# Clinical Characteristics and Results of Patients Who Underwent Minor Salivary Gland Biopsy with the Suspicion of Sjogren Syndrome

## Sjögren Sendromu Şüphesi ile Minör Tükürük Bezi Biyopsisi Yapılan Hastaların Klinik Özellikleri ve Sonuçları

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**Objective:** To evaluate the value and accuracy of biopsy in diagnosing Sjogren syndrome (SS) by analyzing the results of patients who underwent minor salivary gland biopsy (MSGB) with suspicion of SS.

**Materials and Methods:** This retrospective study included 127 patients who underwent a biopsy for SS diagnosis. Clinical and laboratory characteristics of the patients who underwent MSGB were retrieved from their files. SS diagnosis was determined using the 2016 ACR/EULAR classification criteria or based on expert opinion.

**Results:** Out of 127 patients, 113 met the inclusion criteria. Among them, 72 patients were diagnosed with SS—56 based on the 2016 ACR/EULAR classification criteria and 16 based on expert opinion. Of the 113 patients, 57 had positive MSGB outcomes (55 with SS and 2 without SS), while 56 had negative MSGB outcomes (17 with SS and 39 without SS). The sensitivity of MSGB for SS diagnosis was 76.4%, and the specificity was 95.1%.

**Conclusion:** Although all of our patients had antibody test results, the number of objective tests included in the classification criteria, such as salivary flow rate and Schirmer test, was low. Despite being considered an invasive technique, minor salivary gland biopsy is valuable in reaching a definitive diagnosis in patients with suspected SS, especially when other objective tests are not available.

**Keywords:** Sjogren syndrome, diagnosis, minor salivary gland biopsy

**Amaç:** Sjögren sendromu şüphesi ile minör tükürük bezi biyopsisi yapılan hastaların sonuçlarının değerlendirilerek biyopsinin Sjögren sendromu (SS) tanısındaki yerini ve değerini saptamak.

**Gereç ve Yöntem:** Çalışma, SS tanısı için biyopsi yapılan 127 hastanın sonuçlarının geriye dönük değerlendirilmesi ile planlandı. Minör tükürük bezi biyopsisi uygulanan hastaların klinik ve laboratuvar özellikleri dosyalarından kaydedildi. SS teşhisi, 2016 ACR/EULAR sınıflandırma kriterlerine göre veya uzman görüşüne göre konuldu.

**Bulgular:** 113 hasta çalışmaya dahil edilme kriterlerini karşıladı. Sjögren sendromu tanısı konulan 72 hasta vardı. 72 hastanın 56 tanesine 2016 ACR/EULAR sınıflandırma kriterlerine göre tanı konulurken, 16 tanesine uzman görüşüne göre tanı konuldu. Minör tükürük bezi biyopsi sonucu pozitif 57 (55 SS, 2SS değil), negatif 56 (17SS, 39SS değil) kişi vardı. Minör tükürük bezi biyopsisinin SS tanısı için duyarlılığı %76,4, özgüllüğü ise %95,1 idi.

**Sonuç:** Hastalarımızın tamamında antikor testi sonucu vardı ancak tükürük akış hızı ve Schirmer gibi sınıflandırma kriterlerinde yer alan objektif testi olan hasta sayısı düşüktü. Minör tükürük bezi biyopsisi invaziv bir teknik olarak görülse de SS şüphesi olan ve diğer objektif testlerin uygulanmadığı hastalarda kesin karara varılmasında yardımcı olacaktır.

**Anahtar Kelimeler:** Sjögren sendromu, tanı, minör tükürük bezi biyopsisi

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## INTRODUCTION

Sjogren syndrome (SS) is a chronic autoimmune inflammatory disease characterized by reduced lacrimal and salivary gland functions, resulting in ocular and oral dryness (Ramos-Casals and Tzioufas, 2005; Pertovaara et al., 1999). SS may also have systemic involvement, with clinical features divided into exocrine glandular involvement and extra-glandular involvement. SS is defined as primary SS when it occurs alone, while it is referred to as secondary SS if it accompanies other rheumatic diseases. The most common diseases associated with SS are rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (Asmussen et al., 1996). For the diagnosis of SS, which is more frequently observed in women compared to men, anamnesis, Schirmer and ocular staining tests to identify dryness symptoms, salivary flow rate, serological tests, and minor salivary gland biopsy (MSGB) are used. Although various classification criteria have been defined for SS, disease diagnosis can be made for clinically consistent and serologically positive individuals. The aim of this study was to assess the results of our minor salivary gland biopsy performed with SS suspicion in our rheumatology clinic and to evaluate the role of biopsy in disease diagnosis.

## MATERIALS AND METHODS

The study was planned as a retrospective assessment of 127 patients who underwent biopsy for SS diagnosis in a rheumatology clinic. The files of patients who had MSGB performed due to suspicion of SS were accessed, and their demographic characteristics, dryness symptoms, systemic symptoms such as fatigue, arthritis, and arthralgia, as well as antibody and MSGB results, were recorded.

In assessing the salivary gland biopsy results, the Chisholm and Mason classification was used to illustrate lymphocyte infiltration of the gland (Chisholm and Mason, 1968). In minor salivary gland biopsy, a lymphocyte infiltration focus was defined as 50 or more lymphocytes per 4 $mm^2$, and staging was based on the presence of this focus.

SS diagnosis was determined using the rating system according to the ACR/EULAR classification criteria published in 2016 (Shiboski et al., 2017). If these criteria were not met, diagnosis was based on expert opinion for patients clinically and serologically consistent with SS. The ACR/EULAR classification criteria published in 2016 are based on classifying SS in patients with at least 4 points from the following: positive salivary gland biopsy (3 points), anti-Ro antibody positivity (3 points), ocular staining test (1 point), Schirmer test (1 point), and unstimulated salivary flow rate (1 point).

### *Statistical analysis and ethical aspects*

Descriptive statistics are summarized as frequency (n), percentage (%), mean, and standard deviation (SD) values. The assumption of normal distribution was checked with the Shapiro-Wilk test. The Pearson chi-square test and Fisher's exact test assessed correlations between categoric variables. The mean ages of patients with and without diagnosis of SS were compared with the independent t-test, and the mean ages of diagnosis subgroups were compared with one-way ANOVA. To assess the diagnostic performance of anti-Ro, biopsy, points, and biopsy+points for identification of Sjogren disease, sensitivity, specificity, negative and positive prediction values, and accuracy were calculated. All analyses were performed with the IBM SPSS 23.0 program (IBM Corp., Armonk, NY). P values less than 0.05 were accepted as statistically significant.

This project was approved by the Ethics Committee for Clinical Research at Antalya Training and Research Hospital on October 13, 2022 (protocol number 19/6)

## RESULTS

A total of 127 patients who underwent salivary gland biopsy were identified. Data for 14 patients could not be accessed, so they were excluded from the study. Data for the remaining 113 patients were collected. The demographic characteristics of these 113 patients who underwent MSGB were examined. The mean

age (SD) was 48.96 ± 13.25 years, with 108 women and 5 men.

The most frequent dryness symptom was ocular dryness, observed in 86.7% of patients, while the most common systemic symptom was fatigue, seen in 80.5%. Schirmer tests were performed on 34 patients (31.1%), and 30 of these patients tested positive (88.2%). Among the patients, 72.6% had a positive ANA test (≥1/100 titers), 74.3% were positive for anti-Ro antibody, 31.9% were positive for anti-La antibody, and 33.6% were RF positive. The most common rheumatic disease in patients who underwent biopsy was RA, found in 18.6% (n: 21). Of the 113 patients who underwent MSGB, 72 were diagnosed with SS (63.7%) (Table 1).

**Table 1.** Demographic and clinical characteristics of the patients

| **Parameters** | **n=113 n(%)** |
|---|---|
| Age (years) mean±SD | 48,96±13,25 |
| Gender, n(%) | |
| Women | 108(95,6) |
| Men | 5(4,4) |
| Dry mouth | 79(69,9) |
| Dry eyes | 98(86,7) |
| Arthritis | 28(24,8) |
| Arthralgia | 82(72,6) |
| Fatigue | 91(80,5) |
| Schimer | 34(31,1) |
| Schimer (n=34) | |
| Positive | 30(88,2) |
| Negative | 4(11,8) |
| Anti-Ro | |
| Positive | 84(74,3) |
| Anti-La | |
| Positive | 36(31,9) |
| RF | |
| Positive | 38(33,6) |
| ANA (1/ 100, 1/320 ) | 82 (%72,6) |
| RA | 21(18,6) |
| Focal Sialoadenitis (focus score ≥ 1) | 57(50,4) |
| Sjogrens syndrome | 72(63,7) |

RF: Rheumatoid factor ANA: Antinuclear antibodies RA: Rheumatoid arthritis

The mean age of patients diagnosed with SS was 46.8 years, which was significantly lower compared to patients without a diagnosis ($p < 0.05$). Among patients with SS diagnosis, 91.7% were positive for anti-Ro antibody, 34.7% were positive for anti-La antibody, and 26.4% were positive for both anti-Ro and anti-La antibodies. The positivity for anti-Ro and anti-Ro + anti-La antibodies was statistically significantly high in patients with SS ($p < 0.05$), while anti-La antibody positivity alone was not significant (Table 2).

RF positivity was present in 47.2% of patients with SS diagnosis, which was significantly higher ($p < 0.05$) compared to patients without a diagnosis. Of the patients, 22.2% were ANA negative, 8.2% were ANA:1/100 positive, and 69.4% were ANA:1/320 positive. The most frequent ANA staining pattern was granular (68.1%). On the ANA screening test, after anti-Ro and anti-La antibodies, the most frequently observed antibody was anti-histone, found in 13.9% of patients, which was significantly high ($p < 0.05$) in those diagnosed with SS.

Of the 72 patients diagnosed with SS, 54 had primary SS, and 18 had secondary SS (16 with RA, 1 with SLE, and 1 with scleroderma) (Figure 1). Among patients with SS, referrals to our clinic from other departments included one patient with autoimmune hepatitis, 1 with monoclonal gammopathy of undetermined significance (MGUS), 3 with leukopenia, 1 with immune thrombocytopenic purpura (ITP), 1 with optic neuritis, and 1 with chronic parotitis. When examining the comorbid autoimmune diseases in patients with SS, 16 had RA, 1 had SLE, 1 had scleroderma, 2 had familial Mediterranean fever (FMF), 1 had autoimmune hepatitis, 1 had sacroiliitis, 1 had optic neuritis, and 1 had MGUS.

**Table 2.** General characteristics of patients with and without SS diagnosis

| Parameters | SS diagnosis (n=72) n(%) | Without SS (n=41) n(%) | p |
|---|---|---|---|
| Age (years) mean±SD | 46,83±12,57 | 52,71±13,74 | 0,023 |
| Anti-Ro | | | |
| Positive | 66(91,7) | 18(43,9) | <0,001 |
| Anti-La | | | |
| Positive | 25(34,7) | 11(26,8) | 0,387 |
| Anti-Ro, Anti-La | | | |
| Positive | 19(26,4) | 1(2,4) | 0,001 |
| RF | | | |
| Positive | 34(47,2) | 4(9,8) | <0,001 |
| ANA | | | |
| Negative | 16(22,2)[a] | 15(36,6)[a] | <0,001 |
| 1/100 | 6(8,3)[a] | 15(36,6)[b] | |
| 1/320 | 50(69,4)[a] | 11(26,8)[b] | |
| Granular | 49(68,1) | 26(63,4) | |
| RA | 16(22,2) | 5(12,2) | 0,188 |
| Histone | 10(13,9) | 0(0) | 0,013 |
| Focal Sialoadenitis (focus score ≥ 1) | | | |
| Negative | 17(23,6) | 39(95,1) | <0,001 |
| Positive | 55(76,4) | 2(4,9) | |

ANA: Antinuclear antibodies RA: Rheumatoid arthritis SS: Sjogren syndrome Independent t-test, Pearson chi-square test, Fisher's Exact test. Same letters in a row denote the lack of statistically significant difference.

Patients were divided into three groups: those with four or more points according to the 2016 ACR-EULAR classification criteria (Group 1), those with less than 4 points but with a strong suspicion of SS based on clinical and test results, and diagnosed based on expert opinion (Group 2), and patients without a diagnosis (Group 3) (Table 3).

Anti-Ro positivity was significantly higher in Groups 1 and 2 ($p < 0.05$) compared to Group 3, while there was no significant difference in anti-La positivity between the groups. RF positivity was significantly higher in Groups 1 and 2 ($p < 0.05$) compared to Group 3. ANA test positivity (≥1/100 titer) was significantly higher in Groups 1 and 2, while anti-histone positivity on the ANA screening test was higher in Group 1. The presence of arthritis was significantly higher in Group 2 ($p < 0.05$) compared to the other groups. The number of patients with MSGB positivity (focus score ≥1) was highest in Group 1 and lowest in Group 3. The outcomes and diagnosis distribution for patients with MSGB performed are shown in Figure 2. There were 57 patients with a positive MSGB outcome (55 with SS, 2 without SS) and 56 patients with a negative MSGB outcome (17 with SS, 39 without SS). The sensitivity of MSGB for SS diagnosis was 76.4%, and the specificity was 95.1%. The positive predictive value was 96.5%, the negative predictive value was 69.6%, and the accuracy level was 83.2%.

**Table 3.** General characteristics of patients according to diagnosis subgroups

| Parameters | Diagnosed According to the classification criteria(≥4) (n=56) n(%) | Diagnosed based on expert opinion (n=16) n(%) | Patients without diagnosis (n=41)n(%) | p |
|---|---|---|---|---|
| Age (years) mean±SD | 47,09±12,7 | 45,94±12,43 | 52,71±13,74 | 0,072 |
| Anti-Ro | | | | |
| Positive | 54(96,4)[a] | 12(75)[b] | 18(43,9)[c] | <0,001 |
| Anti-La | | | | |
| Positive | 19(33,9) | 6(37,5) | 11(26,8) | 0,663 |
| Anti Ro+Anti La | | | | |
| Positive | 16(28,6)[a] | 3(18,8)[a,b] | 1(2,4)[b] | 0,004 |
| RF | | | | |
| Positive | 28(50)[a] | 6(37,5)[a] | 4(9,8)[b] | <0,001 |
| ANA | | | | |
| Negative | 12(21,4)[a] | 4(25)[a] | 15(36,6)[a] | <0,001 |
| 100 | 5(8,9)[a] | 1(6,3)[a] | 15(36,6)[b] | |
| 320 | 39(69,6)[a] | 11(68,8)[a] | 11(26,8)[b] | |
| Histone | 10(17,9)[a] | 0(0)[b] | 0(0)[b] | 0,003 |
| Dry mouth | 39(69,6) | 9(56,3) | 31(75,6) | 0,358 |
| Dry eyes | 46(82,1) | 16(100) | 36(87,8) | 0,173 |
| Arthritis | 14(25)[a,b] | 8(50)[a] | 6(14,6)[b] | 0,021 |
| Arthralgia | 37(66,1) | 13(81,3) | 32(78) | 0,299 |
| Fatigue | 43(76,8) | 13(81,3) | 35(85,4) | 0,572 |
| Focal Sialoadenitis (focus score ≥ 1) | | | | |
| Negative | 6(10,7)[a] | 11(68,8)[b] | 39(95,1)[c] | <0,001 |
| Positive | 50(89,3)[a] | 5(31,3)[b] | 2(4,9)[c] | |

RF:Rheumatoid factor ANA: Antinuclear antibodies One-way ANOVA, Pearson chi-square test, Fisher's Exact test. Same letters in a row denote the lack of statistically significant difference.

## DISCUSSION

Our study revealed several striking findings regarding the diagnosis of SS. Firstly, despite the invasiveness of MSGB, our results underscore its significant role in diagnosing SS, particularly when other objective tests, such as saliva flow rate and ocular staining scores, are not available. This highlights the value of MSGB as a diagnostic tool in cases where conventional tests are impractical or cannot be performed. Additionally, our findings suggest that MSGB can provide essential diagnostic insights that may help confirm SS in challenging scenarios.

In our study, the diagnosis of SS was made based on the 2016 classification criteria or expert opinion for patients with clinical and laboratory features suggestive of SS but not meeting the criteria. Previous classification criteria for SS diagnosis included subjective symptoms of eye/mouth dryness reported by the patient, as well as objective tests to assess dryness symptoms and antibody tests (Shiboski et al., 2012). The 2016 ACR-EULAR classification criteria classify SS based on patients receiving at least 4 points from objective tests performed for those with ocular or oral dryness. Among these tests, anti-Ro antibody and MSGB positivity each receive 3 points, with a total of 6 points indicating SS. In our clinic, antibody values were examined for all patients who underwent MSGB due to suspected SS. Although MSGB is an invasive technique, it provides high points for both objective and classification criteria. Among the criteria, the Schirmer test, ocular staining score, and identification of reductions in unstimulated saliva flow rate each receive 1 point.

These tests are linked to other clinical situations, are not performed in every clinic, and require time. The easiest of these tests, the Schirmer test, was only performed in 31.1% (n = 34/113) of patients with a biopsy due to SS suspicion, and there were no patients with ocular staining test or unstimulated saliva flow rate test performed. However, of the 72 patients diagnosed with SS, 55 were positive for MSGB. Only 20 of these 55 patients had the Schirmer test performed, and of these, 17 had a positive Schirmer test. Although the Schirmer test is easy to perform, it is notable that the number of patients undergoing this test was very low in our study.

Giovelli et al. (2015) conducted a study on MSGB outcomes involving 216 patients with suspected SS and found that 36.5% had positive MSGB results, whereas in our study, this rate was 50.4%. The ANA test positivity in Giovelli et al.'s study was 46.2%, compared to 72.6% in our study. Anti-Ro positivity was 16.6% in their study, while it was significantly higher at 74.3% in ours. RF positivity was 18.5% in their study and 33.6% in ours. However, unlike our study, their study included the Schirmer test and unstimulated saliva flow rate. In our study, only 31.1% of patients underwent the Schirmer test, and no patients had the unstimulated saliva flow rate examined. As MSGB is an invasive procedure, the high rates of antibody positivity and biopsy outcomes in patients with ocular/oral dryness symptoms suggest that these laboratory tests are effective for diagnosing SS in patients undergoing biopsy. This may explain the higher positivity rates for antibodies and biopsy outcomes observed in our study.

In our study, 72 patients (63.7%) were diagnosed with SS. Of these, 54 had primary SS (76.4%), and 18 had secondary SS (23.6%) (Figure 1). Secondary SS is defined as SS occurring alongside a rheumatic disease, with RA being the most commonly associated condition (Chisholm and Mason, 1968). Among our patients, the most frequent comorbid rheumatic disease was RA (22%, n = 16), followed by one patient each with SLE and scleroderma. Edelstein et al. (2021) studied 50 saliva biopsies and diagnosed SS in 39 patients, with 11 classified as secondary SS (28% secondary SS, 72% primary SS). Similar to our findings, RA was the most common rheumatic disease accompanying secondary SS in their study.

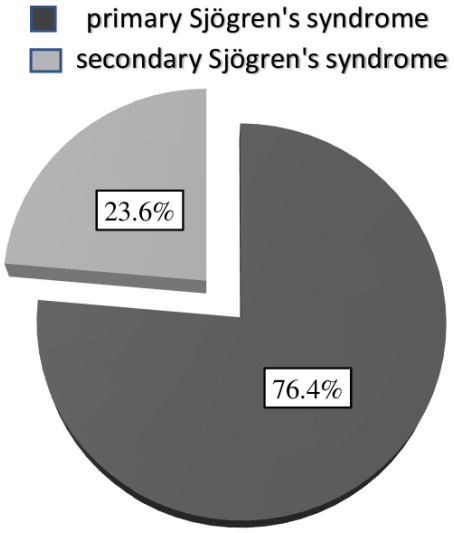


**Figure 1.** Distribution of primary and secondary Sjogrens syndrome patients

When examining the characteristics of patients with SS diagnosis, anti-Ro, RF, and ANA (1/320) positivity were significantly higher in patients with SS compared to those without the diagnosis. Although anti-La positivity was higher in the diagnosed group, it did not reach statistical significance. Previous SS classification criteria (Shiboski et al., 2012) included anti-Ro/La, RF, and ANA (1/320) positivity, whereas the 2016 criteria removed antibodies other than anti-Ro from the classification. In the 2016 criteria, anti-Ro positivity is assigned 3 points, which is equivalent to the weight given to MSGB. Nevertheless, as observed in our study, RF and ANA (1/320) positivity were significantly higher in patients diagnosed with SS. SS suspicion can arise not only from dryness symptoms but also from extra-glandular manifestations. Patients with such symptoms may be referred to rheumatology clinics from other departments with a suspicion of SS. Giovelli et al. (2015) found that 5.5% of patients presented with symptoms such as arthritis, vasculitis, and polyneuropathy. In our study, this rate was 7.9%, with patients presenting with leukopenia (3), multiple

sclerosis (2), ITP (1), MGUS (1), autoimmune hepatitis (1), and optic neuritis (1).

Among the 72 patients diagnosed with SS, 56 met the ACR-EULAR 2016 classification criteria (points ≥4) (Group 1), while 16 were diagnosed based on clinical and serological evidence despite scoring fewer than 4 points (Group 2). All 16 patients in Group 2 had eye dryness, and this group exhibited a statistically significant higher presence of arthritis compared to other groups. Although 11 patients in Group 2 had negative MSGB results, their rates of ANA, RF, and anti-Ro antibody positivity were similar to those in Group 1 and were higher compared to patients without a diagnosis.

Only one patient in Group 2 underwent the Schirmer test. The lower scores in Group 2 are likely due to MSGB negativity and the absence of other objective tests (Schirmer test, saliva flow rate measurement, and ocular staining tests) included in the criteria. These patients were diagnosed with SS based on their clinical features and serological tests. The diagnosis and MSGB outcome distributions for these patients are illustrated in Figure 2.

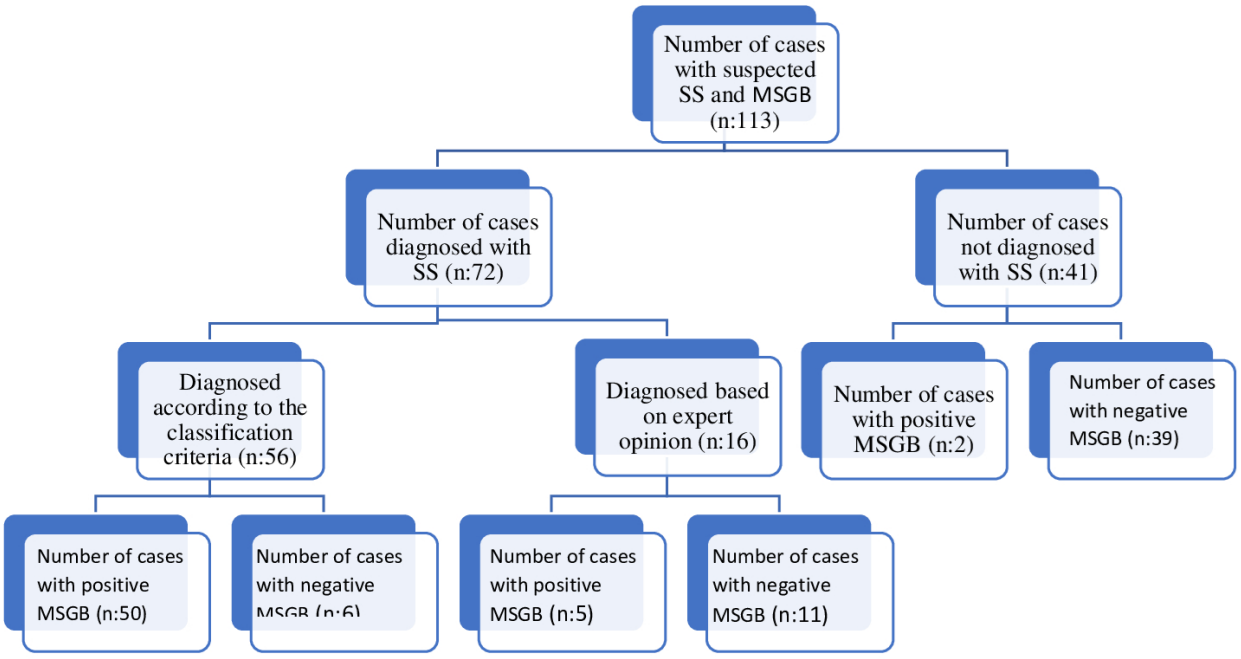


**Figure 2:** Distribution of patients who underwent MTBB by diagnosis.

7 Other studies (Guellec et al., 2013) evaluating the sensitivity and specificity of MSGB reported values ranging from 63.5-93.7% and 61.2-100%, respectively. In our study, the sensitivity of MSGB was 76.4%, and the specificity was 95.1%, which is consistent with findings from other studies.

## Limitations

We have no data about any complications developing after MSGB in our patients. As our study was retrospective, data related to this situation were not encountered in patient files. Complications after biopsy, such as pain, bruising, and hemorrhage, are rarely encountered; however, these symptoms generally tend to heal within a short duration. Additionally, our study used the 2016 ACR-EULAR classification criteria for SS diagnosis; however, very few patients had the Schirmer test performed (31%). The absence of ocular staining scores and unstimulated saliva flow rate tests in our patient group further limits the study. These missing tests hindered our ability to fully assess and comment on the relationship between these measures and disease presence. Future research should consider incorporating

these tests to provide a more comprehensive evaluation of ocular and salivary gland function.

## CONCLUSION

As demonstrated in our study, although MSGB is an invasive technique, it can assist in making the final diagnosis for patients with suspected SS who cannot undergo other objective tests. This technique, despite its invasive nature, provides valuable diagnostic information that can be crucial when other methods, such as saliva flow rate and ocular staining scores conducted by different specialties, are not available. The findings of this study highlight the importance of considering MSGB as a reliable diagnostic tool in the management of SS, especially in cases where conventional objective tests are not feasible. Further research is needed to explore the full range of applications and potential limitations of MSGB in diagnosing SS, and to establish guidelines for its use in clinical practice.

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**Ethics approval and consent to participate:** This Project was approved by the Ethics Committee in Antalya Training and Research Hospital on October 13, 2022 (protocol number 19/6). The study was conducted in line with the principles of the "Helsinki Declaration."

**Availability of Data and Materials:** Data are available on request due to privacy or other restrictions.

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