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Salivary gland ultrasound is linked to the autoimmunity profile in patients with primary Sjögren's syndrome

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Abstract

Objective: Salivary gland ultrasound (SGU) is a reliable technique for assessing the salivary glands in patients with primary Sjögren's syndrome (pSS). The aim of this study was to elucidate the relationship between SGU findings and autoimmunity in patients with pSS.

Methods: Patients with pSS underwent an SGU assessment. The patients were classified into three groups according to their autoimmunity profile: the complete positive group (positive rheumatoid factor, antinuclear antibodies, and anti-Ro/anti-La antibodies), the partial seropositive group (positivity of at least one autoantibody but not all), and the seronegative group.

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Results: In total, 93 patients were evaluated. Eighty-six (92.5%) were female, and their median age was 49.5 years. The median disease duration was 12.3 years. Pathological SGU findings were present in 32 (34.4%) patients [25 of 36 (78.1%) in the complete positive group and 7 of 44 (21.9%) in the partial positive group]. Patients with pathological SGU findings had a shorter disease duration and slightly higher European League Against Rheumatism Sjögren's syndrome disease activity index.
Conclusions: The autoimmunity profile and pathological SGU findings are strongly associated with each other in patients with pSS. However, the disease duration does not seem to be related to pathological SGU findings.

Keywords
Sjögren's syndrome, salivary gland ultrasound, autoantibodies, autoimmunity profile, disease duration, disease activity index

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Introduction

Primary Sjögren's syndrome (pSS) is a chronic inflammatory disease characterized by lymphocytic infiltration of the exocrine glands and marked B-lymphocytic cell hyperreactivity involving a variety of serum autoantibodies.[1] A delay between the clinical onset of pSS and its final diagnosis usually occurs.[2] Both the diagnosis and clinical evaluation of pSS are challenging. Fortunately, a validated activity index for pSS symptoms [European League Against Rheumatism (EULAR) Sjögren's syndrome patient reported index (ESSPRI)] and extraglandular involvement [EULAR Sjögren's syndrome disease activity index (ESSDAI)] have been developed in the last several years.[3–5]

At the end of the last century, the most widely used classification criteria for pSS were the 1993 European criteria.[6] Since then, several new classification criteria have been proposed.[7–10] During the past 15 years, the 2002 American-European Consensus Group (AECG) criteria[4] and the provisional 2012 National Institutes of Health-funded Sjögren's International Collaborative Clinical Alliance (SICCA)/American College of Rheumatology (ACR) criteria replaced the previous criteria. In 2016, investigators from the AECG and SICCA/ACR groups developed the ACR/EULAR criteria.[9,10] All of these classification criteria for pSS include a combination of subjective and objective findings of eye and mouth dryness.[6–10] To fulfill the 1993 European classification criteria, patients were required to have four of six items, but no single item was mandatory.[3] To fulfill the most accurately and accepted classification criteria currently in use,[7–10] patients must have lymphocytic infiltration in a minor salivary gland biopsy (SGB) and/or positive autoantibodies such as rheumatoid factor (RF), antinuclear antibodies (ANA), or anti-Ro/anti-La antibodies.

Salivary gland ultrasound (SGU) is a reliable technique with which to assess the major salivary glands.[11,12] Furthermore, SGU seems to be as sensitive as sialography and salivary gland scintigraphy,[13] but more specific in the assessment of the salivary glands in patients with pSS.[14] Moreover, researchers have proposed inclusion of SGU in the AECG or ACR classification criteria for pSS[15] in addition to or instead of sialography and salivary gland scintigraphy.[16] However, SGU was not included in the most recently published classification criteria.[17] Recent studies have also shown a

possible relationship between pathological SGU findings and positive SGB results.[18,19] Moreover, some authors have proposed exchanging SGB for SGU; however, this change resulted in a significant reduction in sensitivity from 77.9% to 68.8%.[20] Most interestingly, pathological SGU findings can be associated with extraglandular involvement, a higher risk of lymphoma,[21] and autoantibody positivity.[21–26] These associations could help to select a subpopulation of patients with potentially severe pSS.

A relationship between autoimmunity and pathological SGU findings has been suggested based on the high frequency of positive ANA, RF, or anti-Ro antibodies separately in patients with pSS and pathological SGU findings.[21–26] The present study was performed to compare the SGU findings between patients with pSS classified according to the AECG or SICCA/ACR criteria and patients who only fulfilled the 1993 European criteria.

Materials and Methods

We carried out a transverse observational single-center study. Patients classified as having pSS according to the 1993 European classification criteria[2] were randomly selected from the Systemic Autoimmune Rheumatic Diseases (SARD) Registry of the Rheumatology Department. We performed an SGU assessment of all patients and collected data on demographics, glandular and extraglandular involvement, and laboratory findings. Our local ethics committee approved the study, and all patients agreed to participate and provided written informed consent before SGU assessment.

Demographics (age, sex, age at disease onset, and disease duration) and cumulative clinical data (glandular and extraglandular involvement, parotid swelling, and lymphoma) were collected from the electronic clinical history. Extraglandular involvement was considered in the following different domains according to the EULAR definitions[4]: constitutional (fever or involuntary weight loss), articular (arthralgia or synovitis), lymphadenopathy (presence of lymphadenopathy or B-cell proliferative disorder), renal (nephrotic or nephritic syndrome with proteinuria or renal tubular acidosis), peripheral nervous system (cranial nerve involvement, inflammatory demyelinating polyneuropathy, vasculitis, or pure sensory axonal polyneuropathy), cutaneous (erythema multiforma, cutaneous vasculitis, purpura, or urticarial vasculitis), neurological (cerebrovascular stroke, optic neuritis, seizures, cerebral vasculitis, or multiple sclerosis-like syndrome), hematological (anemia, lymphopenia, thrombocytopenia, or neutropenia), pulmonary (interstitial pneumonitis or serositis), and biological (hypocomplementemia or hypergammaglobulinemia). The ESSDAI at the time of SGU assessment was calculated for each patient.[4] The SGB results were collected in the few patients in whom SGB was performed. The laboratory data collected were the erythrocyte sedimentation rate, C-reactive protein level, and presence of autoantibodies.

Ultrasonography

An expert rheumatologist in SGU who was blinded to the clinical, histological, and immunological data performed an SGU assessment using a real-time, high-resolution ultrasound machine (LOGIQ E9; GE Medical Systems Ultrasound and Primary Care Diagnostics, Wauwatosa, WI, USA) using a 6- to 15-MHz linear transducer (frequency of 7.5 MHz and gain of 35 dB). The patients were assessed lying on the bed in the supine position with the neck slightly extended and turned away from the assessed side. Both the parotid and submandibular glands were assessed; the submandibular glands were assessed only in the longitudinal scan, and the parotid glands were assessed in both the

longitudinal and transverse scans. To assess the homogeneity of the salivary gland parenchyma using B-mode SGU, we used a simple semiquantitative score ranging from 0 to 3 as previously described.[12] Briefly, grade 0 was a homogeneous gland similar to normal thyroid parenchyma, grade 1 was a gland with mild inhomogeneity without rounded hypoechoic areas, grade 2 was a gland with rounded hypoechoic areas within the gland parenchyma with some normal areas, and grade 3 was a gland with hypoechoic areas and complete inhomogeneity of the gland parenchyma. We considered grades 0 and 1 to be normal and grades 2 and 3 to represent pathological SGU findings.

Autoantibodies

Serum samples were tested twice for the presence of ANA, RF, anti-Ro, and anti-La antibodies. ANA (positive at >1:80) were measured by indirect immunofluorescence according to standard procedures on cryostat sections of rat tissues (kidney, liver, and stomach) and in cultured HEp-2 cells (MarDx Diagnostics, Carlsbad, CA, USA) using a fluorescein-conjugated rabbit anti-human antibody (DAKO, Copenhagen, Denmark). RF (positive at >20 IU/mL) was measured by laser nephelometry (Beckman Coulter, Brea, CA, USA). Anti-Ro and anti-La antibodies were detected by enzyme-linked immunosorbent assay (Rheuma ELISA™ System; Whittaker Bioproducts, Walkersville, MD, USA).

We compared clinical characteristics, including extraglandular involvement, and laboratory characteristics between patients with pathological and normal SGU findings. We classified patients into the following subgroups according to their autoimmunity profile: patients with simultaneously or sequentially detected ANA, RF, and anti-Ro or anti-La antibodies (complete positive group), patients with any of these autoantibodies but not all together (partial seropositive group), and patients with no autoantibodies (seronegative group). We compared the SGU findings among these three groups.

Finally, we confirmed fulfillment of the AECG and/or SICCA/ACR classification criteria for pSS[6,7] to define two subgroups: patients fulfilling the 1993 European criteria and the AECG and/or the SICCA/ACR criteria (hereafter referred to as pSS criteria patients), and patients only fulfilling the 1993 European criteria (hereafter referred to as sicca syndrome patients). We did not use the 2016 ACR criteria because these criteria include no imaging techniques as an item. We compared clinical characteristics, extraglandular involvement, and laboratory characteristics with respect to the presence of normal or pathological SGU findings.

Statistical analysis

Quantitative measures are expressed as mean, range, and standard deviation. Categorical measures are expressed as absolute frequency and percentage. Comparison between groups was performed using *t* tests for quantitative measures or the Mann–Whitney test depending on departure of normality and using chi-square tests or Fisher's exact test for categorical measures. In the chi-square test, analysis of Haberman standardized residuals was performed as needed to detect cells with frequencies higher or lower than expected according to the independence hypothesis at level 0.05. Differences were considered statistically significant at a p value of <0.05.

Results

One hundred patients were included in the study, but seven patients were excluded because they had secondary SS. Table 1 shows the data of the 93 patients finally included. The patients' mean age at disease onset and mean disease duration were 49.5

Table 1. Demographic and clinical data of 93 patients classified according to the 1993 pSS criteria: comparison between patients with and without an SGU pSS pattern.

	Total	Pathological SGU	Normal SGU	p
	n = 93	n = 32	n = 61	
Age at disease onset, years	49.5 ± 13.2	50.7 ± 11.6	48.9 ± 14.0	0.539
Female	86 (92.5)	31 (96.9)	55 (90.2)	0.244
Disease duration, years	12.3 ± 6.6	12.2 ± 4.5	12.4 ± 7.5	0.837
ESSDAI	0.9 ± 1.46	1.72 ± 1.84	0.48 ± 0.99	**0.001**
Elevated ESR	47 (50.5)	14 (43.8)	33 (54.1)	0.343
Lymphoma	3 (3.2)	1 (3.1)	2 (3.3)	1.00
Autoimmune thyroiditis	27 (29.0)	13 (40.6)	14 (23.0)	0.094
Extraglandular involvement	76 (81.7)	27 (84.4)	49 (80.3)	0.631
Parotid swelling	57 (61.3)	23 (71.9)	34 (55.7)	0.129

Data are presented as mean ± standard deviation or n (%).
pSS: primary Sjögren's syndrome; SGU: salivary gland ultrasound; ESSDAI: European League Against Rheumatism Sjögren's syndrome disease activity index; ESR: erythrocyte sedimentation rate.

Table 2. Autoantibodies and autoimmunity profile of 93 patients who fulfilled the 1993 pSS criteria: comparison between patients with and without an SGU pSS pattern.

	Total	Pathological SGU	Normal SGU	
	n = 93	n = 32	n = 61	p
Complete positive group	36 (38.7)	25 (78.1)↑	11 (18.0) ↓	**<0.001**
Partial seropositive group	44 (47.3)	7 (21.9)↓	37 (60.7) ↑	
Seronegative group	13 (14.0)	0 (0.0)↓	13 (21.3) ↑	
ANA + (n = 90)	70 (76.9)	31 (96.9)	39 (66.1)	**0.001**
RF + (n = 92)	55 (59.1)	28 (87.5)	27 (44.3)	**<0.001**
Anti-SSA/Ro + (n = 86)	46 (52.9)	27 (84.4)	19 (34.5)	
Anti-SSB/La + (n = 86)	28 (33.3)	19 (63.3)	9 (16.7)	

Data are presented as n (%).
pSS: primary Sjögren's syndrome; SGU: salivary gland ultrasound; ANA: antinuclear antibodies; RF: rheumatoid factor
Analysis of residuals: cells show more (↑) or fewer (↓) observed patients than expected under the independence hypothesis ($p < 0.05$).

and 12.5 years, respectively, and 86 patients were female (92.5%). Demographics and extraglandular involvement were comparable between patients with normal and pathological SGU findings. Disease activity at the time of SGU assessment was higher in patients with pathological than normal SGU findings (ESSDAI of 1.72 (1.84) vs. 0.48 (0.99), respectively; $p < 0.001$).

Autoimmunity profile

Data concerning the autoimmunity profiles and SGU findings are shown in Table 2. All autoantibodies, ANA, RF, and anti-Ro/anti-La antibodies were more frequent in patients with pathological SGU findings. The complete positive group had the highest frequency of pathological SGU findings

(78.1%). Most patients in the partial seropositive group (60.7%) and all seronegative patients had normal SGU findings. When we analyzed only pSS criteria patients (n = 59), the complete positive group also had a higher frequency of pathological SGU findings than the partial positive group [25/36 (80.6%) vs. 6/23 (19.4%), respectively; $p < 0.001$].

Classification criteria

Of all patients, 34.4% (32/93) had pathological SGU findings. The frequency of pathological SGU findings increased to 52.5% (31/59) when we analyzed only pSS criteria patients. Moreover, a higher number of patients fulfilled these criteria when they had pathological SGU findings than normal SGU findings [31/32 (96.9%) vs. 28/61 (45.9%), respectively; $p < 0.001$). Both pSS criteria and sicca syndrome patients had similar demographic data and extraglandular involvement with the exception of disease duration and parotid swelling. The disease duration was longer and parotid swelling was less frequent in pSS criteria patients (Table 3). Pathological SGU findings were also more frequent in pSS criteria patients [31/59 (52.5%) vs. 1/34 (2.9%). respectively; $p < 0.001$] than in sicca syndrome patients. Disease activity was similar between both groups [ESSDAI pSS criteria, 1.27 (1.64) vs. 0.94 (1.37)].

When we analyzed only the 59 pSS criteria patients (48 fulfilled the 2002 criteria, 58 fulfilled the 2012 criteria, and 47 fulfilled both), those with pathological SGU findings had a shorter disease duration (12.0 ± 4.5 vs. 15.6 ± 8.2 years, $p = 0.049$) and more frequent articular manifestations [22/31 (71.0%) vs. 12/28 (42.9%), $p = 0.029$) than patients with normal SGU findings (Table 4). Disease activity at the time of the SGU assessment was higher in patients with pathological SGU findings [ESSDAI, 1.77 (1.84) vs. 0.71 (1.18); $p < 0.001$]. No differences were found in the rest of the demographic parameters, laboratory

Table 3. Demographic and clinical data of 93 patients who fulfilled the 1993 pSS criteria: comparison between 59 patients who fulfilled both the 1993 and 2002/2012 pSS criteria, and 34 patients who only fulfilled the pSS 1993 criteria.

	Total	pSS fulfilling 2002/2012 criteria	pSS fulfilling only 1993 criteria	p
	n = 93	n = 59	n = 34	
Age at disease onset, years (n = 88)	49.5 ± 13.2	48.1 ± 12.6	52.0 ± 14.0	0.179
Female	86 (92.5)	56 (88.2)	30 (94.9)	0.240
Disease duration, years (n = 88)	12.3 ± 6.6	13.7 ± 6.7	9.9 ± 5.7	**0.008**
ESSDAI	0.90 ± 1.46	1.27 ± 1.64	0.94 ± 1.37	0.301
Elevated ESR	47 (50.5)	30 (50.8)	17 (50.0)	0.937
Pathologic SGU (grade 2 or 3)	32 (34.5)	31 (52.5)	1 (2.9)	**<0.001**
Lymphoma	3 (3.2)	2 (3.4)	1 (2.9)	0.173
Autoimmune thyroiditis	27 (29.0)	20 (33.9)	7 (20.6)	0.138
Extraglandular involvement	76 (81.7)	46 (78.0)	30 (88.2)	0.217
Parotid swelling	12 (12.9)	4 (6.8)	8 (23.5)	**0.020**

Data are presented as mean ± standard deviation or n (%).

pSS: primary Sjögren's syndrome; SGU: salivary gland ultrasound; ESSDAI: European League Against Rheumatism Sjögren's syndrome disease activity index; ESR: erythrocyte sedimentation rate.

Table 4. Demographic, laboratory, and clinical data of the 59 pSS criteria patients: comparison between patients with and without pathological SGU findings.

	Total	Pathological SGU	Normal SGU	p
	n = 59	n = 31	n = 28	
Age at disease onset, years (n = 56)	48.1 ± 12.6	50.5 ± 11.8	45.5 ± 13.1	0.142
Female	56 (94.9)	30 (96.8)	26 (92.9)	0.599
Disease duration, years (n = 56)	13.7 ± 6.7	12.0 ± 4.5	15.6 ± 8.2	**0.049**
ESSDAI	1.27 ± 1.64	1.77 ± 1.84	0.71 ± 1.18	**0.012**
Elevated ESR	30 (50.8)	13 (41.9)	17 (60.7)	0.150
Lymphoma	2 (3.4)	1 (3.2)	1 (3.6)	1.000
Autoimmune thyroiditis	20 (33.9)	13 (41.9)	7 (25.0)	0.170
Parotid swelling	4 (6.8)	3 (9.7)	1 (3.6)	0.614
Extraglandular involvement	46 (78.0)	26 (83.9)	20 (71.4)	0.250
Articular involvement	34 (57.6)	22 (71.0)	12 (42.9)	**0.029**
Cutaneous	17 (28.8)	8 (25.8)	9 (32.1)	0.592
Pulmonary	1 (1.7)	0 (0.0)	1 (3.6)	0.475
Renal	1 (1.7)	1 (3.2)	0 (0.0)	1.00
Neurological	6 (10.2)	2 (6.5)	4 (14.3)	0.409
Hematological	21 (35.6)	10 (32.3)	11 (39.3)	0.573

Data are presented as mean ± standard deviation or n (%).
pSS: primary Sjögren's syndrome; SGU: salivary gland ultrasound; ESSDAI: European League Against Rheumatism Sjögren's syndrome disease activity index; ESR: erythrocyte sedimentation rate.

Table 5. Autoantibodies and autoimmunity profile of the 59 pSS criteria patients: comparison between patients with and without an SGU pSS pattern.

	Total	Pathological SGU	Normal SGU	
	n = 59	n = 32	n = 28	p
Complete positive group	36 (61.0)	25 (80.6)	11 (39.3)	0.001
Partial seropositive group	23 (39.0)	6 (19.4)	17 (60.7)	
Negative group				
ANA + (n = 59)	58 (98.3)	31 (100.0)	27 (96.4)	0.475
RF + (n = 59)	46 (78.0)	27 (87.1)	19 (67.9)	0.075
Anti-SSA/Ro + (n = 58)	46 (79.3)	27 (87.1)	19 (70.4)	0.117
Anti-SSB/La + (n = 55)	28 (50.9)	19 (65.5)	9 (34.6)	0.022

Data are presented as n (%).
pSS: primary Sjögren's syndrome; SGU: salivary gland ultrasound; ANA: antinuclear antibodies; RF: rheumatoid factor
Analysis of residuals: cells with more (↑) or fewer (↓) observed patients than expected under the independence hypothesis ($p < 0.05$).

parameters, or extraglandular involvement. Only anti-La/SS-B antibodies were significantly more frequent in patients with pathological SGU findings [19/31 (65.5%) vs. 9/28 (34.6%), p = 0.022) (Table 5).

Discussion

The prevalence of pSS is 0.05% in the general population,[24] exhibiting a very broad spectrum[27,28] and resulting in considerable

annual healthcare costs.[29] Given the diverse range of symptoms, different classification criteria have been proposed during the past 25 years[6–10]; however, their clinical usefulness remains controversial. Using the 1993 European criteria, which are quite sensitive but have low specificity, we can classify a patient as having pSS only by the presence of sicca syndrome, without autoantibodies or positive SGB findings. To exclude these patients, both the AECG[7] and SICCA/ACR[8] criteria require the presence of positive SGB findings or autoantibodies, anti-Ro, and/or anti-La antibodies in both criteria or both RF and ANA in the second case. Therefore, we can define two different groups of sicca patients: those who fulfill the AECG[3] or SICCA/ACR[7] criteria can be classified as having pSS, and those who fulfill only the 1993 European criteria can be classified as having non-Sjögren sicca syndrome. The clinical features of non-Sjögren sicca syndrome are similar to those of pSS and have been previously reported,[30] but no information about SGU findings is given.

In the present study, we compared patients with pSS who fulfilled the AECG/ACR classification criteria and those who only fulfilled the 1993 European criteria.[6] Pathological SGU findings were present in one-third of the patients who fulfilled the 1993 European criteria.[6] However, as in other studies,[18–23] slightly more than half of the patients had pathological SGU findings when we analyzed only patients who fulfilled the AECG[4] or SICCA/ACR[8] classification criteria. Patients classified as having pSS according to the AECG/ACR criteria had a longer disease duration, more frequent pathological SGU findings, and more frequent parotid swelling than patients with sicca syndrome. In contrast, the subgroup of pSS criteria patients with pathological SGU findings had a shorter disease duration, more frequent articular manifestations, and positive anti-La antibodies. Therefore, the presence of pathological SGU findings in patients with pSS could be the related to more frequent extraglandular manifestations, as other authors have suggested[21]; in the present study, this presented as articular involvement.

In some studies, the disease duration was suggested to be related to the presence of pathological SGU findings based on the hypothesis that a longer disease duration could be associated with more salivary gland destruction. However, our results showed a longer disease duration in pSS criteria patients with pathological than normal SGU findings. Pathological SGU findings might not be associated with the disease duration but instead with a more severe subtype of pSS, and this could help to stratify patients with pSS with more extraglandular involvement and a higher risk of lymphoma.[21]

Supporting this idea, some authors have reported promising data relating pathological SGU findings with extraglandular involvement, a higher risk of lymphoma, positive autoimmunity, and positive SGB findings.[21,22,24] In the present study, the frequency of extraglandular involvement and lymphoma was similar between patients with normal and pathological SGU findings. This lack of difference could be related to the low frequency of lymphoma and severe extraglandular involvement in our cohort. Disease activity was slightly higher in patients with pathological SGU findings, both in the whole sample and in patients who fulfilled the AECG/ACR criteria. Despite this statistically significant difference between the groups, it is not possible to make strong conclusions because of the small activity measured by the ESSDAI (mean, 1.72 vs. 0.48). Further studies are mandatory to confirm this difference.

The relationship between pathological SGU findings and positive autoimmunity has been shown in previous studies and is strongly supported by our results.[21–25]

Moreover, a higher number of positive autoantibodies was associated with having the highest probability of pathological SGU findings in our cohort. Interestingly, none of the patients without autoantibodies had a typical pSS SGU pattern.

Some limitations of this study should be noted. Because this was an observational study, it had the usual inherent limitations such as missing data. However, clinical data were available for the majority of patients. SGB has been accepted as the gold standard in the diagnosis of pSS because of its high specificity for the disease.[2,31] A pathological SGB finding is one of the mandatory items needed to fulfill the most recently published classification criteria for pSS.[9,10,32] However, SGB is only a moderately sensitive and reliable test. In addition, it is an invasive procedure associated with short- and long-term complications,[33] and patient consent is required. In our experience, if no lymphoma or other causes of sicca syndrome are suspected, a significant proportion of patients with sicca syndrome refuse to undergo SGB. Nevertheless, the lack of SGB is a major limitation of our study. Finally, because the SGU assessment was not performed at the time of diagnosis, how the disease duration or treatment could influence our findings remains unknown. Further studies and an international collaborative effort are needed to elucidate the role of SGU in patients with pSS.

A link between pathological SGU findings and positive autoimmunity has been established,[21–25] and recent studies have shown that SGU is a strong predictor of positive SGB findings in patients with sicca symptoms.[18,19] Thus, there is a link among SGU findings, autoimmunity, and salivary gland histopathology in patients with pSS. Pathological SGU findings would be helpful in the study of patients with sicca syndrome in that they would provide a distinction between patients with pSS and those with sicca syndrome, but they cannot exclude a pSS diagnosis. Like SGB or anti-Ro antibodies, SGU may predict a patient's classification according to the most recent pSS criteria, but as stressed by Mossel et al.,[19] SGU cannot fully replace SGB.

Conclusions

There is a strong link between the autoimmunity profile and having pathological SGU findings, but the disease duration does not seem to be associated with pathological SGU findings in patients with pSS. In the present study, articular involvement was more frequent in patients with pathological SGU findings.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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