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Determinants and clinical correlates of minor salivary gland biopsy findings for suspected Sjögren disease: a single center retrospective analysis

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Abstract

This study aims to investigate the clinical and pathological characteristics of patients who underwent minor salivary gland biopsy (mSGB) for suspected Sjögren disease (SjD). A total of one hundred five patients who underwent mSGB at a tertiary rheumatology center over a two-year period were included in the study. Demographic and disease characteristics of patients were recorded from electronic health records. The histopathological evaluation of the mSG was performed according to focus score (FS). The ESSDAI and ESSPRI scores were used for disease activity. The study data were analyzed by dividing patients into groups according to whether they met the SjD Classification Criteria and had focal lymphocytic sialadenitis (FLS). The median symptom duration of patients was 28.0 (8–102) months, and 68.5% (72; 105) of them met the SjD Classification Criteria before biopsy. 11.1% of SjD patients (8; 72) had also overlap syndrome. The number of patients with FS ≥ 1 (42, 58.33% vs. 11, 33.33%; $p < 0.001$), ESSDAI (4.21 ± 2.23 vs. 3.64 ± 2.12; $p = 0.023$), and ESSPRI-dryness scores (5.12 ± 1.51 vs. 4.72 ± 1.54; $p = 0.018$) were significantly higher in patients who met the SjD classification criteria than in patients who did not meet the criteria. According to histopathology findings, xerostomia (86.7% vs. 75.0%; $p = 0.012$), xerophthalmia (75.4% vs. 63.5%; $p = 0.024$), fatigue (54.7% vs. 42.3%; $p = 0.035$), ANA (81.1% vs. 69.2%; $p < 0.001$), SSA (35.8% vs. 26.9%; $p = 0.041$), and SSB (18.8% vs. 13.4%; $p = 0.047$) positivity rates were significantly higher in FLS positive (FS ≥ 1) group than the negative group (FS < 1). The unstimulated whole saliva flow [OR (95% CI) = 2.58 (0.94–7.02)] and Schirmer's test [OR (95% CI) = 2.89 (1.04–7.97)] were identified as predictors of FS. This study demonstrated that, whereas diagnostic biopsy findings are predominantly observed in seropositive patients and/or meeting the criteria, FLS positivity is relatively frequent in seronegative individuals who do not fulfill SjD classification criteria. The present study also represented that objective measurements of the sicca symptoms predict FLS.

Keywords Sjögren disease · Minor salivary gland biopsy · Xerostomia · Focal lymphocytic sialadenitis · Diagnosis

Introduction

Sjögren disease (SjD) is a chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, especially the salivary and lacrimal glands [1, 2]. The manifestation of SjD can occur in isolation or in conjunction with various systemic autoimmune rheumatic diseases. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis could be overlap with SjD [2, 3].

Lymphocytic infiltration has been documented as a hallmark feature in the etiopathogenesis of SjD, manifesting within the exocrine glands [1]. Lesions that are histopathologically identified as benign lymphoepithelial sialadenitis have the potential to progress to B-cell lymphoma in a

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chronic process [4]. The observation of focal lymphocytic sialadenitis (FLS) on minor salivary gland biopsy (mSGB) specimens is a highly sensitive and specific diagnostic and classification tool for the disease [4, 5].

In the clinical setting, patients presenting to the rheumatology outpatient clinic with sicca and non-sicca symptoms should be considered in the differential diagnosis. These patients may have a variety of underlying conditions, including diabetes, anticholinergic drug use, active hepatitis C infection, ionizing radiation to the neck region, acquired immunodeficiency syndrome (AIDS), amyloidosis, graft versus host disease, IgG4-related disease, and sarcoidosis [1, 4, 6]. The mSGB is recommended in patients with clinical and laboratory suspicion of SjD [6, 7]. While the biopsy result is frequently compatible with SjD, there is no clinicopathologic concordance in several cases [8]. In overlap syndromes, FLS in the salivary gland is observed, compatible with SS, and symptoms and findings related to secondary rheumatic disease are also noted [2].

In this study, we aimed to evaluate the results of mSGB performed in patient with a suspicion of SjD who were admitted to the rheumatology outpatient clinic, together with clinical data from the last two years. The findings of this study will shed light on the decision-making process for patients undergoing mSBG in rheumatology clinical practice.

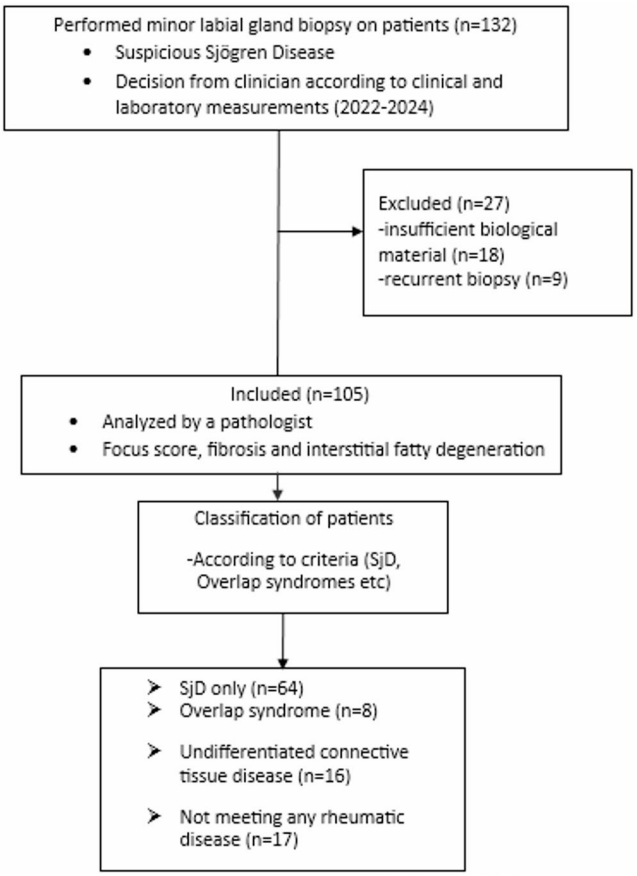

Fig. 1 Flowchart of the study

Materials and methods

Study design and population

This study retrospectively included patients who submitted applications to a tertiary rheumatology center and underwent mSGB with suspicion of SjD within a two-years (December 2022–December 2024).

To ensure standardization in patient selection, the decision to perform a mSGB in patients with a suspicion of SjD was made by the same clinician (KA; a rheumatologist with over 10 years of clinical experience) at a single tertiary rheumatology center. Undergoing a biopsy, patients presenting to the outpatient clinic with various symptoms are evaluated using a standardized form. The evaluation encompasses a series of components, including rheumatic symptomatology, physical examination findings, and laboratory test results.

The demographic and clinical data of the patients were obtained from the electronic patients' records. The inclusion criteria encompassed individuals who were at least 18 years of age and had undergone a mSGB, with a preliminary diagnosis of SjD.

Exclusion criteria were active hepatitis C infection, ionizing radiation to the neck, AIDS, amyloidosis, graft versus host disease, IgG4-related disease, sarcoidosis, and a history of malignant/premalignant lesions in the parotid and submandibular glands. The flow diagram illustrating the study's methodology is presented in Fig. 1.

The present study was formally endorsed by the Kastamonu Medical School Ethics Committee (approval date: 23/10/2024 and protocol number: 2024-KAEK-83). Written informed consent was signed by all participants before the mSGB. During the study period, the World Medical Association Helsinki Declaration (the latest version as of December 2024) and Good Clinical Practice Guidelines were implemented.

Clinical characteristics and disease activity measurements

The clinical data included the patient's diagnosis, the first symptom and time of onset, current clinical manifestations, laboratory test results, the Schmer test results (mm/5 min), the salivary flow rate test results (ml/15 min), medications, comorbidities, and disease activity. Laboratory tests included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complete blood count parameters,

complement 3 and 4 levels, rheumatoid factor (RF), antinuclear antibodies (ANA), and anti-Ro (SS-A) and anti-La (SS-B) antibodies.

The EULAR Sjögren's syndrome disease activity index (ESSDAI) and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) were used as disease activity measures. The ESSPRI is a patient-based numerical scale that measures pain, fatigue, and dryness. Each score is evaluated on a scale of 0 to 10. A high score indicates high disease activation. The ESSDAI is a physician-centered clinical index consisting of 12 domains: cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, lymphadenopathic, and biological. Each domain is graded into three to four levels of activity. Each activity level has a numeric value ranging from 0 to 18 [9]. These two indices have been validated in numerous studies and are considered the gold standard for measuring disease activity in patients with pSS [10, 11].

Pathologic evaluation of minor salivary glands

The histopathological evaluation of the minor salivary gland was performed in accordance with the definition proposed by Fisher et al., as outlined in the classification criteria [5]. Consequently, the presence of FLS was evaluated for the purpose of SjD classification. The term "FLS" refers to the histopathologic pattern characterized by the presence of one or more foci in biopsies, while the tissue surrounding these foci consists primarily of unaffected parenchyma. The term "focus" is defined as the sum of 50 lymphocytes, and the focus score (FS) is the total number of foci per 4 mm^2 of salivary gland tissue. An FS$\geq$1 in the examined material is considered a positive biopsy and is classified as SjD [5, 7]. In addition to the FS, the presence of tissue fibrosis and interstitial fatty degeneration in the salivary gland was also evaluated.

Disease classification criteria

In this study, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) 2016 Classification Criteria were used to classify patients as SjD [7]. This criterion was based on the weighted sum of the following five items: positivity for anti-SSA/Ro antibodies, FLS, an abnormal ocular staining score, a reduced Schirmer's test, and a reduced unstimulated salivary flow rate [7]. Subjects exhibiting signs and/or symptoms indicative of SjD, with a score exceeding 4 for the items as mentioned earlier, meet the 2016 ACR/EULAR Classification Criteria for SjD, exhibiting excellent sensitivity and specificity. This criterion was developed and validated an updated set of classification criteria [12]. Furthermore, patients were classified according to the 2019 EULAR/ACR classification criteria for the diagnosis of SLE [13], the 2010 RA classification criteria for the diagnosis of RA [14], and the 2013 classification criteria for SSc [15] for the diagnosis of SSc. The diagnosis of mixed connective tissue disease (MCTD) was determined by the presence of U1-RNP antibody positivity, in conjunction with clinical involvement. The diagnosis of relapsing polychondritis (RP) was made based on clinical findings, which included the presence of inflammation in cartilage tissues, primarily in the nose, ears, airways, and joints.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, Version 21.3, Chicago, IL). software. The variables were investigated using both visual and analytic methods (Shapiro–Wilk/Kolmogorov–Smirnov test) to determine whether they were normally distributed. The descriptive parameters reported included the mean (±standard deviation), median (min–max), frequency distribution, and percentage. To compare variables between patients who met the SjD Classification Criteria and those who did not, the Student T test was used for normally distributed variables, and the Chi-square test was used for categorical variables. A comparative analysis was conducted between patients with an FS of $\geq$1 and those with a FS of $<$1. To define independent risk factors associated with the the outcome variable (FS$\geq$1 in biopsy), univariate and multivariate logistic regression analysis was used. To circumvent multicollinearity, the most clinically important risk factor among statistically highly correlated risk factors was included in the multiple logistic regression analysis. The Hosmer and Lemeshow Test and Nagelkerke R Square were used to assess the model's fit. Receiver operating characteristic (ROC) analysis was employed to determine variables that predict focal lymphocytic sialadenitis. The area under the curve (AUC) was estimated from the ROC curves. A p value of less than 0.05 and a 95% confidence interval (CI) of were set as statistically significant for all comparisons.

Results

In this study, the mean age of 105 patients included was 53.07(±11.46) years, and the median symptom duration was 28.0(8-102) months. The three most common initial symptoms were xerostomia (38; 36.5%), arthralgia (20; 19.0%) and fatigue (13; 12.4%), and the most current symptoms were xerostomia (85; 80.9%), arthralgia (78; 74.3%) and xerophthalmia (72; 68.5%).

Table 1 Demographic and clinical characteristics of patients receiving minor salivary gland biopsy

	All patients ($n=105$)
Age, mean (±SD)	53.07 (±11.46)
Sex, female, n (%)	99 (94.3)
BMI, mean (±SD)	26.72 (±3.43)
Tobacco use, n (%)	30 (28.57)
Symptom duration, month, med (min–max)	28.0 (8–102)
First symptom, n (%)	
Xerophthalmia	10 (9.6)
Xerostomia	38 (36.5)
Xerophthalmia & xerostomia	9 (8.7)
Arthralgia	20 (19.0)
Raynaud phenomenon	6 (5.7)
Fatigue	13 (12.4)
Others	9 (8.6)
Xerostomia, n (%)	85 (80.9)
Xerophthalmia, n (%)	72 (68.5)
History of parotitis, n (%)	6 (5.7)
Sialomegaly, n (%)	3 (2.9)
Hyperlobulation of tongue, n (%)	2 (1.9)
Arthralgia, n (%)	78 (74.3)
Raynaud phenomena, n (%)	15 (14.3)
Fatigue, n (%)	51 (48.7)
Diabetes mellitus, n (%)	12 (11.4)
Hypothyroidism, n (%)	11 (10.4)
RF positivity, n (%)	20 (19.0)
ANA positivity, n (%)	79 (75.2)
Anti-Ro (SS-A) positivity, n (%)	33 (31.4)
Anti-La (SS-B) positivity, n (%)	17 (16.2)
Unstimulated whole saliva flow rate≤0.1 ml/m, n (%)	54 (51.4)
Schirmer's test≤5 mm/5 m in at least one eye, n (%)	65 (61.9)
Meeting SjD classification criteria before biopsy	72 (68.5)

RF rheumatoid factor, *BMI* body mass index, *ANA* anti-nuclear antibody, *SjD* Sjögren disease

ANA positivity (79; 75.2%), anti-Ro positivity (33; 31.4%), and anti-La positivity (17; 16.2%) were observed. The rate of salivary test abnormality (unstimulated whole saliva flow rate≤0.1 ml/m) was 51.4%, and the rate of Schirmer's test positivity was 61.9%. In contrast, the rate of patients classified as SjD (according to SjD classification criteria) before biopsy was 68.5%. Other demographic and clinical data of the patients are summarized in Table 1.

Among patients who met the SjD classification criteria prior to a mSGB, the number of patients with FS≥1 (42, 58.33% vs. 11, 33.33%; $p<0.001$), tissue fibrosis (20, 27.78% vs. 6, 18.18%; $p=0.012$), and interstitial fatty degeneration (38, 52.78% vs. 10, 30.30%; $p=0.002$) were higher than those who did not meet the SjD classification criteria. The ESSDAI score (4.21±2.23 vs. 3.64±2.12; $p=0.023$) and ESSPRI-dryness score (5.12±1.51 vs. 4.72±1.54; $p=0.018$) were significantly higher in those who met the SjD classification criteria. However, ESSPRI-fatigue and ESSPRI-pain scores were similar in both groups ($p=0.246$ and $p=0.312$, respectively) (Table 2).

Table 2 Comparison of patients who Met and did not Meet the SjD classification criteria before minor salivary gland biopsy

	Group 1 (meeting the SjD classification criteria) $n=72$	Group 2 (not meeting the SjD classification criteria) $n=33$	*P*
Focus score≥1, n (%)	42 (58.33)	11 (33.33)	**<0.001**
Tissue fibrosis, n (%)	20 (27.78)	6 (18.18)	**0.012**
Interstitial fatty degeneration, n (%)	38 (52.78)	10 (30.30)	**0.002**
ESSDAI score	4.21 (±2.23)	3.64 (±2.12)	**0.023**
ESSPRI-dryness score	5.12 (±1.51)	4.72 (±1.54)	**0.018**
ESSPRI-fatigue score	4.46 (±1.35)	4.41 (±1.32)	0.246
ESSPRI-pain score	4.76 (±1.14)	4.67 (±1.18)	0.312
CRP (mg/L)	6.12 (±2.24)	4.13 (±3.28)	0.078
Erythrocyte sedimentation rate(mm/h)	15.86 (±7.89)	11.12 (±8.97)	0.117
Leukocytes (*10^3) (n/mcL)	6.77 (±2.27)	6.57 (±2.68)	0.248
Hemoglobin (mg/L)	13.48 (±1.47)	13.27 (±1.59)	0.346
Platelet (*10^3) (n/mcL)	271.38 (±90.32)	258.24 (±75.19)	0.108
Low Complement 3, n(%)	6 (8.33)	1 (3.03)	0.428
Low Complement 4, n(%)	6 (8.33)	0 (0.0)	0.173

ESSDAI EULAR Sjögren's syndrome disease activity index, *ESSPRI* the EULAR Sjögren's Syndrome Patient Reported Index, *CRP* C-reactive protein. The statistical significant p values are represented by bold characters

Regarding to pathology results, when the patients were divided into two groups as FS≥1, and FS<1 on pathology and compared, xerostomia (86.7% vs. 75.0%; $p=0.012$), xerophthalmia (75.4% vs. 63.5%; $p=0.024$), history of parotitis (7.5% vs. 3.8%; $p=0.048$), sialomegaly (3.8% vs. 1.9%; $p=0.034$), and fatigue (54.7% vs. 42.3%; $p=0.035$) were significantly higher in the group with FS≥1. In addition, ANA positivity (81.1% vs. 69.2%; $p<0.001$), SS-A (35.8% vs. 26.9%; $p=0.041$), and SS-B (18.8% vs. 13.4%; $p=0.047$) positivity rates were significantly higher in those with higher pathology scores (Table 3).

In univariate analysis, which examining the factors affecting the FS (positive FLS), ESSPRI-dryness score [OR (95% CI)=1.39 (1.05–1.84), $p=0.018$], unstimulated whole saliva flow [OR (95% CI)=4.62 (2.02–10.56), $p<0.01$], and Schirmer's test [OR (95% CI)=4.64 (1.96–11.01), $p<0.01$] were found to be significant. In multivariable regression analysis, only Schirmer's test [OR (95%

Table 3 Comparison of patients with focus score ≥ 1 and < 1 according to minor salivary gland biopsy results

Variables, *n* (%)	Patient with ≥1 focus score (*n* = 53)	Patients with < 1 focus score (*n* = 52)	*P*
Smoking	13 (24.5)	17 (32.6)	0.322
Diabetes mellitus	7 (13.2)	5 (9.6)	0.587
Hypothyroidism	7 (13.2)	4 (7.6)	0.112
Xerostomia	46 (86.7)	39 (75.0)	**0.012**
Xerophthalmia	40 (75.4)	33 (63.5)	**0.024**
History of parotitis	4 (7.5)	2 (3.8)	**0.048**
Sialomegaly	2 (3.8)	1 (1.9)	**0.034**
Hyperlobulation of tongue	1 (1.9)	1 (1.9)	0.978
Arthralgia	40 (75.4)	38 (73.1)	0.910
Raynaud phenomenon	7 (13.2)	8 (15.4)	0.719
Fatigue	29 (54.7)	22 (42.3)	**0.035**
ANA positivity	43 (81.1)	36 (69.2)	**< 0.001**
SS-A positivity	19 (35.8)	14 (26.9)	**0.041**
SS-B positivity	10 (18.8)	7 (13.4)	**0.047**

ANA anti-nuclear antibody. The statistical significant p values are represented by bold characters

CI) = 2.89 (1.04–7.97), $p = 0.040$] were found to have a significant relationship with focus score (Table 4). Receiver operating characteristic (ROC) analyses were conducted to identify factors that predict FLS. The analyses revealed that unstimulated whole saliva flow (AUC = 0.683, $p = 0.001$), Schirmer's test (AUC = 0.681, $p = 0.002$), and the ESSPRI-dryness score (AUC = 0.637, $p = 0.016$) were statistically significant predictors (Fig. 2).

Of the 72 patients who met the SjD classification criteria, 64 were classified based on salivary gland biopsy results and clinical data, while eight had overlap syndrome accompanying pSS. When comparing SjD patients with and without overlap syndrome, arthritis (62.5% vs. 20.31%, $p = 0.009$), Raynaud's phenomenon (50.0% vs. 10.93%, $p = 0.004$), photosensitivity (50.0% vs. 18.75%, $p = 0.045$), and dyspnea (25.0% vs. 4.68%, $p = 0.033$) were statistically significantly more common in the overlap group. Rheumatoid factor positivity (62.5% vs. 20.31%, $p = 0.009$), CRP level (9.79 (±6.76) vs. 4.99 (±3.77), $p = 0.049$), cytopenia frequency ($p < 0.05$ for all series), and ESSDAI score (7.62 (±5.62) vs. 4.03 (±2.31), $p = 0.001$) were statistically higher in the overlap group. In comparison, positive Schirmer's test (50.0% vs. 85.93%, $p = 0.013$) and unstimulated whole saliva flow rate (37.5% vs. 75.0%, $p = 0.028$) were higher in SjD patients without overlap syndrome (Table 5). Of the eight patients with overlap syndrome, two met the classification criteria for SSc, two for MCTD, two for RA, one for SLE, and one for RL. Details of the eight patients with overlap syndrome are summarized in Supplementary Table 1.

Table 4 Univariable and multivariable regression results on analysis of factors affecting minor salivary gland pathology (dependent variable focus score ≥ 1)

Independent variables	Binary Logistic regression			Multivariable regression models					
				Model 1		Model 2		Model 3 (final model)	
	Beta	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (older)	0.025	1.02 (0.99–1.06)	0.155	–	–	–	–	–	–
Symptom duration	0.020	1.02 (0.99–1.04)	0.089	1.00 (0.97–1.03)	0.882	–	–	–	–
Smoking	0.431	1.53 (0.65–3.61)	0.323	–	–	–	–	–	–
Diabetes mellitus	0.336	1.40 (0.41–4.73)	0.588	–	–	–	–	–	–
Xerostomia	0.549	1.73 (0.64–4.66)	0.278	0.90 (0.20–3.95)	0.890	0.98 (0.23–4.16)	0.979	–	–
Xerophthalmia	0.418	1.51 (0.65–3.51)	0.328	0.50 (0.13–1.87)	0.303	0.46 (0.12–1.71)	0.251	–	–
Parotitis	0.693	2.00 (0.35–11.42)	0.436	1.51 (0.09–25.55)	0.772	1.75 (0.08–37.35)	0.717	–	–
Fatigue	0.465	1.59 (0.73–3.45)	0.239	1.35 (0.50–3.65)	0.553	1.54 (0.60–3.98)	0.364	–	–
Sialomegaly	– 0.673	0.51 (0.04–5.80)	0.587	0.81 (0.01–41.24)	0.921	0.63 (0.01–33.88)	0.823	–	–
ESSDAI	0.133	1.14 (0.96–1.34)	0.116	–	–	–	–	–	–
ESSPRI-dryness	0.335	1.39 (1.05–1.84)	**0.018**	1.13 (0.74–1.71)	0.557	1.10 (0.74–1.65)	0.622	1.06 (0.76–1.46)	0.721
ESSPRI-fatigue	0.139	1.14 (0.86–1.53)	0.345	1.04 (0.70–1.55)	0.823	1.10 (0.75–1.61)	0.600	–	–
ESSPRI-pain	0.272	1.31 (0.93–1.85)	0.121	1.28 (0.83–1.95)	0.252	–	–	–	–
ANA	0.583	1.79 (0.71–4.47)	0.211	1.43 (0.44–4.59)	0.542	1.39 (0.45–4.34)	0.562	–	–
SS-A (anti-Ro)	0.210	1.23 (0.53–2.82)	0.618	0.95 (0.27–3.27)	0.935	0.90 (0.26–3.11)	0.879	–	–
SS-B (anti-La)	0.380	1.46 (0.51–4.19)	0.480	1.08 (0.26–4.45)	0.913	1.13 (0.28–4.49)	0.856	–	–
Unstimulated whole saliva flow rate ≤ 0.1 ml/m, n (%)	1.531	4.62 (2.02–10.56)	**< 0.01**	2.63 (0.81–8.53)	0.107	2.96 (0.94–9.32)	0.062	2.58 (0.94–7.02)	0.063
Schirmer's test ≤ 5 mm/5 m in at least one eye, n (%)	1.536	4.64 (1.96–11.01)	**< 0.01**	3.54 (0.23–53.28)	0.360	3.06 (0.22–42.22)	0.403	2.89 (1.04–7.97)	**0.040**

ESSDAI EULAR Sjögren's syndrome disease activity index, *ESSPRI* the EULAR Sjögren's Syndrome Patient Reported Index, *CRP* C-reactive protein, *ANA* anti-nuclear antibody, *CI* confidence interval. The statistical significant p values are represented by bold characters

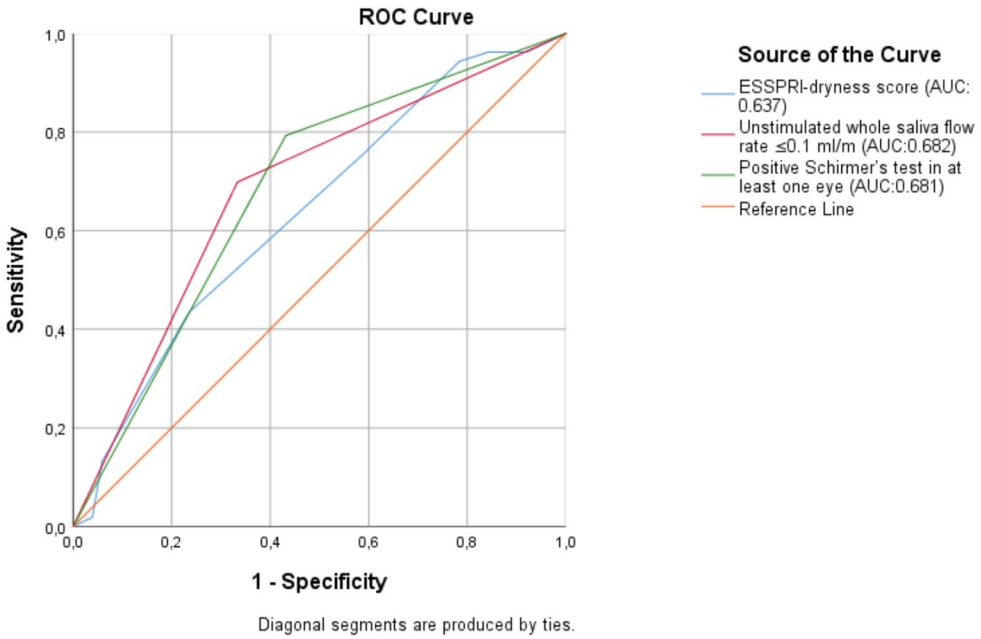

Fig. 2 Receiver operating characteristic curve for the focal lymphocytic sialadenitis (focus score ≥ 1)

Discussion

This study demonstrates that rheumatic manifestations particularly arthralgia and fatigue, should be incorporated into the diagnostic evaluation of patients undergoing mSGB, as well as sicca. For these patients, the presence of specific antibody positivity (anti-Ro and anti-La) is of significant. However, ANA positivity alone should be evaluated meticulously.

While meeting the pSjD classification criteria prior to biopsy appears to be compatible with a positive FLS, a positive biopsy result is observed in patients who do not meet the criteria at a significant rate (approximately one-third of patients). Furthermore, objective measurements of tear and saliva levels, as opposed to patient-reported symptoms, were found to be associated with a positive biopsy outcome.

Which patients should perform mSGB at the outpatient clinic?

The diagnosis of SjD is based on a combination of clinical findings, serologic and functional tests, and histologic evaluation [1]. Furthermore, ultrasonographic evaluation of the parotid and submandibular glands in patients presenting with sicca symptoms also provides supportive information in the diagnosis of SjD [16]. Although biopsies are performed from major salivary glands for scientific purposes, histopathological examination is performed from minor salivary glands because it is less invasive and easier [17].

Fatigue is observed in 50% of SjD patients. The subjective nature of the fatigue assessment and its susceptibility to social factors, the prevalence of fatigue may vary (30.1–69.1%) across different cohorts [18–20]. In this study, patients may have experienced relatively low levels of fatigue due to several factors. One potential explanation is that the patients were newly diagnosed with Sjögren syndrome and had experienced a relatively brief period of symptoms.

The mSGB is a crucial component of the diagnostic process for patients with SjD. This procedure enables precise classification and differential diagnosis, which can include conditions such as sarcoidosis and amyloidosis [17]. In our clinic, mSGB is performed in every patient with suspicion of SjD, regardless of whether the current findings meet the classification criteria. In clinical practice, a systematic decision process must be implemented to select patients for biopsy in cases where SjD is suspected [21]. A recent study has indicated that smoking and antihistamine use should be evaluated before performing mSGB in seronegative patients with sicca symptoms [22]. In the same study, FLS was found to be associated with SS-A positivity and xenophthalmia [22]. Our comprehensive two-year dataset revealed that arthralgia, fatigue, and Raynaud's phenomenon should be considered in conjunction with sicca symptoms when planning for a biopsy.

According to the SjD classification criteria, the presence of anti-Ro/anti-La positivity or histologic FLS is considered an essential criterion for the diagnosis of SjD [7]. In our study, the specific serologic test positivity rate before biopsy was low (maximum anti-Ro; 31.4%) and ANA positivity was higher (75.2%). As is well-documented in the existing literature, some patients with SjD are specific antibody-negative [23]. Additionally, the importance of ANA and RF for SjD classification was observed in an observational study

Table 5 Comparison of Sjögren disease patients with and without overlap syndromes

	Sjögren patients with overlap syndromes ($n=8$)	Sjögren patients without overlap syndromes ($n=64$)	*P*
Age, mean (±SD)	55.87 (±14.98)	53.29 (±10.95)	0.549
Sex, female, n (%)	7 (87.5)	60 (93.75)	0.512
BMI, mean (±SD)	25.66 (±3.47)	26.82 (±3.47)	0.379
Symptom duration, month, med (min–max)	37.00 (12–98)	30.00 (8-100)	0.406
Xerostomia, n (%)	7 (87.5)	56 (87.5)	1.000
Xerophthalmia, n (%)	5 (62.5)	51 (79.68)	0.270
Parotitis, n (%)	1 (12.5)	4 (6.25)	0.455
Fatigue, n (%)	4 (50.0)	32 (50.0)	1.000
Arthralgia, n (%)	7 (87.5)	45 (70.31)	0.306
Arthritis, n (%)	5 (62.5)	13 (20.31)	**0.009**
Raynaud phenomena, n (%)	4 (50.0)	7 (10.93)	**0.004**
Photosensitivity, n (%)	4 (50.0)	12 (18.75)	**0.045**
Oral ulcer, n (%)	2 (25.0)	10 (15.62)	0.502
Dyspnea, n (%)	2 (25.0)	3 (4.68)	**0.033**
ESSDAI (±SD)	7.62 (±5.62)	4.03 (±2.31)	**0.001**
ESSPRI-dryness (±SD)	4.62 (±1.76)	5.34 (±1.27)	0.115
ESSPRI-fatigue (±SD)	4.12 (±1.80)	4.54 (±1.18)	0.298
ESSPRI-pain (±SD)	5.37 (±1.30)	4.79 (±1.12)	0.374
CRP, mg/L, (±SD)	9.79 (±6.76)	4.99 (±3.77)	**0.049**
ANA positivity, n (%)	7 (87.5)	53 (82.80)	0.737
SS-A (anti-Ro) positivity, n (%)	4 (50.0)	23 (35.93)	0.439
SS-B (anti-La) positivity, n (%)	1 (12.5)	15 (23.43)	0.674
RF positivity, n (%)	5 (62.5)	13 (20.31)	**0.009**
Leucopenia, n (%)	3 (37.5)	4 (6.25)	**0.005**
Lymphopenia, n (%)	3 (37.5)	3 (4.68)	**0.002**
Anemia, n (%)	2 (25.0)	3 (4.68)	**0.033**
Thrombocytopenia, n (%)	2 (25.0)	1 (1.56)	**0.002**
Hypergammaglobulinemia, n (%)	1 (12.5)	1 (1.56)	0.211
Hypocomplementemia, n (%)	2 (25.0)	4 (6.25)	0.130
Pulmonary involvement, n (%)	2 (25.0)	2 (3.12)	0.058
Unstimulated whole saliva flow rate≤0.1 ml/m, n (%)	3 (37.5)	48 (75.0)	**0.028**
Schirmer's test≤5 mm/5 m in at least one eye, n (%)	4 (50.0)	55 (85.93)	**0.013**
Focus score≥1, n (%)	5 (62.5)	45 (70.31)	0.651

ESSDAI EULAR Sjögren's syndrome disease activity index, *ESSPRI* the EULAR Sjögren's Syndrome Patient Reported Index, *CRP* C-reactive protein, *ANA* anti-nuclear antibody, *RF* rheumatoid arthritis. The statistical significant p values are represented by bold characters

by Santiago et al. [24]. Consequently, in instances where isolated ANA positivity is observed to be associated with clinical findings, and where the suspicion of SjD is present, minor SGB should be recommended for these patients.

Does meeting the SjD classification criteria before biopsy predict the histopathological outcome?

The present study demonstrated that patients who met the SjD classification criteria prior to mSGB were more likely to have a positive biopsy result. Concurrently, these patients exhibit elevated disease activation and increased rates of hypocomplementemia. In support of this result, numerous studies have demonstrated a correlation between elevated the ESSDAI scores and lymphocytic inflammation in the salivary gland [25–27]. The present study identified a statistically significant relationship between positive FLS and the Schirmer's test as well as the unstimulated whole saliva flow rate. These results suggest that objective measurement methods of sicca symptoms are more indicative of the necessity of biopsy.

On the other hand, this study found that one-third of patients who did not meet the SjD criteria before biopsy (the majority of whom were antibody-negative) had positive biopsy results. These results imply that fulfilling the SjD criteria predicts the biopsy outcome; however, a significant proportion of patients may have a biopsy outcome that is independent of the criteria.

Are patients with a positive mSGB for FLS different from those with a negative biopsy?

In this study, patients exhibiting a focus score≥1 manifested cyclical symptoms, fatigue, major salivary gland involvement, and higher seropositivity compared to patients with a FS<1. Approximately one-third of patients who were negative for FLS were classified as having SjD. Concurrently, a non-diagnostic patient phenotype of mSGB has been documented in the exist literature [28, 29]. Moreover, it was reported that interferon-mediated inflammation and frequency of anti-La decreased in these patients [29]. On the other hand, FLS is identified with non-negligible prevalence in the non SjD individuals in the recent meta-analysis [30]. These results suggest that although FLS is a histologic hallmark of SjD, its absence does not rule out Sjögren, nor does its presence confirm it.

A potential explanation for the failure to detect FLS in biopsy cases may be that the size of the salivary gland tissue examined was smaller than the recommended size, or that technical deficiencies related to pathological examination processes were in effect [31]. In the present study, patients with inadequate salivary gland specimens were excluded

from the study. The examination processes for the biological material were performed in accordance with the recommendations of Fisher et al. [5].

How often do we think about overlap syndrome in patients who undergo mSGB?

Overlap syndromes are prevalent in the practice of rheumatology. The most common overlap syndrome is the concurrent manifestation of SjD and RA. The diagnoses observed in the eight patients with overlap syndromes seen in this study were RA, SLE, SSc, MCTD and RP. The presence of Raynaud's phenomenon, purpuric, livedoid or subacute cutaneous lupus erythematosus rash, cytopenia, and interstitial pulmonary involvement along with non-sicca findings as initial symptoms in SjD patients suggests the existence of overlap syndromes [2]. In our study, similar to the existing literature, arthritis, Raynaud's phenomenon, photosensitivity, dyspnea, and cytopenia were found to be more prevalent in the overlap group.

Specific antibody positivity is important when overlap syndrome is suspected [2]. However, RF, anti-cyclic citrullinated peptide (anti-CCP), anti-centromere, anti-dsDNA, and antiphospholipid antibodies can be observed in up to 15–20% of SjD patients without overlap syndrome [2]. Likewise, RF positivity is more prevalent among our patients with overlap syndrome. Therefore, these patients should be evaluated based on their clinical involvement, laboratory results, and disease-specific classification criteria.

The potential limitation of this study is that it did not include the results of major salivary gland ultrasonography, which plays a vital role in diagnosing the disease. In our clinic, we perform major salivary gland ultrasonography (bilateral parotid and submandibular) in addition to other laboratory evaluations before biopsy in patients with suspected SjD. Since we were unable to access these data, we could not include them in the study. The study's most significant strength is that it provides valuable information for selecting patients who should undergo biopsy, making comparisons between those who meet and do not meet SjD classification criteria, as well as between those with a positive and negative FS.

Conclusion

The study indicated that objective saliva and tear measurements could effectively predict the presence of FLS in minor salivary glands. Also, although diagnostic biopsy findings are more prevalent in patients who are seropositive and meet the classification criteria, a significant proportion of patients who are seronegative and do not meet the SjD classification criteria are positive for FLS. Furthermore, the study highlighted the need to consider the potential overlap syndromes associated with SjD.

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Declarations

Conflict of interest All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version. This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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