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Research Article

Sicca severity in primary Sjögren's disease reflects symptom amplification rather than systemic inflammatory activity

Primer Sjögren hastalığında sicca şiddeti sistemik inflamasyonu değil, semptom amplifikasyonunu yansıtır

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Abstract

Aim: To clarify whether sicca symptom severity reflects systemic inflammatory activity or symptom amplification in primary Sjögren's disease (pSD), and to examine its relationship with functional impairment and mood disturbance in a predominantly treated cohort.

Material and Methods: In this cross-sectional, single-center study, adult patients fulfilling the 2016 ACR/EULAR classification criteria for pSD were evaluated. Systemic disease activity was assessed using the EULAR Sjögren's Syndrome Disease Activity Index. Oral and ocular dryness severity were measured using visual analog scales. Health-related quality of life was assessed with the EQ-5D-5L index and Short Form 36 physical and mental component scores, and depressive symptoms with the Beck Depression Inventory. Logistic regression models examined associations with systemic disease activity. Receiver operating characteristic analyses assessed the performance of dryness severity for identifying systemic activity and fibromyalgia. Symptom heterogeneity was explored using unsupervised cluster analysis.

Results: Among 107 patients, 86.9 percent had low systemic disease activity. Sicca severity showed no association with systemic disease activity and did not predict moderate to high disease activity. Pulmonary involvement, fibromyalgia, and erythrocyte sedimentation rate were independently associated with higher systemic disease activity. Although dryness severity showed poor discrimination for inflammatory activity, it was strongly associated with fibromyalgia, depressive symptoms, and impaired quality of life. Cluster analysis identified a symptom amplification phenotype characterized by marked functional and psychological impairment despite moderate dryness severity.

Conclusion: In pSD, sicca symptom severity primarily reflects functional and psychological burden rather than systemic inflammation, supporting phenotype-oriented, patient-centered assessment strategies.

Keywords: Primary Sjögren's disease, sicca symptoms, functional impairment, mood disturbance, ESSDAI, quality of life, fibromyalgia, symptom amplification

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Öz

Amaç: Primer Sjögren hastalığında (pSD) sicca semptom şiddetinin sistemik inflamatuvar aktiviteyi mi yoksa semptom amplifikasyonunu mu yansıttığını netleştirmek; ayrıca kuruluk şiddetinin fonksiyonel bozukluk ve duygu durum bozukluğu ile ilişkisini ağırlıklı olarak tedavi gören bir kohortta incelemektir.

Gereç ve Yöntemler: Bu kesitsel, tek merkezli çalışmada, 2016 ACR/EULAR sınıflandırma kriterlerini karşılayan yetişkin pSD hastaları değerlendirilmiştir. Sistemik hastalık aktivitesi "EULAR Sjögren's Syndrome Disease Activity Index" (ESSDAI) kullanılarak belirlenmiştir. Oral ve oküler kuruluk şiddeti görsel analog skalalar (VAS) ile ölçülmüştür. Sağlıkla ilişkili yaşam kalitesi EQ-5D-5L indeksi ve Kısa Form-36 (SF-36) fiziksel ve zihinsel bileşen skorları ile; depresif semptomlar ise Beck Depresyon Envanteri ile değerlendirilmiştir. Sistemik hastalık aktivitesi ile ilişkiler lojistik regresyon modelleriyle incelenmiştir. Kuruluğun sistemik aktiviteyi ve fibromiyaljiyi belirlemedeki performansı "Receiver Operating Characteristic" (ROC) analizleri ile değerlendirilmiştir. Semptom heterojenliği gözetimsiz kümeleme (unsupervised cluster) analizi ile araştırılmıştır.

Bulgular: İncelenen 107 hastanın %86,9'unda düşük sistemik hastalık aktivitesi mevcuttur. Sicca şiddeti sistemik hastalık aktivitesi ile ilişki göstermemiş ve orta-yüksek hastalık aktivitesini öngörmemiştir. Akciğer tutulumu, fibromiyalji ve eritrosit sedimentasyon hızı (ESH), yüksek sistemik hastalık aktivitesi ile bağımsız olarak ilişkili bulunmuştur. Kuruluk şiddeti inflamatuvar aktivite için zayıf bir ayırt edicilik gösterse de; fibromiyalji, depresif semptomlar ve bozulmuş yaşam kalitesi ile güçlü bir ilişki sergilemiştir. Kümeleme analizi; orta dereceli kuruluk şiddetine rağmen belirgin fonksiyonel ve psikolojik bozulma ile karakterize bir "semptom amplifikasyon" fenotipi tanımlamıştır.

Sonuç: pSD'de sicca semptom şiddeti sistemik inflamasyondan ziyade fonksiyonel ve psikolojik yükü yansıtmaktadır. Bu bulgular, fenotip odaklı ve hasta merkezli değerlendirme stratejilerini desteklemektedir.

Anahtar Kelimeler: primer Sjögren hastalığı, sicca semptomları, fonksiyonel bozukluk, duygu durum bozukluğu, essdai, yaşam kalitesi, fibromiyalji, semptom amplifikasyonu

Introduction

Primary Sjögren's disease (pSD) is a chronic, systemic autoimmune condition characterized by lymphocytic infiltration and progressive dysfunction of exocrine glands, most prominently affecting the salivary and lacrimal glands. Although sicca symptoms such as oral and ocular dryness represent the hallmark clinical features, pSD is increasingly recognized as a heterogeneous systemic disease with potential involvement of the musculoskeletal, pulmonary, renal, neurological, and hematological systems, contributing substantially to long term morbidity and impaired quality of life [1].

To capture this multidimensional disease burden, the European League Against Rheumatism developed two complementary instruments: the EULAR Sjögren's Syndrome Disease Activity Index, designed to quantify objective systemic disease activity across predefined organ domains, and the EULAR Sjögren's Patient Reported Index, which reflects patient perceived symptom severity, particularly dryness, pain, and fatigue. While ESSDAI has become the standard outcome measure for assessing systemic activity in clinical trials and observational studies, ESSPRI and other patient reported outcome measures are increasingly emphasized in both research and routine clinical care to better capture the patient experience [2,3].

Despite the widespread use of these instruments, the relationship between subjective symptom burden and objective systemic inflammation in primary Sjögren's disease remains incompletely understood. Multiple studies have demonstrated that patient reported symptoms, including dryness severity and fatigue, often show weak or inconsistent correlations with ESSDAI defined systemic activity. This dissociation suggests that symptom burden may be driven by mechanisms beyond measurable inflammatory organ involvement, such as irreversible glandular damage, neuropathic dysfunction, central sensitization, and psychological comorbidities [3–5].

Health related quality of life impairment in primary Sjögren's disease is substantial and frequently disproportionate to systemic disease activity. Instruments such as the EQ 5D and Short Form 36 have consistently demonstrated reduced physical and mental health scores even among patients with low ESSDAI values. Depression, anxiety, and fibromyalgia are particularly prevalent comorbidities and have been identified as major contributors to functional impairment and reduced quality of life, often exceeding the impact of objective inflammatory disease activity [6–8].

Dryness severity, although central to the clinical identity of primary Sjögren's disease, presents a particular conceptual challenge. Sicca symptoms are influenced by structural glandular damage, autonomic dysfunction, mucosal sensitivity, and symptom amplification processes, and may persist independently of ongoing immune mediated inflammation, particularly in patients receiving active treatment. Consequently, high dryness scores may exert a disproportionate impact on daily functioning, mood, and perceived disease severity without reliably indicating active systemic disease [5,9].

In this context, a comprehensive evaluation integrating objective disease activity indices, detailed patient reported outcomes, and symptom based phenotyping may provide deeper insight into the heterogeneity of primary Sjögren's disease. Clarifying whether sicca symptom severity primarily reflects systemic inflammation, functional impairment, or mood disturbance has direct implications for patient stratification, treatment decision making, and outcome interpretation in clinical studies [4,9,10].

Accordingly, the present study aimed to investigate the relationship between sicca symptom severity, systemic disease activity assessed by ESSDAI, and functional and psychological patient reported outcomes in a well characterized cohort of patients with primary Sjögren's disease. By combining conventional statistical analyses with regression modeling and symptom based clustering approaches, this study sought to delineate whether dryness severity reflects inflammatory activity or symptom amplification in a predominantly treated population.

Material and Methods

Study Design and Population

This cross-sectional observational study was conducted at a single tertiary rheumatology center. Adult patients aged 18 years or older who fulfilled the 2016 ACR/EULAR classification criteria for primary Sjögren's disease were consecutively enrolled. Patients with secondary Sjögren's disease associated with other systemic autoimmune rheumatic diseases were excluded. Additional exclusion criteria included incomplete clinical or patient-reported outcome data and comorbid conditions that could interfere with reliable questionnaire completion.

All participants provided written informed consent prior to inclusion. The study was conducted in accordance with the Declaration of Helsinki and was approved by an independent local non-interventional clinical research ethics committee.

Clinical and Laboratory Assessment

Demographic characteristics, smoking status, disease duration, and current treatment regimens were recorded at the time of assessment. Systemic involvement domains, including musculoskeletal, pulmonary, renal, and neurological manifestations, were evaluated based on clinical examination, laboratory findings, and available imaging or histopathological data.

Systemic disease activity was assessed using the EULAR Sjögren's Syndrome Disease Activity Index. Patients were categorized into low or moderate to high systemic disease activity groups according to established ESSDAI thresholds.

Laboratory assessments included erythrocyte sedimentation rate, C reactive protein, complement C3 and C4 levels, and immunological parameters including antinuclear antibodies, anti-SSA/Ro, anti-SSB/La antibodies, and rheumatoid factor. Minor salivary gland biopsy findings were recorded when available.

Fibromyalgia status was determined based on a documented clinical diagnosis established by experienced rheumatologists during routine clinical care. Although formal retrospective verification using standardized classification criteria, including the 2016 American College of Rheumatology criteria

incorporating the Widespread Pain Index and Symptom Severity Scale or the 1990 ACR tender point criteria, was not uniformly available for all patients, all fibromyalgia diagnoses had been made in accordance with contemporary clinical practice and were reconfirmed during follow-up visits. The potential implications of this methodological limitation were addressed in the Discussion section.

Patient-Reported Outcome Measures

Subjective dryness severity was assessed using separate visual analog scales for oral and ocular dryness, ranging from 0 indicating no symptoms to 10 indicating maximum severity. Health-related quality of life was evaluated using the EQ-5D-5L index and the Short Form-36, including Physical and Mental Component Summary scores. Depressive symptoms were assessed using the Beck Depression Inventory.

All patient-reported outcome measures were completed on the same day as the clinical assessment to ensure temporal alignment between objective disease activity and subjective symptom reporting.

Statistical Analysis

Statistical analyses were performed using Python version 3.10 and IBM SPSS Statistics version 26. Continuous variables were assessed for normality using the Shapiro Wilk test and summarized as mean with standard deviation or median with interquartile range, as appropriate. Categorical variables were presented as frequencies and percentages. Between-group comparisons according to systemic disease activity category were conducted using independent samples t tests or Mann Whitney U tests for continuous variables and chi square or Fisher exact tests for categorical variables. Associations between patient-reported outcomes, including oral and ocular dryness visual analog scale scores, EQ-5D-5L index values, Short Form-36 component scores, and Beck Depression Inventory scores, were examined using Spearman rank correlation coefficients.

Univariable logistic regression analyses were initially performed to explore factors associated with systemic disease activity. Variables demonstrating clinical relevance or a p value below 0.10 in univariable analyses were entered into multivariable logistic regression models. Moderate to high systemic disease activity was coded as the outcome variable, with moderate to high ESSDAI defined as 1 and low ESSDAI defined as 0. Odds ratios with 95 percent confidence intervals were reported, and model discrimination was assessed using the area under the receiver operating characteristic curve. The diagnostic performance of oral and ocular dryness visual analog scale scores for identifying comorbid fibromyalgia was evaluated using receiver operating characteristic curve analysis. Optimal cut-off values were determined using Youden's index, and corresponding sensitivity and specificity values were calculated. To explore symptom heterogeneity, unsupervised k-means clustering was performed based on standardized patient-reported outcome variables. Cluster separation and internal structure were evaluated using principal component analysis. All statistical tests were two-sided, and a p value below 0.05 was considered statistically significant.

Results

A total of 107 patients with primary Sjögren's disease were included in the analysis. The mean age of the cohort was 50.4 ± 11.7 years, and the majority of patients were female (94.4%). The mean disease duration was 7.7 ± 7.5 years. Oral and ocular sicca symptoms were reported by 83.2% and 88.8% of patients, respectively. Arthritis was present in 69.2% of the cohort, and fibromyalgia was identified in 51.4%. Detailed demographic characteristics, clinical features, laboratory findings, and patient-reported outcomes are summarized in Table 1.

The mean ESSDAI score was 1.2 ± 1.0, with 86.9% of patients classified as having low systemic disease activity. Health-related quality of life was moderately impaired, as reflected by a mean EQ-5D-5L index value of 0.777 ± 0.178. Mean SF-36 Physical and Mental Component Summary scores were 79.9 ± 13.4 and 76.2 ± 12.6, respectively. Based on Beck Depression Inventory scores, 42.1% of patients exhibited moderate-to-severe depressive symptoms.

When patients were stratified according to systemic disease activity, those with moderate–high ESSDAI scores showed a significantly higher prevalence of pulmonary involvement compared with patients with low ESSDAI scores (42.9% vs 6.5%, $p < 0.001$). Fibromyalgia was also significantly more frequent in the moderate–high ESSDAI group (85.7% vs 46.2%, $p = 0.014$).

Erythrocyte sedimentation rate values were significantly lower in patients with moderate–high ESSDAI compared with those with low ESSDAI (15.21 ± 11.01 mm/hour vs 22.17 ± 12.83 mm/hour, p = 0.049). In parallel, patient-reported outcome measures were consistently worse in the moderate–high ESSDAI group, including lower EQ-5D-5L index values, reduced SF-36 Physical and Mental Component Summary scores, and higher depression scores, as detailed in Table 2.

In univariable logistic regression analyses, pulmonary involvement, fibromyalgia, lower EQ-5D-5L index values, lower SF-36 Physical and Mental Component Summary scores, and higher Beck Depression Inventory scores were associated with systemic disease activity status. In multivariable logistic regression analysis, pulmonary involvement, fibromyalgia, and erythrocyte sedimentation rate remained independently associated with systemic disease activity, whereas patient-reported outcome measures were not retained in the final adjusted model. The complete regression results are presented in Table 3, and the corresponding forest plot illustrating adjusted odds ratios is shown in Figure 1.

Figure 1. Independent predictors of moderate–high systemic disease activity in primary Sjögren's disease

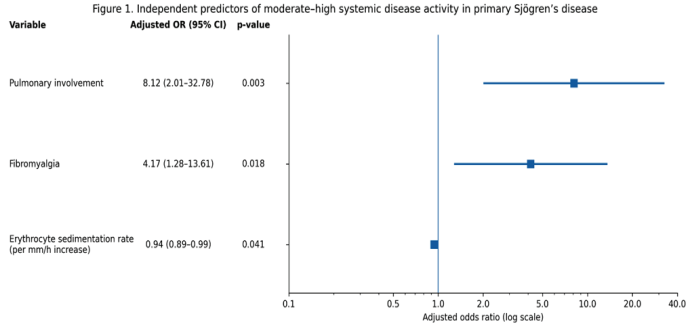

Figure 1. Forest plot illustrating adjusted odds ratios (ORs) with 95% confidence intervals derived from multivariable logistic regression analysis. Pulmonary involvement and fibromyalgia were independently associated with increased odds of moderate–high systemic disease activity, whereas higher erythrocyte sedimentation rate was inversely associated. The vertical reference line represents an OR of 1.0.

Oral and ocular dryness visual analog scale scores were not correlated with ESSDAI and did not predict systemic disease activity in logistic regression models. Receiver operating characteristic analyses demonstrated limited discriminative performance of dryness severity for identifying moderate–high ESSDAI, with area under the curve values of 0.60 for oral dryness and 0.61 for ocular dryness, indicating poor discrimination. In contrast, higher dryness scores were significantly associated with the presence of fibromyalgia. Using cut-off values derived from Youden's index, severe oral and ocular dryness was associated with approximately three- to four-fold higher odds of fibromyalgia. Detailed receiver operating characteristic analyses and diagnostic performance metrics are provided in Tables 4 and 5, with corresponding curves shown in Figures 2.

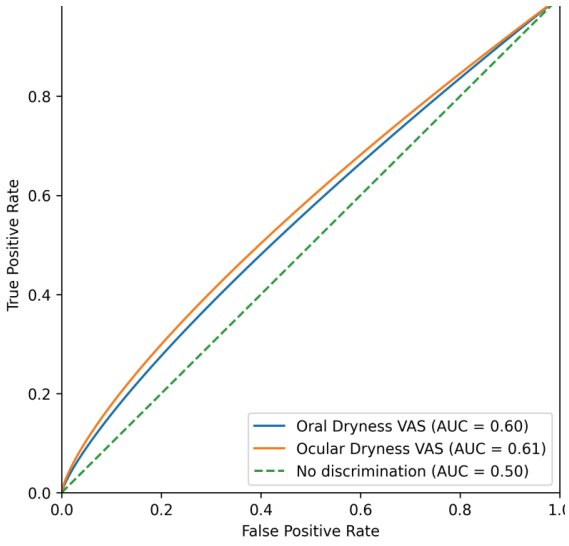

Figure 2. ROC curves demonstrate the diagnostic performance of oral and ocular dryness visual analog scale (VAS) scores for identifying comorbid fibromyalgia. Both measures showed limited discriminative ability, with area under the curve (AUC) values of 0.60 for oral dryness and 0.61 for ocular dryness. The dashed diagonal line represents no discriminative ability (AUC = 0.50).

Unsupervised k-means cluster analysis based on patient-reported outcome measures identified three distinct symptom phenotypes. These included a dryness-dominant cluster, a low-burden cluster characterized by preserved quality of life, and a high symptom-amplification cluster marked by severe impairment in quality of life and elevated depression scores despite only moderate dryness severity. The distribution of patients across clusters and their defining characteristics are presented in Supplementary Table S1, with additional supporting correlation analyses provided in Supplementary Table S3.

Table 1. Demographic characteristics, clinical features, laboratory findings, and patient-reported outcomes of the study cohort, including EQ-5D-5L Index (mean ± SD).

Variable		Value
Age (years), mean ± SD		50.4 ± 11.7
Female sex, n (%)		101 (94.4)
Body Mass Index (kg/m^2), mean ± SD		27.7 ± 4.5
Disease Duration (years), mean ± SD		7.7 ± 7.5
Smoking, n (%)		27 (25.2)
Oral sicca, n (%)		89 (83.2)
Ocular sicca, n (%)		95 (88.8)
Arthritis, n (%)		74 (69.2)
Pulmonary involvement, n (%)		12 (11.2)
Renal involvement, n (%)		2 (1.9)
Neurological involvement, n (%)		3 (2.8)
Salivary gland biopsy positive, n (%)		66 (61.7)
Fibromyalgia, n (%)		55 (51.4)
Laboratory assessment		
ANA positivity, n: 96 (89,8%)	1/80	34 (31.8)
	1/160	23 (21.5)
	1/320	19 (17.8)
	1/640	11 (10.3)
	1/1280	9 (8.4)
Anti-SSA positivity, n (%)		66 (61.7)
Anti-SSB positivity, n (%)		32 (29.9)
Rheumatoid factor positivity, n (%)		48 (44.9)
C3, mean ± SD		1.42 ± 0.62
C4, mean ± SD		0.29 ± 0.15
CRP (mg/L), mean ± SD		3.94 ± 3.27
ESR (mm/h), mean ± SD		21.3 ± 12.8
Disease activity, function, PROs		
Oral VAS, mean ± SD		4.3 ± 3.2
Ocular VAS, mean ± SD		4.2 ± 2.7
ESSDAI score, mean ± SD		1.2 ± 1.0
ESSDAI group, n (%)	Low activity	93 (86.9)
	Moderate activity	7 (6.5)
	High activity	7 (6.5)
EQ-5D Index, mean ± SD		0.777 ± 0.178
SF-36 PCS, mean ± SD		79.9 ± 13.4
SF-36 MCS, mean ± SD		76.2 ± 12.6
Beck Depression Score, mean ± SD		16.7 ± 11.5
Depression group, n(%)	Minimal	39 (36.4)
	Mild	23 (21.5)
	Moderate	28 (26.2)
	Severe	17 (15.9)

Values are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate. ANA: antinuclear antibody; RF: rheumatoid factor; ESSDAI: EULAR Sjögren's Disease Activity Index; VAS: visual analog scale; EQ-5D-5L: EuroQol 5-dimension 5-level index; SF-36 PCS: Short Form-36 Physical Component Summary; SF-36 MCS: Short Form-36 Mental Component Summary; BDI: Beck Depression Inventory.

Table 2. Comparison of clinical, laboratory, and patient-reported outcomes according to systemic disease activity (ESSDAI categories).

Variable	Low ESSDAI (n=93)	Moderate–High ESSDAI (n=14)	p
Age (years), mean ± SD	50.48 ± 11.89	50.21 ± 10.96	0.875
Female sex, n (%)	88 (94.6%)	13 (92.9%)	1.000
Smoking, n (%)	21 (22.6%)	6 (42.9%)	0.194
Disease Duration (years), mean ± SD	7.38 ± 7.22	10.00 ± 9.04	0.327
Oral sicca, n (%)	77 (82.8%)	12 (85.7%)	1.000
Ocular sicca, n (%)	81 (87.1%)	14 (100.0%)	0.331
Arthritis, n (%)	62 (66.7%)	12 (85.7%)	0.259
Pulmonary involvement, n (%)	6 (6.5%)	6 (42.9%)	<0.001
Salivary gland biopsy positive, n (%)	56 (60.2%)	10 (71.4%)	0.610
Fibromyalgia, n (%)	43 (46.2%)	12 (85.7%)	0.014
EQ-5D-5L index < 0.80, n (%)	58 (62.4%)	4 (28.6%)	0.036
Laboratory assessment			
ANA positivity, n (%)	85 (91.4)	11 (78.6)	0.316
Anti-SSA positivity, n (%)	58 (62.4%)	8 (57.1%)	0.936
Anti-SSB positivity, n (%)	30 (32.3%)	2 (14.3%)	0.291
Rheumatoid factor positivity, n (%)	41 (44.1%)	7 (50.0%)	0.899
C3, mean ± SD	1.37 ± 0.48	1.74 ± 1.17	0.712
C4, mean ± SD	0.29 ± 0.15	0.29 ± 0.12	0.474
CRP (mg/L), mean ± SD	4.09 ± 3.39	2.96 ± 2.15	0.166
ESR (mm/h), mean ± SD	22.17 ± 12.83	15.21 ± 11.01	0.049
Disease activity, function, PROs			
Oral VAS, mean ± SD	4.37 ± 3.22	3.93 ± 3.38	0.538
Ocular VAS, mean ± SD	4.20 ± 2.65	4.43 ± 3.32	0.920
SF36_PCS	81.40 ± 12.65	69.62 ± 14.15	0.004
SF36_MCS	77.46 ± 12.05	68.12 ± 13.94	0.021
Beck Depression Score, mean ± SD	15.54 ± 11.12	24.36 ± 11.65	0.009

Patients were stratified according to systemic disease activity defined by ESSDAI as low versus moderate–high activity. Continuous variables were compared using the independ-ent-samples t test or Mann–Whitney U test, and categorical variables using the chi-square or Fisher's exact test, as appropriate. EQ-5D-5L index < 0.80 was used to define impaired health-related quality of life. ESSDAI: EULAR Sjögren's Disease Activity Index; EQ-5D-5L: EuroQol 5-dimension 5-level index; SF-36 PCS: Short Form-36 Physical Component Summary; SF-36 MCS: Short Form-36 Mental Component Summary; BDI: Beck Depres-sion Inventory.

Table 3. Multivariable logistic regression analysis identifying predictors of moderate–high ESSDAI (reference: low ESSDAI).

Variable	Adjusted OR	95% CI	p
Pulmonary involvement	8.12	2.01–32.78	0.003
Fibromyalgia	4.17	1.28–13.61	0.018
Erythrocyte sedimentation rate (per mm/h in-crease)	0.94	0.89–0.99	0.041

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using multivariable logistic regression analysis. Moderate–high systemic disease activity as assessed by the EU-LAR Sjögren's Syndrome Disease Activity Index (ESSDAI) was defined as the outcome variable, with low ESSDAI used as the reference category. The multivariable model includ-ed clinically relevant variables identified in univariable analyses and selected to minimize model overfitting.

Table 4. Diagnostic performance of oral and ocular dryness severity for identifying fibromyalgia in primary Sjögren's disease.

Measure	Optimal Cut-off (Youden Index)	Sensitivity	Specificity	Youden J
Oral Dryness VAS	≥ 7.0	0.46	0.76	0.22
Ocular Dryness VAS	≥ 5.0	0.43	0.82	0.25
Combined Oral and Ocular Dryness*	Oral ≥ 7.0 and Ocular ≥ 5.0	0.34	0.88	0.22

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of oral and ocular dryness visual analog scale (VAS) scores, as well as combined dryness categories, for identifying comorbid fibromyalgia. Optimal cut-off values derived from Youden's index, sensitivity, specificity, and corresponding odds ratios are presented.

Table 5. Association between dryness severity and fibromyalgia primary Sjögren's dis-ease.

Dryness Measure (Cut-off)	Fibromyalgia (%) – High VAS	Fibromyalgia (%) – Low VAS	Odds Ratio (OR)	p
Oral Dryness VAS ≥ 7	69.7	43.2	3.02	0.020
Ocular Dryness VAS ≥ 5	68.9	38.7	3.51	0.0039
Combined Oral and Ocular Dry-ness*	76.7	41.6	4.62	0.0023

Receiver operating characteristic (ROC) curve analysis was conducted to assess the dis-criminative ability of oral dryness, ocular dryness, and combined oral–ocular dryness visu-al analog scale (VAS) scores for identifying fibromyalgia. Diagnostic accuracy is summa-rized using area under the curve (AUC), sensitivity, specificity, and odds ratios.

Supplementary Table S1. Symptom-based clusters identified by unsupervised analysis in primary Sjögren's disease

Cluster	Oral VAS	Ocular VAS	EQ-5D Index	SF-36 PCS	SF-36 MCS	Beck Depression Score	Clinical Interpreta-tion
Cluster 1 (Dryness-dominant)	7.7	7.3	0.72	78.5	74.4	15.5	Severe dryness with moderate functional impairment
Cluster 2 (Low-bur-den)	2.3	2.6	0.92	89.3	84.8	9.9	Mild symptoms and preserved quality of life (best profile)
Cluster 3 (High symp-tom amplifi-cation)	4.1	3.8	0.56	62.2	61.1	32.1	Severe depression, poor quality of life, likely fibromyalgia phenotype

This table presents the characteristics of symptom-based clusters identified using unsupervised k-means clustering analysis. Clustering was performed using standardized patient-reported outcome measures, including oral and ocular dryness visual analog scale (VAS) scores, EQ-5D index values, SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, and Beck Depression Inventory scores. Values are presented as mean ± standard deviation. The clusters represent dis-tinct symptom profiles within the study population.

Supplementary Table 2. Distribution of immunosuppressive and symptomatic treatments in patients with Primary Sjögren's Disease (n = 107).

Treatment Regimen	n	%
No treatment	4	3.7
Hydroxychloroquine	35	32.7
Hydroxychloroquine + Steroid	16	15.0
Hydroxychloroquine + Azathioprine + Steroid	4	3.7
Hydroxychloroquine + Steroid + Pilocarpine	16	15.0
Pilocarpine only	4	3.7
Cevimeline	2	1.9
Hydroxychloroquine + Leflunomide	3	2.8
Methotrexate	3	2.8
Non-steroidal anti-inflammatory drugs	1	0.9
Hydroxychloroquine + Pilocarpine	14	13.1
Pilocarpine + Steroid	1	0.9
Pilocarpine + Leflunomide	1	0.9
Methotrexate + Hydroxychloroquine + Pilocarpine	1	0.9
Azathioprine + Hydroxychloroquine + Pilocarpine	2	1.9

This table summarizes current immunomodulatory and symptomatic treatment regimens at the time of clinical assessment. Treatments are presented as number (percentage) of pa-tients receiving each therapy. Combination therapies reflect routine real-world clinical practice. Percentages are calculated based on the total study population.

Supplementary Table S3. Spearman correlation matrix of patient-reported outcome measures in Primary Sjögren's Disease.

Variable	Oral Dryness VAS	Ocular Dryness VAS	EQ-5D Index	SF-36 PCS	SF-36 MCS	Beck De-pression Score
Oral Dryness VAS	1.00	0.75	–0.39	–0.25	–0.26	0.20
Ocular Dryness VAS	0.75	1.00	–0.35	–0.24	–0.24	0.17
EQ-5D Index	–0.39	–0.35	1.00	0.90	0.88	–0.76
SF-36 PCS	–0.25	–0.24	0.90	1.00	0.86	–0.76
SF-36 MCS	–0.26	–0.24	0.88	0.86	1.00	–0.75
Beck Depression Score	0.20	0.17	–0.76	–0.76	–0.75	1.00

This table shows Spearman rank correlation coefficients between patient-reported outcome measures, including oral and ocular dryness visual analog scale (VAS) scores, EQ-5D index val-ues, SF-36 Physical Component Summary (PCS), SF-36 Mental Component Summary (MCS), and Beck Depression Inventory scores. Correlation coefficients indicate the strength and direction of associations between variables.

Discussion

The present study demonstrates that sicca symptom severity and systemic inflammatory activity in primary Sjögren's disease represent largely independent yet interacting dimensions of disease burden. Although oral and ocular dryness remain the defining and most distressing manifestations of pSD, our findings indicate that the intensity of sicca symptoms does not parallel systemic disease activity as assessed by ESSDAI. This dissociation reinforces the growing recognition that patient-perceived symptom burden and objective inflammatory involvement constitute distinct clinical domains that should be interpreted in a complementary rather than interchangeable manner [11].

The absence of a meaningful association between dryness severity and systemic disease activity is consistent with prior studies reporting weak or inconsistent correlations between patient-reported symptoms and objective inflammatory indices in pSD. Sicca manifestations are shaped by multiple non-inflammatory mechanisms, including irreversible glandular damage, epithelial–immune cell dysregulation, autonomic dysfunction, altered sensory processing, and central symptom amplification. Importantly, these processes may persist or even progress despite adequate suppression of immune-mediated inflammation, particularly in patients with long-standing disease. Consequently, high dryness scores are more likely to reflect cumulative tissue damage and symptom amplification rather than active systemic inflammation. From a clinical standpoint, this distinction is critical, as misinterpreting severe sicca symptoms as markers of inflammatory activity may lead to inappropriate escalation of immunosuppressive therapy with limited symptomatic benefit [11].

Notably, the majority of patients in the present cohort were receiving ongoing immunomodulatory or symptomatic treatments at the time of assessment. This real-world treatment context likely contributed to the predominance of low ESSDAI scores and attenuation of measurable systemic inflammatory activity. At the same time, the persistence of sicca symptoms, impaired quality of life, and psychological distress despite active treatment highlights that symptom burden in treated pSD does not necessarily resolve in parallel with inflammatory control. These findings suggest that the observed dissociation between dryness severity and systemic activity reflects disease behavior under conditions of routine clinical management rather than untreated disease, thereby enhancing the clinical relevance and generalizability of our results.

In contrast to sicca severity, objective systemic involvement emerged as a key determinant of higher disease activity. Pulmonary manifestations were independently associated with moderate to high ESSDAI scores, underscoring their central role in defining systemic disease severity in pSD. This observation aligns with previous evidence identifying pulmonary involvement as a major contributor to morbidity and adverse long-term outcomes in pSD. Beyond reflecting current disease activity, pulmonary and other organ involvements may cluster with broader systemic immune dysregulation and increased risk of severe complications, including lymphoproliferative disorders in susceptible patient subsets [12].

Fibromyalgia emerged as an independent correlate of higher systemic disease activity in multivariable analysis. Although traditionally considered a non-inflammatory comorbidity,

fibromyalgia is highly prevalent in pSD and closely associated with pain, fatigue, and global symptom burden. Central sensitization, a core pathophysiological mechanism in fibromyalgia, may amplify a broad spectrum of somatic symptoms attributed to pSD, while chronic immune-mediated disease may predispose to or perpetuate sensitization. These bidirectional interactions position fibromyalgia as an active modulator of symptom perception rather than a passive epiphenomenon, with important implications for clinical assessment and management. Systematic screening for fibromyalgia and implementation of tailored, symptom-oriented interventions should therefore be considered integral components of comprehensive pSD care [13].

Health-related quality-of-life impairment was substantial across the cohort and demonstrated strong internal correlations across measurement instruments. However, quality-of-life indices did not retain independent associations with systemic disease activity after adjustment, indicating that reduced quality of life predominantly represents a downstream consequence of symptom burden rather than a direct surrogate of inflammatory disease severity. Psychological comorbidities, particularly depressive symptoms, emerged as major contributors to overall disease impact, often exerting a stronger influence on patient well-being than objective inflammatory measures. These findings further underscore the importance of integrating psychosocial assessment and support into routine pSD management [13].

The cluster analysis provides additional insight into the heterogeneity of pSD and represents a key strength of this study. The identification of a symptom-amplification phenotype characterized by pronounced impairment in quality of life and psychological burden, despite only moderate dryness severity and limited systemic activity, highlights the limitations of single-domain assessment tools. This phenotype was not driven by extreme sicca severity or high ESSDAI scores but by disproportionate mental and functional impairment, supporting the existence of distinct non-inflammatory, symptom-driven subgroups within pSD. Such stratification offers a clinically actionable framework, whereby patients within symptom-amplification clusters may derive greater benefit from multimodal strategies targeting central sensitization and mood disturbance, whereas patients with objective systemic involvement warrant closer monitoring and optimization of immunomodulatory therapy [14].

Limitations of the study

Several limitations should be acknowledged. The cross-sectional design precludes causal inference, and the single-center setting may limit generalizability. In addition, the relatively small number of patients with moderate to high systemic disease activity resulted in a limited event-per-variable ratio in multivariable analyses, raising the possibility of model instability. Furthermore, fibromyalgia diagnosis was based on documented clinical assessment rather than uniform application of standardized classification criteria, which may have introduced misclassification bias. These limitations should be considered when interpreting fibromyalgia-related findings. Nevertheless, the comprehensive integration of objective disease activity indices, detailed patient-reported outcomes, and advanced analytical approaches, including regression modeling and clustering, constitutes a major strength of the present study.

In conclusion, in primary Sjögren's disease, sicca symptom severity predominantly reflects functional impairment and psychological burden rather than systemic inflammatory activity. While objective systemic involvement, particularly pulmonary manifestations, together with fibromyalgia, emerged as key determinants of higher disease activity, dryness intensity showed limited utility for identifying active systemic disease. These findings highlight the multidimensional and heterogeneous nature of pSD and support a phenotype-oriented, patient-centered assessment strategy that integrates objective inflammation with symptom burden, central sensitization, and psychosocial factors to guide individualized management and avoid unnecessary immunosuppression [11–14].

Declaration of conflicting interests

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Ethics approval

This study was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (Approval No: E-60116787-020-738231; Decision Date: 12 August 2025).

Authors' contribution

U.B.: Conceptualization, methodology, formal analysis, investigation, data curation, writing - original draft, visualization, project administration. T.İ.D.: Conceptualization, methodology, resources, validation, writing - review & editing, supervision.

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