | 22.5 |
| IgG (g/L) | | | 15.3±6.5 | 15.0 |
| C3 (g/L) | | | 1.2±0.2 | 1.2 |
| C4 (g/L) | | | 0.2±0.1 | 0.2 |
| Frequency | | | | |
| Female | 48 | 96 | | |
| Autoantibodies, positive | | | | |
| ANA | 44 | 88 | | |
| SSA | 38 | 76 | | |
| SSB | 18 | 36 | | |
| MSGB | | | | |
| Grade 0-2 | 8 | 16 | | |
| Grade 3 | 9 | 18 | | |
| Grade 4 | 16 | 32 | | |
| Insufficient material | 1 | 2 | | |
| Not performed | 16 | 32 | | |

PSS: Primary Sjögren's syndrome; SD: Standard deviation; WUSFR: Whole unstimulated salivary flow rate; ESSDAI: EULAR Sjögren's syndrome disease activity index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; GFR: Glomerular filtration rate; CK: Creatinine kinase; ESR: Erythrocyte sedimentation rate; ANA: Antinuclear antibody; SSA: Sjögren's syndrome-related antigen A; SSB: Sjögren's syndrome-related antigen B; MSGB: minor salivary gland biopsy.

in a measuring cup with a modular wide-mouth funnel on it.

Several procedures were performed on PSS patients to detect the disease activity as assessed by EULAR Sjögren's syndrome disease activity index (ESSDAI) in PSS patients. Plasma samples were taken for routine complete blood count, biochemical tests, C3, C4, immunoglobulin G (IgG), protein electrophoresis, C-reactive protein (CRP), and erythrocyte sedimentation rate tests. Posteroanterior chest X-rays were taken, and if there was any doubt about any pathological finding on radiographs, thorax computed tomography was performed. When pathological findings were detected in neurological examination, patients were managed according to clinical routine algorithms. In addition, PSS patients were evaluated with EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) to determine self-reported disease activity. In this patient-reported index, PSS patients were asked to rate their dryness, fatigue, and pain levels on a numerated rating scale out of 10. The ESSPRI score was determined based on the average of all three questions.

### Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). When comparing the continuous data between the two groups, Student's t-test was used if there was a normal distribution, and the Mann-Whitney U test was used if there was no normal distribution. The chi-square or Pearson chi-square test was used to compare categorical data. To determine whether there was fatigue in PSS patients, the cut-off value according to the FS score was accepted as 30.5. This cut-off value was the FS score with the highest specificity plus

**Tablo 2.** The comparison of FACIT-F, PDQ, BDI, BAI, and ISI results and PTs, frequency of fibromyalgia, and self-reported fatigue in PSS patients and HCs

| | HCs (n=60) | | | | PSS patients (n=50) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | Median | n | % | Mean±SD | Median | *p* |
| FACIT-F score | | | 125.2±19.9 | 121.0 | | | 100.7±24.4 | 97.5 | **<0.001** |
| PWB | | | 22.4±3.9 | 22.0 | | | 17.9±4.9 | 17.0 | **<0.001** |
| SWB | | | 22.1±4.3 | 21.0 | | | 18.0±5.7 | 21.0 | **0.001** |
| EWB | | | 19.8±3.4 | 20.0 | | | 16.5±4.3 | 16.5 | **<0.001** |
| FWB | | | 20.7±4.2 | 20.5 | | | 17.3±4.2 | 18.0 | **<0.001** |
| FS | | | 41.2±7.8 | 42.5 | | | 31.0±11.3 | 30.0 | **<0.001** |
| PDQ | | | 4.7±4.2 | 5.0 | | | 8.2±6.9 | 7.5 | **0.001** |
| BDI | | | 6.8±5.2 | 6.0 | | | 10.2±8.1 | 8.5 | **0.013** |
| BAI | | | 5.6±4.3 | 4.0 | | | 11.5±8.3 | 10.0 | **<0.001** |
| ISI | | | 5.8±4.4 | 5.0 | | | 9.6±6.0 | 8.0 | **<0.001** |
| NPBS | | | 2.0±2.0 | 1.0 | | | 4.1±2.6 | 4.0 | **<0.001** |
| Pain thresholds | | | | | | | | | |
| Right | | | 8.9±3.6 | 9.0 | | | 9.3±3.4 | 9.0 | 0.371 |
| Left | | | 9.5±3.2 | 10.0 | | | 9.2±3.7 | 9.3 | 0.070 |
| Frequency | | | | | | | | | |
| Fatigue* | 23 | 38.3 | | | 33 | 66.0 | | | **0.003** |
| FS score <30.5 | 5 | 8.3 | | | 27 | 54.0 | | | **<0.001** |
| NP (PDQ >18)† | 2 | 3.3 | | | 5 | 10.0 | | | 0.242 |
| NPBS ≥6 | 7 | 11.7 | | | 17 | 34.0 | | | **0.005** |
| Fibromyalgia‡ | 5 | 8.3 | | | 15 | 30.0 | | | **0.003** |
| MD (BDI ≥11)§ | 15 | 25.0 | | | 22 | 44.0 | | | **0.036** |
| Anxiety (BAI ≥22)◊ | 1 | 1.7 | | | 7 | 14.0 | | | **0.022** |
| Insomnia (ISI >14)° | 14 | 23.3 | | | 12 | 24.0 | | | 0.935 |

FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue; PDQ: Pain DETECT questionnaire score; BDI: Beck Depression Inventory; BAI: Bath Anxiety Inventory; ISI: Insomnia Severity Index; PTs: Pain thresholds; PSS: Primary Sjögren's syndrome; HCs: Healthy controls; SD: Standard deviation; PWB: Physical well-being; SWB: Social/family well-being; EWB: Emotional well-being; FWB: Functional well-being; FS: Fatigue subscale; NPBS: Number of painful body sites; * According to patients' self-report; NP: Neuropathic pain; † Neuropathic pain component is likely (>90%); ‡ According to the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy criteria; MD: Mood disturbance; § From mild mood disturbance to extreme depression; ◊ Moderate to severe anxiety; ° Moderate and severe insomnia, indicating clinically significant insomnia.

sensitivity in the receiver operating characteristics curve when analyzed to predict the condition in which PSS patients describe themselves as not tired. The correlation of one continuous variable with another continuous variable or an ordinal variable was evaluated by Spearman's correlation analysis. Initially, possible predictive variables were analyzed with the enter method in the univariate model to determine the predictors of fatigue in PSS patients, and the predictors that were significant in the univariate model were analyzed with the forward likelihood ratio method in the multivariate model with logistic regression analysis. A p-value <0.05 was considered statistically significant.

## RESULTS

HCs and PSS patients were not different in terms of age and sex (p=0.620 and p=0.586, respectively). Characteristics and laboratory test results of patients with PSS are shown in Table 1.

The comparison of FACIT-F, PDQ, BDI, BAI, and ISI results and PTs, frequency of fibromyalgia, and self-reported fatigue in PSS patients and HCs is presented in Table 2. The mean FACIT-F total score was 125.2±19.9 and 100.7±24.4 in HCs and PSS patients, respectively (p<0.001). In addition, mean scores in all subscales of FACIT-F (PWB, SWB, EWB, FWB, and FS) were lower in PSS patients (p<0.01). The mean scores of PDQ, BDI, BAI, and ISI were higher in PSS patients than in HCs (p=0.001, p=0.013, p<0.001, and p<0.001, respectively). PSS patients had a higher frequency of self-reported fatigue (66% *vs.* 38.3%), fatigue evaluated by the FS score (54% *vs.* 8.3%), fibromyalgia (30% *vs.* 8.3%), mood disturbance (44% *vs.* 25%), and anxiety (14% *vs.* 1.7%) than HCs. However, the level of PTs assessed on both sides and the frequency of neuropathic pain and insomnia did not differ significantly between the groups.

Correlations of age, disease duration, disease activity, dryness severity, pain, emotional state, and insomnia level with fatigue assessed by FACIT-F, FS, and ESSPRI fatigue in PSS patients is shown in Table 3. Age, disease duration, parameters of dryness severity, and PTs were not correlated with FACIT-F, FS, or ESSPRI fatigue scores. However, the ESSDAI score negatively

**Table 3.** Correlations of age, disease duration, disease activity, dryness severity, pain, emotional state, and insomnia level with fatigue assessed by FACIT-F, FS, and ESSPRI fatigue in PSS patients

| | FACIT-F score | | Fatigue subscale | | ESSPRI fatigue | |
|---|---|---|---|---|---|---|
| | Rho | *p* | Rho | *p* | Rho | *p* |
| Age (year) | -0.074 | 0.611 | 0.076 | 0.602 | 0.032 | 0.826 |
| Disease duration (year) | -0.094 | 0.516 | 0.019 | 0.893 | -0.010 | 0.944 |
| Disease activity | | | | | | |
| ESSDAI | -0.304 | 0.032 | -0.345 | 0.014 | 0.034 | 0.813 |
| Dryness severity | | | | | | |
| Schirmer (mean) | 0.085 | 0.556 | 0.015 | 0.919 | -0.186 | 0.195 |
| WUSFR | 0.033 | 0.818 | 0.033 | 0.819 | -0.131 | 0.364 |
| Pain | | | | | | |
| Pain thresholds (mean) | 0.169 | 0.241 | 0.212 | 0.139 | -0.175 | 0.225 |
| Number of painful body sites | -0.518 | <0.001 | -0.460 | 0.001 | 0.313 | 0.027 |
| Pain DETECT questionnaire | -0.561 | <0.001 | -0.465 | 0.001 | 0.355 | 0.011 |
| Emotional state | | | | | | |
| Beck Depression Inventory | -0.893 | <0.001 | -0.804 | <0.001 | 0.582 | <0.001 |
| Beck Anxiety Inventory | -0.712 | <0.001 | -0.586 | <0.001 | 0.449 | 0.001 |
| Insomnia | | | | | | |
| Insomnia Severity Index | -0.554 | <0.001 | -0.483 | <0.001 | 0.398 | 0.004 |

FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; PSS: Primary Sjögren's syndrome; ESSDAI: EULAR Sjögren's syndrome disease activity index; WUSFR: Whole unstimulated salivary flow rate.

correlated with both the FACIT-F (Rho=-0.304) and the FS score (Rho=-0.345) but not with the ESSPRI fatigue score (Rho=0.034). In addition, the number of painful body sites (NPBS) and PDQ, BDI, BAI, and ISI scores were negatively correlated with the FACIT-F and FS scores and positively correlated with the ESSPRI fatigue score. The scatter plot of correlations of BDI, BAI, ISI, ESSDAI, NPBS, and PDQ scores with the FS is shown in Figure 1. Nineteen of the PSS patients included in the study had hypergammaglobulinemia (plasma globulin/plasma albumin >25%). In PSS patients with and without hyperglobulinemia, mean FACIT-F scores were found to be 108.0±22.0 and 96.3±25.1 (p=0.100), and mean FS scores were 33.3±11.6 and 29.6±11.0 (p=0.256), respectively.

The comparison of age, disease duration, disease activity, dryness severity, pain, emotional state, insomnia level, and frequency of FMS, antibodies, and currently used drugs in PSS patient subgroups with an FS score ≥30.5 and FS score <30.5 is shown in Table 4.

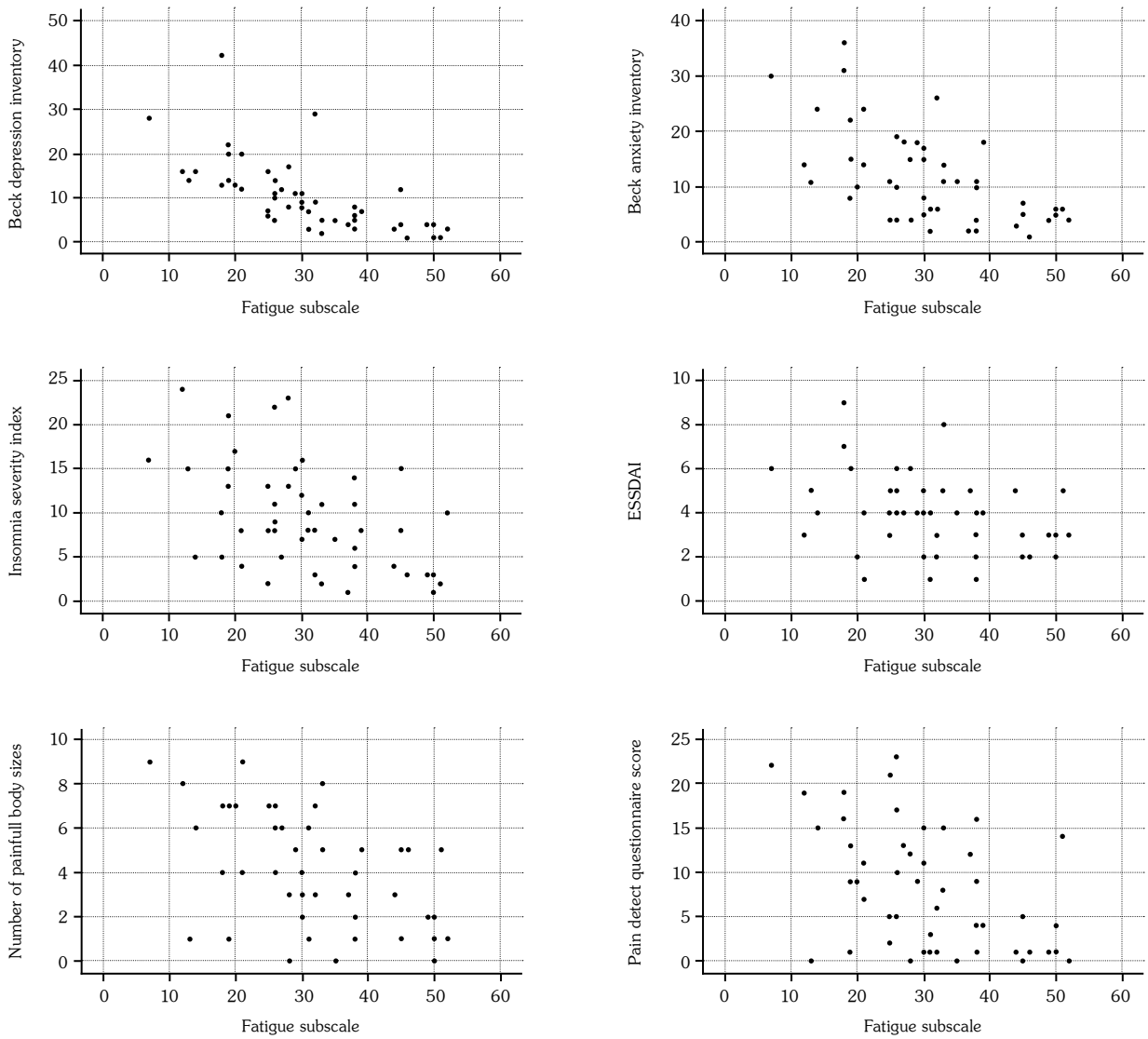


**Figure 1.** The scatter plot of correlations of BDI, BAI, ISI, ESSDAI, NPBS, and PDQ scores with the FS.

BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; ISI: Insomnia Severity Index; ESSDAI: EULAR Sjögren's Syndrome Patient Reported Index; NPBS: Number of painful body sites; PDQ: Pain DETECT questionnaire; FS: Fatigue subscale.

**Tablo 4.** Comparison of demographic data, disease duration, disease activity, dryness severity, pain, emotional state, insomnia level, and frequency of FMS, antibodies, and currently used drugs in PSS patient subgroups with FS scores ≥30.5 and <30.5

| | FS score ≥30.5 (n=23) | | | FS score <30.5 (n=27) | | | |
|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | n | % | Mean±SD | *p* |
| Age (year) | | | 49.7±11.6 | | | 48.1±10.2 | 0.793 |
| Disease duration (year) | | | 3.4±1.2 | | | 3.6±1.6 | 0.490 |
| Disease activity | | | | | | | |
| ESSDAI | | | 3.3±1.6 | | | 4.4±1.9 | **0.016** |
| Dryness severity | | | | | | | |
| Schirmer (mean) | | | 8.9±7.5 | | | 10.1±7.4 | 0.453 |
| WUSFR | | | 1.0±1.3 | | | 0.8±0.6 | 0.777 |
| Pain | | | | | | | |
| pain thresholds (mean) | | | 9.8±3.5 | | | 8.8±3.3 | 0.242 |
| PDQ | | | 4.7±5.2 | | | 11.1±6.9 | **0.001** |
| NPBS | | | 3.1±2.3 | | | 5.0±2.6 | **0.010** |
| Emotional state | | | | | | | |
| BDI | | | 5.5±5.8 | | | 14.2±7.6 | **<0.001** |
| BAI | | | 7.3±5.9 | | | 15.1±8.5 | **<0.001** |
| Insomnia | | | | | | | |
| ISI | | | 6.3±4.1 | | | 12.3±6.0 | **<0.001** |
| Frequency | | | | | | | |
| Female | 21 | 91.3 | | 27 | 100.0 | | 0.207 |
| FMS[1] | 1 | 4.3 | | 14 | 51.9 | | **<0.001** |
| NP (PDQ >18)† | 0 | 0 | | 5 | 18.5 | | **0.030** |
| MD (BDI ≥11) § | 3 | 13.1 | | 19 | 70.4 | | **<0.001** |
| Anxiety (BAI ≥22)◊ | 1 | 4.3 | | 6 | 22.2 | | 0.069 |
| Insomnia (ISI >14)° | 1 | 4.3 | | 11 | 40.7 | | **0.003** |
| ANA | 20 | 87.0 | | 24 | 88.9 | | 0.834 |
| SSA | 17 | 73.9 | | 21 | 77.8 | | 0.750 |
| SSB | 8 | 34.8 | | 10 | 37.0 | | 0.869 |
| Hydroxychloroquine | 22 | 95.7 | | 23 | 85.0 | | 0.219 |
| Corticosteroid | 8 | 34.8 | | 10 | 37.0 | | 0.869 |
| Duloxetine | 7 | 30.4 | | 12 | 44.4 | | 0.309 |
| Pregabalin | 2 | 8.7 | | 3 | 11.1 | | 0.777 |

FMS: Fibromyalgia syndrome; PSS: Primary Sjögren's syndrome; FS: Fatigue subscale; SD: Standard deviation; ESSDAI: EULAR Sjögren's syndrome disease activity index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; WUSFR: Whole unstimulated salivary flow rate; PDQ: Pain DETECT questionnaire; NPBS: Number of painful body sites; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; ISI: Insomnia Severity Index; [1] The Analgesic; Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy criteria; NP: Neuropathic pain; † Neuropathic pain component is likely (>90%); MD: Mood disturbance; § From mild mood disturbance to extreme depression; ◊ Moderate to severe anxiety; ° Moderate and severe insomnia, indicating clinically significant insomnia.

The mean age, disease duration, Schirmer, WUSFR, PT, and the frequency of sex, anxiety, autoantibodies, and currently used drugs were comparable between subgroups. In PSS patients with an FS score <30.5, the mean ESSDAI, PDQ, NPBS, BDI, BAI, and ISI scores were higher than in those with an FS score ≥30.5. The frequency of fibromyalgia (51.9% *vs.* 4.3%), neuropathic pain (18.5% *vs.* 0%), depression (70.4% *vs.* 13.1%), and insomnia (40.7% *vs.* 4.3%) was significantly higher in PSS patients with an FS score <30.5 than in those with an FS score ≥30.5.

The evaluation of predictors of fatigue determined according to the FS score cut-off value of 30.5 by logistic regression analysis in PSS patients is shown in Table 5. ESSDAI, PDQ, BDI, BAI, and ISI scores and the presence of fibromyalgia were predictive of fatigue in PSS patients in univariate analysis. BDI, ISI, and ESSDAI scores and the presence of fibromyalgia were found to be independent predictors of fatigue in PSS patients in multivariate analysis. The BDI alone predicted

**Table 5.** Evaluation of predictors of fatigue determined according to the FS score cut-off value of 30.5 by logistic regression analysis in PSS patients

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Age | 0.986 | 0.936-1.039 | 0.599 | | | |
| Disease duration | 1.110 | 0.743-1.659 | 0.610 | | | |
| Schirmer (mean) | 1.024 | 0.948-1.107 | 0.546 | | | |
| WUSFR | 0.726 | 0.373-1.410 | 0.344 | | | |
| ESSDAI | 1.440 | 1.005-2.065 | 0.047 | 1.824 | 1.033-3.220 | **0.038** |
| Pain threshold (mean) | 0.911 | 0.768-1.080 | 0.282 | | | |
| Pain DETECT questionnaire | 1.181 | 1.061-1.315 | **0.002** | | | |
| Fibromyalgia syndrome | 23.692 | 2.783-201.671 | **0.004** | 21.674 | 1.470-319.469 | **0.025** |
| Beck Depression Inventory | 1.356 | 1.139-1.616 | **0.001** | 1.214 | 1.007-1.463 | **0.042** |
| Beck Anxiety Inventory | 1.185 | 1.058-1.327 | **0.003** | | | |
| Insomnia Severity Index | 1.259 | 1.092-1.451 | **0.002** | 1.223 | 1.003-1.492 | **0.047** |

FS: Fatigue subscale; PSS: Primary Sjögren's syndrome; OR: Odds ratio; CI: Confidence interval; WUSFR: Whole unstimulated salivary flow rate; ESSDAI: EULAR Sjögren's syndrome disease activity index.

**Table 6.** Comparison of FACIT-F questionnaire scores in PSS patients grouped according to the presence of mood disturbance

| | No (n=29) | | Yes (n=21) | | |
|---|---|---|---|---|---|
| | Mean±SD | Median | Mean±SD | Median | *p* |
| Age (year) | 47.1±10.6 | 45.0 | 51.3±10.8 | 50.0 | 0.172 |
| FACIT-F score | 116.2±17.0 | 116.0 | 79.4±15.2 | 79.0 | <0.001 |
| PWB | 20.8±3.9 | 21.0 | 14.0±3.2 | 14.0 | <0.001 |
| SWB | 19.9±3.6 | 21.0 | 15.3±6.9 | 19.0 | 0.009 |
| EWB | 18.6±3.7 | 18.0 | 13.5±3.3 | 13.0 | <0.001 |
| FWB | 19.7±3.3 | 20.0 | 14.0±3.0 | 15.0 | <0.001 |
| FS | 37.2±8.8 | 37.0 | 22.3±8.3 | 21.0 | <0.001 |

FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue; PSS: Primary Sjögren's syndrome; SD: Standard deviation; PWB: Physical well-being; SWB: Social/family well-being; EWB: Emotional well-being; FWB: Functional well-being; FS: Fatigue subscale.

the presence of fatigue by 81.5% and its absence by 87%, for an average of 84%. Additionally, BDI and ESSDAI scores and the presence of fibromyalgia together predicted the presence of fatigue by 88.9% and its absence by 91.3%, for an average of 90%.

The comparison of FACIT-F questionnaire scores in PSS patients grouped according to the presence of mood disturbance (BDI ≥10) is shown in Table 6. Age was not different between the groups. The mean FACIT-F total score was 79.4±15.2 and 116.2±17.0 in PSS participants with and without mood disturbance, respectively (p<0.001). The mean scores in all subscales of FACIT-F (PWB, SWB, EWB, FWB, FS) were lower in PSS patients with mood disturbance.

## DISCUSSION

Consistent with the literature, fatigue was detected in more than half of PSS patients in this study, and depression, fibromyalgia,

disease activity, and insomnia were found to be independent predictors of fatigue in PSS patients. Depression was found to be the most important predictor of fatigue in PSS patients, and it was determined that it alone could most likely predict fatigue in PSS patients. There are studies in the literature evaluating the relationship between fatigue and depression in PSS patients. Cui *et al.*[23] found that the frequency of depression (36.9%) in PSS patients was significantly higher than in HCs and was correlated with fatigue. Similarly, Hackett *et al.*[2] found that depression was associated with both physical and mental fatigue in a large cohort of PSS patients. Barendregt *et al.*[24] also found that fatigue was correlated with depression in PSS patients, although they did not find the difference to be different from RA patients. When Segal *et al.*[25] evaluated the effects of behavioral and immunological factors on fatigue in PSS patients, they found that psychogenic factors, including depression, were predictors of fatigue and could explain 62% of fatigue variability in PSS patients. Priori *et al.*[26] also found that the more resilient PSS patients had less fatigue, and the most resilient PSS patients had less depression. The results obtained from all these studies are compatible with the results of the present study in terms of showing the relationship between depression and fatigue in PSS patients. However, the present study is the first to evaluate many different predictors at the same time and show that depression is the most important among all these variables. Based on these results, depression may be an important treatment target for clinicians when combating fatigue in PSS patients. There is also evidence in the literature to support this hypothesis. When Ibn Yacoub *et al.*[27] evaluated the level of fatigue in Moroccan PSS patients, they found that the majority of PSS patients (87.5%) had fatigue, but those who used antidepressants had less fatigue. Myomato *et al.*,[28] in a randomized controlled study, found that exercise reduced the level of fatigue in PSS patients and that the improvement in fatigue was associated with reduced depression in these patients.

In the literature, there are conflicting results in the studies evaluating the relationship between fibromyalgia, another independent determinant of fatigue in PSS patients in the present study, and fatigue in PSS patients. Karageorgas *et al.*[4] determined that the frequency of fibromyalgia was much higher in PSS patients with fatigue than those without fatigue (25.0% *vs.* 4.1%), and they found that fibromyalgia was an independent predictor of fatigue in these patients. However, Koh *et al.*[6] did not detect fibromyalgia as an independent predictor of fatigue in PSS; however, they found the frequency of fibromyalgia to be higher in patients with fatigue than in those without fatigue (10.8% *vs.* 2.8%) in their cohort of PSS patients. The discrepancy between the two studies may be related to the frequency of fibromyalgia in both patient cohorts, as the incidence of fibromyalgia in Koh *et al.*'s[6] PSS cohort (6.2%) was considerably lower than expected.

Studies evaluating the association of fatigue with disease activity and inflammation in PSS patients show a significant positive correlation, although this association is not strong. Omma *et al.*[29] found ESSDAI and ESSPRI correlated with fatigue in PSS patients, while AlEnzi *et al.*[7] found fatigue correlated with ESSDAI but not with ESSPRI in PSS patients. Bårdsen *et al.*[30] found interleukin (IL)-1β-related molecules in the cerebrospinal fluid of PSS patients to be associated with fatigue. They also identified HSP90 (heat shock protein 90) as a fatigue predictor when they evaluated the effect of heat shock proteins on fatigue in PSS patients. Furthermore, in another study, they found depression as an independent predictor in the same study and that its effect on fatigue was stronger than HSP90, which was not found to be different in PSS patient groups with low and high depression scores.[31] All these results are consistent with the data in the present study and show that depression has an independent and stronger association with fatigue than disease activity in PSS patients. Similarly, the effects of anti-inflammatory treatments on fatigue reduction in PSS patients seem to be limited. Arends *et al.*[32] found a patient-acceptable improvement in fatigue in only one-third of PSS patients after rituximab treatment. Norheim *et al.*[33] also found that IL inhibition treatment did not significantly decrease the level of fatigue in PSS patients at week four. In the randomized controlled trial conducted in the largest PSS cohort, rituximab was not found to be successful in reducing the level of fatigue by 30%.[8] Findings so far show that rituximab treatment, which is an important treatment option

in PSS patients with systemic involvement, is not cost effective in the treatment of fatigue in these patients. The solution for the fight against fatigue in PSS patients is perhaps much simpler and cheaper. There is no information in the literature about how the level of fatigue is affected as a result of the treatment of depression in PSS patients, and there is a need to investigate the subject.

There are several limitations to this study. The results of this study are based on patient report outcomes and therefore provide limited information. Although the frequency of fatigue in both HCs and PSS patients is consistent with the literature, according to the cut-off value we used to detect fatigue in this study, the lack of reliable data for the cut-off value is one of the most important shortcomings of the study. Although the FACIT-F questionnaire is a test designed to detect the level of fatigue in patients with chronic diseases, we also used this test to detect the level of fatigue in HCs. Since we could not ask the questions about the underlying disease to the HCs, a modification was applied while scoring the questions according to the scoring procedures of the test. Therefore, our findings in HCs may not fully reflect the level of fatigue in this population. Although we did not include individuals with anemia in this study, hypovitaminosis conditions such as folic acid, b12, and vitamin D, which may be associated with fatigue, were not evaluated in patient selection, which is another shortcoming. Lastly, study data may have been affected in patients using drugs such as pregabalin and duloxetine.

In conclusion, in this study, the possible predictive factors of fatigue were investigated in PSS patients, and depression, fibromyalgia, disease activity, and insomnia were found to be independent predictors of fatigue. Among them, depression was found to be the most significant predictor of fatigue in PSS patients. There is a need for new studies to evaluate the effect of antidepressant treatment approaches on fatigue accompanied by depression in PSS patients.

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## REFERENCES

1. Howard Tripp N, Tarn J, Natasari A, Gillespie C, Mitchell S, Hackett KL, et al. Fatigue in primary Sjögren's syndrome is associated with lower levels of proinflammatory cytokines. RMD Open 2016;2:e000282. doi: 10.1136/rmdopen-2016-000282.
2. Hackett KL, Davies K, Tarn J, Bragg R, Hargreaves B, Miyamoto S, et al. Pain and depression are associated with both physical and mental fatigue independently of comorbidities and medications in primary Sjögren's syndrome. RMD Open 2019;5:e000885. doi: 10.1136/rmdopen-2018-000885.
3. Priori R, Iannuccelli C, Alessandri C, Modesti M, Antonazzo B, Di Lollo AC, et al. Fatigue in Sjogren's syndrome: Relationship with fibromyalgia, clinical and biologic features. Clin Exp Rheumatol 2010;28(6 Suppl 63):S82-6.
4. Karageorgas T, Fragioudaki S, Nezos A, Karaiskos D, Moutsopoulos HM, Mavragani CP. Fatigue in primary Sjögren's syndrome: Clinical, laboratory, psychometric, and biologic associations. Arthritis Care Res (Hoboken) 2016;68:123-31. doi: 10.1002/acr.22720.
5. Chung SW, Hur J, Ha YJ, Kang EH, Hyon JY, Lee HJ, et al. Impact of sleep quality on clinical features of primary Sjögren's syndrome. Korean J Intern Med 2019;34:1154-64. doi: 10.3904/kjim.2017.158.
6. Koh JH, Kwok SK, Lee J, Son CN, Kim JM, Kim HO, et al. Pain, xerostomia, and younger age are major determinants of fatigue in Korean

patients with primary Sjögren's syndrome: A cohort study. Scand J Rheumatol 2017;46:49-55. doi: 10.3109/03009742.2016.1153142.
7. AlEnzi F, Alqahtani B, Alhamad EH, Daghestani M, Tashkandy Y, Othman N, et al. Fatigue in Saudi patients with primary Sjögren's syndrome and its correlation with disease characteristics and outcome measures: A cross-sectional study. Open Access Rheumatol 2020;12:303-8. doi: 10.2147/OARRR.S284985.
8. Bowman SJ, Everett CC, O'Dwyer JL, Emery P, Pitzalis C, Ng WF, et al. Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjögren's syndrome. Arthritis Rheumatol 2017;69:1440-50. doi: 10.1002/art.40093.
9. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, Puéchal X, et al. Treatment of primary Sjögren syndrome with rituximab: A randomized trial. Ann Intern Med 2014;160:233-42. doi: 10.7326/M13-1085.
10. Dass S, Bowman SJ, Vital EM, Ikeda K, Pease CT, Hamburger J, et al. Reduction of fatigue in Sjögren syndrome with rituximab: Results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541-4. doi: 10.1136/ard.2007.083865.
11. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2017;76:9-16. doi: 10.1136/annrheumdis-2016-210571.
12. Smith E, Lai JS, Cella D. Building a measure of fatigue: The functional assessment of Chronic Illness Therapy Fatigue Scale. PM R 2010;2:359-63. doi: 10.1016/j.pmrj.2010.04.017.
13. Çinar D, Yava A. Validity and reliability of functional assessment of chronic illness treatment-fatigue scale in Turkish patients with type 2 diabetes. Endocrinol Diabetes Nutr (Engl Ed) 2018;65:409-17. English, Spanish. doi: 10.1016/j.endinu.2018.01.010.
14. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911-20. doi: 10.1185/030079906X132488.
15. Alkan H, Ardic F, Erdogan C, Sahin F, Sarsan A, Findikoglu G. Turkish version of the painDETECT questionnaire in the assessment of neuropathic pain: A validity and reliability study. Pain Med 2013;14:1933-43. doi: 10.1111/pme.12222.
16. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71. doi: 10.1001/archpsyc.1961.01710120031004.
17. Hisli N. Beck depresyon envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Psikoloji dergisi 1989;7:3-13.
18. Ulusoy M, Hisli Şahin N, Erkmen H. Turkish version of the Beck Anxiety Inventory: Psychometric properties. J Cogn Psychother 1998;12:163-72.
19. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol 1988;56:893-7. doi: 10.1037//0022-006x.56.6.893.
20. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297-307. doi: 10.1016/s1389-9457(00)00065-4.
21. Boysan M, Güleç M, Beşiroğlu L, Kalafat T. (2013). Psychometric properties of the Insomnia Severity Index in Turkish sample. Anadolu Psikiyatri Derg 2010;11:248-52.
22. Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, et al. AAPT diagnostic criteria for fibromyalgia. J Pain 2019;20:611-28. doi: 10.1016/j.jpain.2018.10.008.
23. Cui Y, Xia L, Li L, Zhao Q, Chen S, Gu Z. Anxiety and depression in primary Sjögren's syndrome: A cross-sectional study. BMC Psychiatry 2018;18:131. doi: 10.1186/s12888-018-1715-x.
24. Barendregt PJ, Visser MR, Smets EM, Tulen JH, van den Meiracker AH, Boomsma F, et al. Fatigue in primary Sjögren's syndrome. Ann Rheum Dis 1998;57:291-5. doi: 10.1136/ard.57.5.291.
25. Segal B, Thomas W, Rogers T, Leon JM, Hughes P, Patel D, et al. Prevalence, severity, and predictors of fatigue in subjects with primary Sjögren's syndrome. Arthritis Rheum 2008;59:1780-7. doi: 10.1002/art.24311.
26. Priori R, Giardina F, Izzo R, Gattamelata A, Fusconi M, Colafrancesco S, et al. Resilience in women with primary Sjögren's syndrome. Rheumatol Int 2021;41:1987-94. doi: 10.1007/s00296-021-04899-z.
27. Ibn Yacoub Y, Rostom S, Laatiris A, Hajjaj-Hassouni N. Primary Sjögren's syndrome in Moroccan patients: Characteristics, fatigue and quality of life. Rheumatol Int 2012;32:2637-43. doi: 10.1007/s00296-011-2009-5.
28. Miyamoto ST, Valim V, Carletti L, Ng WF, Perez AJ, Lendrem DW, et al. Supervised walking improves cardiorespiratory fitness, exercise tolerance, and fatigue in women with primary Sjögren's syndrome: A randomized-controlled trial. Rheumatol Int 2019;39:227-38. doi: 10.1007/s00296-018-4213-z.
29. Omma A, Tecer D, Kucuksahin O, Sandikci SC, Yildiz F, Erten S. Do the European League Against Rheumatism (EULAR) Sjögren's syndrome outcome measures correlate with impaired quality of life, fatigue, anxiety and depression in primary Sjögren's syndrome? Arch Med Sci 2018;14:830-7. doi: 10.5114/aoms.2017.70300.

30. Bårdsen K, Brede C, Kvivik I, Kvaløy JT, Jonsdottir K, Tjensvoll AB, et al. Interleukin-1-related activity and hypocretin-1 in cerebrospinal fluid contribute to fatigue in primary Sjögren's syndrome. J Neuroinflammation 2019;16:102. doi: 10.1186/s12974-019-1502-8.
31. Bårdsen K, Nilsen MM, Kvaløy JT, Norheim KB, Jonsson G, Omdal R. Heat shock proteins and chronic fatigue in primary Sjögren's syndrome. Innate Immun 2016;22:162-7. doi: 10.1177/1753425916633236.
32. Arends S, Meiners PM, Moerman RV, Kroese FG, Brouwer E, Spijkervet FK, et al. Physical fatigue characterises patient experience of primary Sjögren's syndrome. Clin Exp Rheumatol 2017;35:255-61.
33. Norheim KB, Harboe E, Gøransson LG, Omdal R. Interleukin-1 inhibition and fatigue in primary Sjögren's syndrome--a double blind, randomised clinical trial. PLoS One 2012;7:e30123. doi: 10.1371/journal.pone.0030123.