MCBU SBED
MANİSA CELAL BAYAR ÜNİVERSİTESİ SAĞLIK BİLİMLERİ ENSTİTÜSÜ DERGİSİ
MANISA CELAL BAYAR UNIVERSITY JOURNAL OF INSTITUTE OF HEALTH SCIENCE
ISSN: 2147-9607

ARAŞTIRMA MAKALESİ
RESEARCH ARTICLE
CBU-SBED, 2025, 12 (1): 117-124

The Relationship Between Pathological Findings of Minor Salivary Gland Biopsy Performed at the Time of Diagnosis and Schirmer Test and Serological Tests in Patients with primary Sjögren's Syndrome

Primer Sjögren Sendromlu Hastalarda Tanı Zamanında Yapılan Minör Tükürük Bezi Biyopsisinin Patolojik Bulguları ile Schirmer Testi ve Serolojik Testler Arasındaki İlişki

Osman Cure,[1] Oguzhan Okcu,[2] Bayram Kizilkaya,[3] Mehmet Serhat Topaloglu,[4] Serdar Durak[5]

[1]Department of Rheumatology, Recep Tayyip Erdogan University, School of Medicine, Rize, Turkey
[2]Department of Pathology, Recep Tayyip Erdogan University, School of Medicine, Rize, Turkey
[3]Department of Internal Medicine, Recep Tayyip Erdogan University, Rize, Turkey
[4]Department of Physical Therapy and Rehabilitation, Recep Tayyip Erdogan University, Rize, Turkey
[5]Department of Gastroenterology, Bayrampaşa Kolan Hospital, Istanbul, Turkey

e-mail: creosman61@gmail.com, oguzhan.okcu@erdogan.edu.tr, dr.bayram_kizilkaya@hotmail.com, mehmetserhat.topaloglu @erdogan.edu.tr, serdardurak@gmail.com
ORCID:0000-0001-5848-6363
ORCID:0000-0001-7481-4718
ORCID:0000-0003-4508-2516
ORCID:000-0003-4525-3928
ORCID:000-0002-8175-9611

*Sorumlu Yazar / Corresponding Author: Osman Cüre
Gönderim Tarihi / Received:30.04.2024
Kabul Tarihi / Accepted:24.02.2025
DOI: 10.34087/cbusbed.1476204.

Öz

Giriş ve Amaç: Primer Sjögren sendromlu (pSS) hastalarda tanı anında yapılan minör tükrük bezi patolojisi ile schirmer testi ve serolojik test sonuçları arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Haziran 2018-Temmuz 2023 tarihleri arasında tanı anında kurumumuzda serolojik testleri, minör tükürük bezi biyopsisi ve schirmer testi yapılıp pSS tanısı alan toplam 41 hasta çalışmaya dahil edildi. Biyopsi örneklerinde odak skoru, atrofi ve fibrozis değerleri skorlandı. Histopatolojik bulgular ile demografik, klinik, schirmer testi ve serolojik testler arasındaki ilişki değerlendirildi.

Bulgular: 41 hastanın 38'i (%92,7) kadın, 3'ü (%7) erkek olup yaş ortalaması 55,54±14,06 idi. Fokus skoru≥1 olan hastalarda; antinükleer antikor değeri≥1/320 (%42,9), romatoid faktör pozitifliği (%28,6), anti Sjögren sendromu (SS) A/SSB pozitifliği (%76,2, %38,1) daha yüksek oranda saptandı. Ayrıca, fokus skoru≥1 olan hastalarda asiner atrofi ve fibrozis daha yüksek olmakla fibrozisle arasında anlamlı ilişki vardı (p<0.008). Yaş ile asiner atrofi ve fibrozis skoru1≥ arasında (p=0,030, p=0,006) ve ağız kuruluğu ile fibrozis arasında (p=0,008) anlamlı ilişki saptandı. Çok değişkenli analizde fokus skorunda schimer testi pozitifliği bağımsız bir risk faktörü olarak gözlendi (OR = 22,531, %95CI 1,369–370,174).

Sonuç: Çalışmamızda yüksek fokus skorunun serolojik testlerin pozitifliği ve ekzokrin fonksiyonların bozulmasıyla ilişkili olduğu, Schirmer testinin pozitif olmasının fokus skorunu artırıcı etkisi olduğu belirlendi.

Anahtar kelimeler: Minör tükürük bezi biyopsisi, Serolojik Testler, Schirmer testi, Sjögren sendromu

A**bstract**

Aim; Our aim was to assess the correlation between minor salivary gland pathology and the results of Schirmer and serological tests conducted during the diagnosis of primary Sjögren's syndrome (pSS).

Method; A total of 41 patients who were diagnosed with pSS after having serological tests, minor salivary gland biopsy and Schirmer test performed at our institution at the time of diagnosis between June 2018 and July 2023 were included in the study. Focus score, atrophy and fibrosis values were scored in biopsy samples. The relationship between histopathological findings and clinical, Schirmer test and serological tests was evaluated.

Results; Of the 41 patients, 38 were female (92.7%), 3 (7%) were male, and the average age was 55.54 ± 14.06. In patients with focal score≥1, antinuclear antibody value≥1/320 (42.9%), rheumatoid factor positivity (28.6%), anti Sjögren's syndrome (SS) A/SSB positivity (76.2%, 38.1%) was detected at a higher rate. Additionally, acinar atrophy and fibrosis were higher in patients with focus score≥1, and there was a significant relationship between fibrosis ($p<0.008$). A significant relationship was detected between age with acinar atrophy and fibrosis score1≥ ($p=0.030$, $p=0.006$) and between dry mouth with fibrosis ($p=0.008$). In multivariate analysis, schimer test positivity in focal score was observed as an independent risk factor (OR = 22.531, 95%CI 1.369–370.174).

Conclusion; In our study, a high focus score was found to be correlated with positive serological tests and impaired exocrine functions, and a positive Schirmer test was found to have an increasing effect on the focus score.

Keywords: Minor salivary gland biopsy, Serological Tests, Schirmer test, Sjögren's syndrome

1. Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease that primarily targets the body's exocrine glands and organs, particularly the salivary and tear glands. Diagnosis involves recognizing typical clinical signs and symptoms, along with specific tests such as salivary gland histopathology and autoantibody screening. pSS is more common in women aged approximately 50-60 years, and the most common complaints in patients are fatigue, muscle and joint pain, dry mouth and eyes, and tooth decay [1,2]. In pSS, in addition to extraglandular organ involvement, involvement in the muscle lymphocytic focus (clusters of at least 50 lymphocytic cells around the duct) in salivary gland biopsies are helpful findings in diagnosis. Different findings have been reported in the literature in terms of the correlation between histopathological findings and clinical and diagnostic tests. [3-6]. In this context, we aimed to evaluate the relationship between histopathological findings in biopsy samples at diagnosis in pSS patients with Schirmer test and serological tests.

2. Subjects and Methods

2.1. Participants

The study covers individuals aged 18 and over who were diagnosed with pSS according to the 2016 American College of Rheumatology diagnostic criteria from June 2018 to July 2023 [3]. The study protocol was approved by the Recep Tayyip Erdogan University School of Medicine Ethics Committee (No:2024/84).

2.2. Exclusion criteria

Those who received radiotherapy, amyloidosis, hepatitis B and C infection, acquired immunodeficiency syndrome, sarcoidosis, and immunoglobulin (Ig)-G4-related diseases did not participate in the work.

2.3. Data collection

joints, lungs, kidneys, skin, hematological and nervous systems is observed [2,3].

The pathogenesis of SS is characterized by the formation of antibodies and immune complexes as a result of autoimmunity in the exocrine glands as well as other systems of our body, increase in inflammatory cytokines and chronic lymphoplasmacytic infiltration. Acinar atrophy, ductal dilatation and fibrosis development as a result of inflammation in salivary gland biopsy samples are common pathological findings in pSS. In addition, focal lymphocytic infiltration and

The patients' data were retrospectively examined using the hospital electronic data system. Demographic data, eye, mouth and other symptoms, and physical examination findings of the patients were determined. The findings of minor salivary gland biopsy performed for diagnosis were recorded in patients with suspected SS who had dry mouth and eyes for more than three months, had a history of swelling in the parotid and other salivary glands, and whose Schirmer test result was ≤5 mm. Indirect immunofluorescence for anti-nuclear antibody, nephelometry for rheumatoid factor, and enzyme-linked immunosorbent assay for anti-Sjögren's syndrome antibody (SSA) and anti-SSB were used.

2.4. Labial salivary gland biopsy and pathological evaluation

Salivary gland biopsy results were evaluated by the same experienced pathologist. Minor salivary gland incisional biopsy samples of the patients were fixed in 10% formaldehyde for 24 hours, followed by a fully automatic tissue tracking device, and paraffin blocks were prepared. 4 micron thick sections obtained from the prepared blocks were stained with hematoxylin and eosin dye and evaluated under an Olympus BX-51 light microscope. Lymphocytic infiltration, presence of lymphocytic focus (aggregate of at least 50 lymphocytic cells around

the duct), acinar atrophy and fibrosis were evaluated in salivary gland biopsies. Lymphocytic infiltration; It was scored as 0-4, with no lymphocytic infiltration, mild lymphocytic infiltration, moderate lymphocytic infiltration, lymphocytic focus ratio of 1, and lymphocytic focus above 1. In the statistical analysis, two different groups were created: cases with 0-2 lymphocytic infiltration as 0, and cases with 3-4 lymphocytic infiltration as 1. Acinar atrophy and fibrosis were scored between 0 and 3 as no, mild, moderate and high.

2.5. Statistical Analysis

Data were analyzed with IBM SPSS. Fisher's exact test, Yates correction and Pearson chi-square test were used to examine demographic and clinical characteristics according to focal score, acinar atrophy and fibrosis status. Multiple comparisons as a result of the Pearson chi-square test were examined with the Bonferroni-corrected Z test. The assumption of normality was examined with the Shapiro-Wilk test. Data that were normally distributed according to groups were compared with an independent two-sample t test, and data that were not normally distributed were compared with the Mann Whitney U test. Risk factors affecting the focus score were examined with univariate and multivariate logistic regression analysis. Analysis results were presented as frequency (percentage) for categorical data and median (minimum – maximum) and mean ± standard deviation for quantitative data. The significance level was set at $p < 0.05$

3. Results and Discussion

A total of 41 patients were included, comprising 38 women (92.7%) and 3 men (7.3%), with a mean age of 55.54±14.06 years. The mean symptom duration of the patients was 8.78 ± 11.98 months (**Table 1**).

Table 1. Demographic, clinical and laboratory characteristics of the patients

Variable, Mean±deviation, Median (min.-max.), Frequency (%)	Total (n=41)
Age	55.54 ± 14.06
Woman	38 (92.7)
Male	3 (7.3)
Complaint duration (month)	8.78 ± 11.98
Dry mouth	31 (75.6)
Dry eye	28 (68.3)
Arthralgia-myalgia	19 (46.3)
Raynaud	3 (7.3)
Swelling in the salivary gland	2 (4.9)
Lung involvement	3 (7.3)
Cytopenia	2 (4.8)
Central nerve involvement	1 (2.4)
Antinuclear Antibody	
1/320 <	28 (68.3)
1/320 ≥	13 (31.7)
Anti SSA	29 (70.7)
Anti SSB	15 (36.6)
Rheumatoid factor	11 (26.8)
Hypergammaglobulinemia	8 (19.5)
CRP	5.68 ± 4.03
ESR	16.68 ± 10.3
Schirmer test (≤5mm/5min)	27 (65.9)

Anti SSA: Anti Sjögren's syndrome antibody A, Anti SSB: Anti Sjögren's syndrome antibody B, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

A significant relationship was found between focus score and fibrosis, and in patients with FS≥1, those with fibrosis value ≥1 were more common (p=0.008). It can be concluded that patients with high focus scores also have high fibrosis values. There was no significant difference between FS and demographic and clinical characteristics, Schirmer test, serological and acinar atrophy values (p>0.05), (**Table 2**).

Table 2. Comparison of clinical and laboratory values according to focus score

Variable, Mean±deviation, Median (min.-max.), Frequency (%)	Focus Score		p
	1 <	1 ≥	
Age	52.55 ± 12.87	58.38 ± 14.86	0.188
Complaint duration (month)	3.5 (3 - 48)	3 (1- 60)	0.550
Dry mouth	13 (65)	18 (85.7)	0.159
Dry eye	14 (70)	14 (66.7)	1.000
Arthralgia-myalgia	9 (45)	10 (47.6)	1.000
Raynaud	1 (5)	2 (9.5)	---
Swelling in the salivary gland	1 (5)	1 (4.8)	---
Lung involvement	3 (15)	0 (0)	---
Cytopenia	1 (5)	1 (4.8)	---
Central nerve involvement	1 (5)	0 (0)	---
Antinuclear Antibody			
1/320 <	16 (80)	12 (57.1)	0.216
1/320 ≥	4 (20)	9 (42.9)	
Anti SSA			
Negative	7 (35)	5 (23.8)	0.657
Positive	13 (65)	16 (76.2)	
Anti SSB			
Negative	13 (65)	13 (61.9)	1.000
Positive	7 (35)	8 (38.1)	
Rheumatoid factor			
Negative	15 (75)	15 (71.4)	1.000
Positive	5 (25)	6 (28.6)	
Hypergammaglobulinemia	5 (25)	3 (14.3)	0.454
CRP	5 (1 - 12)	4 (1 - 14)	0.937
ESR	12 (2 - 46)	16 (5 - 33)	0.354
Schirmer test (≤5mm/5min)	12 (60)	15 (71.4)	0.659
Acinar Atrophy			
0	5 (25)	1 (4.8)	0.093
1-2-3	15 (75)	20 (95.2)	
Fibrosis			
0	13 (65)	4 (19)	**0.008**
1-2-3	7 (35)	17 (81)	

Anti SSA: Anti Sjögren's syndrome antibody A, Anti SSB: Anti Sjögren's syndrome antibody B, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

The mean age of patients with acinar atrophy grade 1-2-3 was 57.49 ± 14.06, while the mean age of patients without acinar atrophy was 44.17 ± 7.41 (p = 0.030). No significant difference was detected between acinar atrophy status and other demographic, clinical characteristics and Schirmer test (p>0.05), (**Table 3).**

Table 3. Comparison of clinical and laboratory results according to acinar atrophy status

Variable, Mean±deviation, Median (min.-max.), Frequency (%)	Asiner Atrofi		p
	0	1-2-3	
Age	44.17 ± 7.41	57.49 ± 14.06	**0.030**
Complaint duration (month)	14.5 (3 - 60)	3 (1 - 24)	0.111
Dry mouth	5 (83.3)	26 (74.3)	1.000
Dry eye	4 (66.7)	24 (68.6)	1.000
Arthralgia-myalgia	4 (66.7)	15 (42.9)	0.390
Raynaud	1 (5)	2 (9.5)	---
Swelling in the salivary gland	1 (5)	1 (4.8)	---
Lung involvement	3 (15)	0 (0)	---
Cytopenia	1 (5)	1 (4.8)	---
Central nerve involvement	1 (5)	0 (0)	---
Antinuclear Antibody			
1/320 <	5 (83.3)	23 (65.7)	0.645
1/320 ≥	1 (16.7)	12 (34.3)	
Anti SSA			
Negative	1 (16.7)	11 (31.4)	0.651
Positive	5 (83.3)	24 (68.6)	
Anti SSB			
Negative	5 (83.3)	21 (60)	0.388
Positive	1 (16.7)	14 (40)	
Rheumatoid factor			1.000
Negative	5 (83.3)	25 (71.4)	1.000
Positive	1 (16.7)	10 (28.6)	
Hypergammaglobulinemia	5 (25)	3 (14.3)	0.077
CRP	7 (1 - 11)	4 (1 - 14)	0.480
ESR	13 (2 - 32)	13 (4 - 46)	0.579
Schirmer test (≤5mm/5min)	12 (60)	15 (71.4)	1.000

Anti SSA: Anti Sjögren's syndrome antibody A, Anti SSB: Anti Sjögren's syndrome antibody B, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

A statistically significant difference was detected between fibrosis status and dry mouth and antinuclear antibody positivity (≥1/320) (p=0.008, p=0.039). The mean age of patients with a fibrosis score ≥1 was 60.5 ± 13.71, while the mean age of patients without fibrosis was 48.53 ± 11.61. (p = 0.006). Dry mouth was observed in 91.7% of patients with a fibrosis score ≥1, while this rate was 52.9% in patients without fibrosis (p=0.008). The number of patients with hypergammaglobulinemia was lower in patients with 1-2-3 degree fibrosis, with 3 (14.3%) (p=0.005), (**Table 4**).

In the examination for risk factors affecting the lymphocytic focus score, no factor associated with lymphocytic focus was observed in the univariate analysis, while Schirmer test positivity (OR = 22.531, 95%CI 1.369–370.174) was detected as an independent risk factor in the multivariate analysis. With the multivariate model created, 70.7% of the cases are classified correctly (**Table 5**).

Table 4. Comparison of clinical and autoantibody results according to fibrosis status

Variable, Mean±deviation, Median (min.-max.), Frequency (%)	Fibrosis		p
	0	1-2-3	
Age	48.53 ± 11.61	60.5 ± 13.71	**0.006**
Complaint duration (month)	5 (3 - 60)	3 (1 - 24)	0.185
Dry mouth	9 (52.9)	22 (91.7)	**0.008**
Dry eye	10 (58.8)	18 (75)	0.450
Arthralgia-myalgia	8 (47.1)	11 (45.8)	1.000
Raynaud	1 (5)	2 (9.5)	---
Swelling in the salivary gland	1 (5)	1 (4.8)	---
Lung involvement	3 (15)	0 (0)	---
Cytopenia	1 (5)	1 (4.8)	---
Central nerve involvement	1 (5)	0 (0)	---
Antinuclear Antibody			
1/320 <	15 (88.2)	13 (54.2)	**0.039**
1/320 ≥	2 (11.8)	11 (45.8)	
Anti SSA		)	
Negative	7 (41.2)	5 (20.8)	0.184
Positive	10 (58.8)	19 (79.2)	
Anti SSB			
Negative	10 (58.8)	16 (66.7)	0.854
Positive	7 (41.2)	8 (33.3)	
Romatoid Faktör			
Negative	14 (82.4)	16 (66.7)	0.309
Positive	3 (17.6)	8 (33.3)	
Hypergammaglobulinemia	5 (25)	3 (14.3)	**0.005**
CRP	5 (1 - 11)	4.5 (1 - 14)	0.852
ESR	12 (2 - 33)	16.5 (5 - 46)	0.124
Schirmer test (≤5mm/5min)	12 (60)	15 (71.4)	0.642

Anti SSA: Anti Sjögren's syndrome antibody A, Anti SSB: Anti Sjögren's syndrome antibody B, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

Table 5. Examination of risk factors affecting focus score with univariate and multivariate logistic regression model

Variable	Univariate		Multivariate	
	OR (%95 GA)	p	OR (%95 GA)	p
Age	1.032 (0.985 - 1.081)	0.187	1.013 (0.954 - 1.076)	0.670
Complaint duration (month)	0.985 (0.933 - 1.039)	0.578	1.014 (0.936 - 1.099)	0.736
Dry mouth	3.231 (0.7 - 14.907)	0.133	3.457 (0.429 - 27.87)	0.244
Dry eye	0.857 (0.229 - 3.203)	0.819	0.065 (0.003 - 1.25)	0.070
Arthralgia-myalgia	1.111 (0.325 - 3.796)	0.867	1.891 (0.26 - 13.743)	0.529
Raynaud				
Antinuclear Antibody (1/320 <)	3 (0.743 - 12.111)	0.123	3.78 (0.451 - 31.669)	0.220
Anti SSA	1.723 (0.442 - 6.721)	0.433	6.418 (0.462 - 89.151)	0.166
Anti SSB	1.143 (0.32 - 4.081)	0.837	4.914 (0.418 - 57.768)	0.205
Rheumatoid factor	1.2 (0.3 - 4.798)	0.797	0.611 (0.09 - 4.161)	0.614
Hypergammaglobulinemia	0.5 (0.102 - 2.444)	0.392	0.136 (0.009 - 1.981)	0.144

CRP	1.011 (0.866 - 1.179)	0.893	1.004 (0.775 - 1.301)	0.975
ESR	1.008 (0.949 - 1.071)	0.791	0.996 (0.902 - 1.101)	0.945
Schirmer test (≤5mm/5 min)	1.667 (0.453 - 6.131)	0.442	22.531 (1.369 - 370.714)	**0.029**

OR: Odds ratio, CI: Confidence interval, Anti SSA: Anti Sjögren's syndrome antibody A, Anti SSB: Anti Sjögren's syndrome antibody B, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

In our study, we examined the relationship between demographic, clinical, Schirmer and serological tests and histopathological findings in pSS patients, and a statistically significant relationship was found in the Schirmer test focus score. Dry mouth complaints are one of the important elements of the pSS classification criteria [7,8]. No statistically significant relationship was reported between dry mouth and eye symptoms and serum anti-SSA/SSB and focal lymphocytic sialadenitis (focal score 1) in participants of the SICCA study [3,9]. Our study was similar to the literature.

On the other hand, in a research carried out by Daniels TE et al., in the labial salivary gland biopsy examination of 1726 patients with SS, FS≥1 scores were found to be statistically significantly associated with serum anti-SSA/SSB positivity and rheumatoid factor, but were not connected with dry mouth or eyes. In the same study, they found that anti-SSA/SSB positive patients were 9 times more likely to have FS>1 than anti-SSA/SSB negative patients [10]. In a research carried out by Triantafyllias K et

al., a significant correlation was detected between FS and ANA and rheumatoid factor positivity in minor salivary gland biopsy examination in patients with SS [11]. In the literature, it has been found that anti-SSA/anti-SSB antibody positive pSS patients have swelling in the salivary glands, more serious dysfunction in the exocrine glands, a high rate of lymphocytic infiltration and extra glandular involvement [12,13]. In our study, although ANA, rheumatoid factor, anti-SSA/SSB positivity was observed to be numerically higher in patients with FS≥1 than in patients with FS<1, no statistically significant difference was detected. This may be due to the small number of patients. There is a need for larger and different centers to work on this subject. Additionally, these differences between studies may be due to heterogeneity of antigen response and phenotypic features of autoantibodies among patients. A positive Schirmer test in at least one eye is among the 2016 ACR-EULAR pSS classification criteria [3]. Schirmer test in a study by Haldorsen K et al. was associated with high focus score, hypergammaglobulinemia and positive anti-SS and SSB tests [14]. In our study, similar to the literature, Schirmer test positivity in lymphocytic focus score was detected as an independent risk factor in multivariate logistic regression analysis.

In a research carried out by Llamas-Gutierrez FJ et al., in 63 patients with SS, acinar atrophy and fibrosis were detected at a higher rate in patients with a FS≥1 in the labial salivary gland pathological examination. In the same study, a correlation was found between ductal dilatation, duct epithelial hyperplasia, adipose infiltration and fibrosis with age [15]. In another study, it was reported that more than one lymphocytic focus is more valuable for the diagnosis of SS and that ductal dilatation, acinar atrophy, and chronicity may occur in SS cases even without lymphocytic infiltration [16]. In our study, similar to the literature, acinar atrophy and fibrosis were detected at higher rates in patients with FS≥1, and a significant relationship was observed between them and fibrosis. Additionally, a significant relationship similar to the literature was observed between age and acinar atrophy and fibrosis.

Limitations: It was single-center, retrospective, and the number of patients was relatively small because labial salivary gland biopsy was required for the diagnosis of pSS. The study's findings may be limited in their applicability due to the small sample size and the single-center setting.

4. Conclusions

In conclusion, acinar atrophy, fibrosis and high focus score detected in salivary gland biopsies in SS patients were observed to correlate with clinical symptoms and serological tests. Schirmer test was detected as a risk factor independent of lymphocytic focus score. Even though salivary gland biopsies are invasive procedures and have various complications, the current results reflect the importance of histopathological findings in the diagnosis of SS and patient management. However, since Schimer test positivity was found to be an independent risk factor for high lymphocytic focus, we think that appropriate clinical symptoms, Schimer test and serological markers remain important for the diagnosis of SS.

5. Acknowledgement

We thank everyone who contributed to our work.

6. References

1. Negrini S, Emmi G, Greco M, et al (2022) Sjögren's syndrome: a systemic autoimmune disease. Clin Exp Med 22(1):9-25. https://doi: 10.1007/s10238-021-00728-6
2. Singh AG, Singh S, Matteson EL (2016) Rate, risk factors and causes of mortality in patients with Sjögren's syndrome: a systematic review and meta-analysis of cohort studies. Rheumatology 55(3):450-60. https:// doi:10.1093/rheumatology/kev354
3. Shiboski CH, Shiboski SC, Seror R, et al (2017) International Sjögren's Syndrome Criteria Working Group. 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 76(1):9-16. https:// doi: 10.1136/annrheumdis-2016-210571
4. Zhan Q, Zhang J, Lin Y, Chen W, Fan X, Zhang D (2023) Pathogenesis and treatment of Sjogren's syndrome: Review and update. Front Immunol 14:1127417.https:// doi:10.3389/fimmu.2023.1127417
5. Konsta OD, Le Dantec C, Charras A, et al (2016) Defective DNA methylation in salivary gland epithelial acini from patients with Sjögren's syndrome is associated with SSB gene expression, anti-SSB/LA detection, and lymphocyte infiltration. J Autoimmun 68:30-8. https://doi: 10.1016/j.jaut.2015.12.002
6. Kyriakidis NC, Kapsogeorgou EK, Tzioufas AG (2014) A comprehensive review of autoantibodies in primary Sjögren's syndrome: clinical phenotypes and regulatory mechanisms. J Autoimmun 51:67-74. https://doi: 10.1016/j.jaut.2013.11.001
7. Hernández-Molina G, Avila-Casado C, Nuñez-Alvarez C, et al (2015) Utility of the American-European Consensus Group and American College of Rheumatology Classification Criteria for Sjögren's syndrome in patients with systemic autoimmune diseases in the clinical setting. Rheumatology (Oxford) 54(3):441-8. https://doi:10.1093/rheumatology/keu352
8. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, et al (2002) and the European Study Group on Diagnostic Criteria for Sjo¨gren's Syndrome. Classification criteria for Sjo¨gren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61:554–8. https://doi: 10.1136/ard.61.6.554. P
9. Daniels, T., Greenspan, J. S., Cox, D., Criswell, L. A., DeSouza, Y., & Dong, Y (2007) Objective measures in Sjögren's syndrome are strongly associated with each other but not with sicca symptoms: analysis of 564 enrollees in the SICCA international registry and repository. Arthritis Rheum 56(Suppl), S446
10. Daniels TE, Cox D, Shiboski CH, et al (2011) Sjögren's International Collaborative Clinical Alliance Research Groups. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. Arthritis Rheum 63(7):2021-30. https://doi: 10.1002/art.30381
11. Triantafyllias K, Bach M, Otto M, et al (2023) Diagnostic Value of Labial Minor Salivary Gland Biopsy: Histological Findings of a Large Sicca Cohort and Clinical Associations.Diagnostics13(19):3117. https://doi:10.3390/diagnostics13193117
12. Tzioufas AG, Tatouli IP, Moutsopoulos HM et al (2012) Autoantibodies in sjögren's syndrome: Clinical presentation and regulatory mechanisms. Presse Med 41:e451–60. https://doi: 10.1016/j.lpm.2012.05.022
13. Ramos-Casals M, Solans R, Rosas J, et al (2008) Primary sjögren syndrome in Spain: Clinical and immunologic expression in 1010 patients. Med (Baltimore) 87:210–9
14. Haldorsen K, Moen K, Jacobsen H, et al (2008) Exocrine function in primary Sjögren syndrome: natural course and prognostic factors. Ann Rheum Dis 67(7):949-54. doi: 10.1136/ard.2007.074203
15. Llamas-Gutierrez FJ, Reyes E, Martínez B, et al (2014) Histopathological environment besides the focus score in Sjögren's syndrome. Int J Rheum Dis 17(8):898-903. https://doi: 10.1111/1756-185X.12502
16. Erkılınç G, Doğru A, Arslan Y, et al (2021) Evaluation of histopathological results of minor salivary gland biopsies in patients with the diagnosis of Sjögren's syndrome. Arch Rheumatol. 2021;37(1):49-58. https://doi: 10.46497/ArchRheumatol.2022.8607