

# Evaluation of salivary gland ultrasonography in primary Sjögren's syndrome: does it reflect clinical activity and outcome of the disease?

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**Key words:** salivary gland ultrasonography, primary Sjögren's syndrome, disease activity

## ABSTRACT

**Objective.** To evaluate associations between salivary gland ultrasonography (SGUS) and clinical characteristics, disease activity and outcome in patients with primary Sjögren's syndrome (pSS).

**Methods.** The parotid and submandibular salivary glands were examined by ultrasonography using two different scoring systems proposed by Hocevar et al. and Milic et al. on 85 pSS patients. Patients with inhomogeneity/hypoechoic areas with scores  $\geq 2$  in parotid and submandibular glands were classified as severe parotid or severe submandibular involvements, respectively. Disease activity and patient-reported severity were evaluated using the European League Against Rheumatism Sjögren's Disease Activity Index (ESSDAI) and the European League Against Rheumatism Sjögren's Patient Reported Index (ESSPRI). Salivary gland functional capacity was investigated by unstimulated whole saliva flow rate (U-WSFR).

**Results.** Of the activity scores, ESSPRI dryness component was higher in pSS patients who had scores above the cut-off values for Hocevar ( $6.1 \pm 2.3$  vs.  $4.9 \pm 2.6$ ,  $p=0.026$ ). The patients with any type of systemic involvement more frequently showed higher SGUS scores, according to both Hocevar (72.4 vs. 44.6%,  $p=0.013$ ) and Milic (75.9 vs. 51.8%,  $p=0.026$ ). These patients also showed a higher percentage of severe parotid/submandibular changes on US imaging (65.5 vs. 33.9%,  $p=0.005$  and 75.9 vs. 51.8%,  $p=0.026$  respectively). Higher SGUS scores according to cut-off values of both scoring systems and severe parotid/submandibular involvements were associated with both anti-Ro or double anti-Ro/La autoantibodies and inversely associated with U-WSFR.

**Conclusion.** SGUS may be a useful imaging modality for the selection of patients with more severe disease status or who may require a tight follow-up schedule.

## Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterised by autoimmune epithelitis, mainly involves exocrine glands resulting in keratoconjunctivitis sicca and xerostomia. Although pSS may present with extraglandular manifestations of several organs, the classification criteria sets were prominently based on hypofunction of salivary and/or lacrimal glands plus serology and/or histopathology of minor salivary glands. To visualise the salivary glands, American-European Consensus Group (AECG) classification criteria for pSS suggested sialography or scintigraphy, while 2016 American College of Rheumatology/European League against rheumatism (ACR/EULAR) classification criteria for primary Sjögren's syndrome included only unstimulated whole salivary flow rate (U-WSFR) (1, 2). However, salivary gland ultrasonography (SGUS) was not included in the recent classification criteria even though some studies have indicated that SGUS has comparable sensitivity and specificity to scintigraphy, sialography and other imaging techniques for the classification of patients as pSS (3-5).

SGUS has been used to assess structural damage of parotid and submandibular glands in patients with pSS. SGUS is a non-invasive and non-irradiating imaging tool widely accessible in rheumatology practice. The diagnostic validity of SGUS was assessed in several studies and the sensitivity and specificity were reported to vary between 46 and 98%

Competing interests: none declared.

(6, 7) SGUS showed good performance for early noninvasive diagnosis of pSS, even in patients with suspected pSS and less than 5 years of symptom duration (8). A number of scoring systems including semiquantitative and quantitative assessments have also been proposed for the evaluation of the salivary glands (6).

A paucity of data exists on possible correlations of SGUS with other outcome measures, *e.g.* Ro/SSA and La/SSB autoantibodies, antinuclear antibodies, as well as controversial findings related to prediction of disease activity by SGUS in patients with pSS (9-11). Concerning these associations, it was suggested that SGUS may be of value in disease stratification (12).

The objective of this study was to investigate the associations between structural damage determined by SGUS and clinical characteristics, serological features, disease activity and outcome in patients with pSS.

## Materials and methods

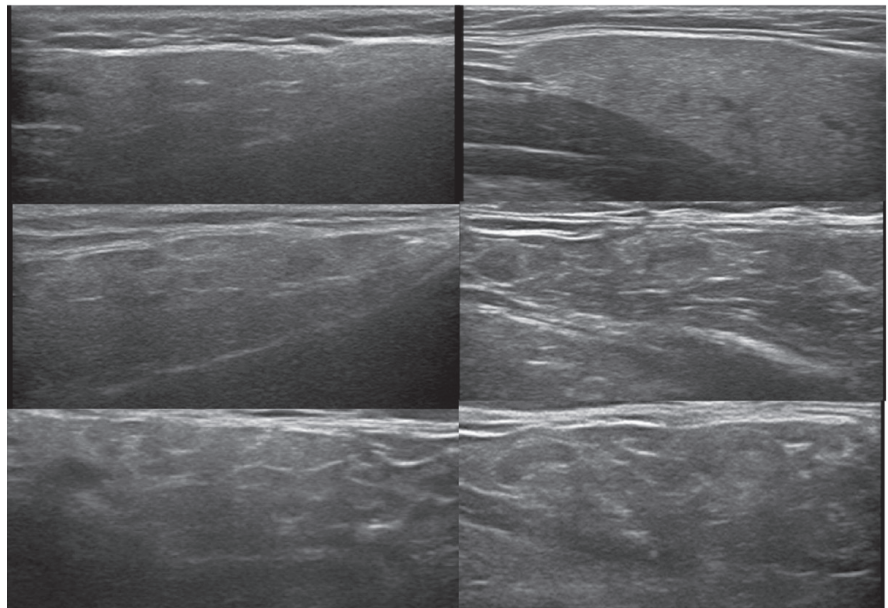
### Study design and patients

Eighty-five consecutive patients (83 females) fulfilling the AECG criteria (2002) for pSS and followed-up every 6 months using a protocol in Rheumatology outpatient clinic, were recruited in this cross-sectional study from January 2017 to March 2018. All participants were over 18 years of age and did not have concomitant diseases like associated connective tissue diseases, hepatitis B or C and sarcoidosis.

Demographics and clinical characteristics, the results of routine tests and serological and radiological findings of the patients were recorded. The study protocol was reviewed and approved by the ethical committee of the Marmara University Medical Faculty (09.2016.329). All patients gave informed consent.

### Assessment of disease activity

pSS patients, with manifestations of lymphadenopathy, interstitial lung disease, arthritis, vasculitis or nervous system involvement, previously or at the time of ultrasonographic evaluation were considered as having systemic involvement. Systemic activity was assessed using both the European League



**Fig. 1.** Ultrasound images of parotid and submandibular glands. Normal parotid (upper left) and submandibular gland (upper right), compared to abnormal parotid (in the middle and bottom left) and submandibular gland (in the middle and bottom right) with structural changes consistent with Sjögren's syndrome. The images in the middle show gland inhomogeneity, hypoechoic areas, hyperechoic stranding, and the ones on the bottom defines poorly defined borders as well.

Against Rheumatism Sjögren's Disease Activity Index (ESSDAI) (0-123) which is a clinician reported outcome index including 12 domains with different weights and activity levels: constitutional, cutaneous, articular, muscular, lymphadenopathy, glandular, pulmonary, central nervous system, peripheral nervous system, haematological, renal and biological (13). Clinical ESSDAI which does not include biological domains of ESSDAI was also used for the evaluation of disease activity of the patients with pSS (14). Patient-reported severity was assessed using the EULAR Sjögren's Patient Reported Index (ESSPRI), a VAS scale (0-10) for dryness, fatigue and pain (15).

### Ultrasonography

Grey-scale ultrasonography (US) of salivary glands was performed with a MyLab 70 US machine (Esaote, Genoa, Italy) equipped with a 18-6 MHz linear array transducer. The assessments were performed by one experienced rheumatologist who was blinded to the patients' data (NI). Bilateral parotid (right/left) and submandibular (right/left) glands were examined in greyscale while the patients were lying in supine position, with extension of the neck. The parotid

glands were scanned in both the longitudinal and transverse planes, while the submandibular glands were scanned only in the longitudinal plane. The representative images of all 85 patients were stored and retrospectively scored according to two validated semiquantitative scoring systems, *i.e.* the Hocevar scoring system (16) and the Milic scoring system (17). Total examination time for scanning and scoring of a patient consumed 10 to 15 minutes. For the Hocevar scoring system, five variables were semiquantitatively assessed for each gland: parenchymal echogenicity, homogeneity, presence of hypoechoic areas, presence of hyperechoic foci, and glandular borders (Fig. 1). Grades for all 4 glands in each of the 5 variables were summed (maximum score of 48 and cut off value  $\geq 17$ ). The Milic scoring system using one parameter for each 4 glands; graded from 0 to 3 for parenchymal inhomogeneity (maximum score of 12 and cut off value  $\geq 6$ ). In addition, patients with inhomogeneity/hypoechoic areas with scores  $\geq 2$  in parotid and submandibular glands were classified as severe parotid or severe submandibular involvements respectively.

To assess intrarater reliability, random sets of ultrasonographic images were

scored. The correlation for the individual scores treated as continuous data was high for both Hocevar and Milic scores (Spearman correlation coefficient 0.944 and 0.870,  $p < 0.001$  respectively). For the binary variables (scores  $< 17$  or  $\geq 17$  for Hocevar and scores  $< 6$  or  $\geq 6$  for Milic), correlation using Cohen's kappa was 0.753 ( $p < 0.001$ ) and 0.673 ( $p < 0.001$ ) respectively.

#### Whole saliva flow rate

All saliva samples were collected in the morning between 9 and 11 a.m. to standardise the sampling procedure due to the circadian rhythm of salivation. Patients sat upright position with their head inclined forward since remaining saliva in the floor of the mouth flows over the lip. For the unstimulated whole saliva samples collection, patients were prohibited smoking, chewing gum and intake of any food or beverage, except drinking water one hour before the procedure. Patients were advised to rinse their mouth several times. After starting timer, patients spit their saliva into a sterile plastic cup without swallowing during fifteen minutes.

Unstimulated samples were expressed as millilitres per minute and hyposalivation is defined by using U-WSFR less than 0.1 ml/min in the study (18).

#### Statistical analysis

All statistics were performed using SPSS, v. 16. Descriptive data were presented as mean  $\pm$  standard deviation (SD) or as percentages of available variables. Patients with and without systemic involvement or antibodies or severe SGUS findings were compared by Spearman correlation test, chi-square or Fisher's exact tests or by Mann-Whitney U-test for independent variables, as appropriate. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated. Intrarater reliability was assessed with Spearman correlation coefficient for the continuous variable and for the binary variables correlation, Cohen's kappa was used.  $p$ -values  $< 0.05$  were considered significant.

#### Results

Of the 85 pSS patients, 83 were women. Mean ( $\pm$ SD) age was  $51 \pm 12$  years.

**Table I.** Demographics and clinical characteristics of pSS patients.

	All patients n=85	SGUS Abnormal n=51	SGUS Normal n=34
<i>Clinical characteristics n (%)</i>			
Sicca symptoms	77 (90)	47 (92)	30 (88)
Arthralgia	71 (84)	43 (84)	28 (82)
Recurrent parotiditis	20 (24)	13 (26)	7 (21)
Raynaud's phenomenon	12 (14)	8 (16)	4 (12)
Peripheral neuropathy	7 (8)	5 (10)	2 (6)
Leukocytoclastic vasculitis	6 (7)	5 (10)	1 (3)
Interstitial lung disease	4 (5)	3 (6)	1 (3)
Newborn with CHB	2 (2.3)	2 (4)	0 (0)
<i>Laboratory characteristics</i>			
Anti-Ro n (%)	39 (46)	29 (57)	10 (29)
Anti-La n (%)	19 (22)	15 (29)	4 (12)
ESR (mm/h), mean $\pm$ SD	32 $\pm$ 19	36 $\pm$ 21	27 $\pm$ 16
CRP (mg/dl), mean $\pm$ SD	5 $\pm$ 6	6 $\pm$ 8	5 $\pm$ 5
<i>Treatment</i>			
HCQ n (%)	75 (88)	44 (86)	31 (91)
Prednisolone n (%)	27 (32)	19 (37)	8 (24)
Dose (mg/day), mean $\pm$ SD	5.8 $\pm$ 2.0	5.83 $\pm$ 1.98	5.83 $\pm$ 2.04
Duration (years), mean $\pm$ SD	2.9 $\pm$ 1.2	2.23 $\pm$ 2.13	2.20 $\pm$ 1.64
Methotrexate n (%)	21 (25)	12 (24)	9 (27)
Dose (mg/week), mean $\pm$ SD	14.2 $\pm$ 2.6	13.6 $\pm$ 2.3	15.0 $\pm$ 2.9
Duration (years), mean $\pm$ SD	3.4 $\pm$ 4.8	3.4 $\pm$ 5.6	3.4 $\pm$ 3.4
Azathioprine n(%)	9 (11)	7 (14)	2 (6)
Rituximab n(%)	4 (5)	3 (6)	1 (3)

**Table II.** Mean values of ESSDAI and ESSPRI among the patients grouped according to the cut-off values of SGUS scores.

	Number (n=85)	Hocevar score		$p$	Milic score		$p$
		$\geq 17$ (n=46)	$< 17$ (n=39)		$\geq 6$ (n=51)	$< 6$ (n=34)	
ESSPRI -total	4.9 $\pm$ 2.2	5.3 $\pm$ 2.3	4.5 $\pm$ 2.1	0.054	5.2 $\pm$ 2.3	4.5 $\pm$ 2.1	0.1
-dryness	5.5 $\pm$ 2.5	6.1 $\pm$ 2.3	4.9 $\pm$ 2.6	<b>0.026</b>	6.0 $\pm$ 2.4	4.9 $\pm$ 2.6	0.055
-fatigue	4.9 $\pm$ 2.8	5.4 $\pm$ 2.8	4.3 $\pm$ 2.9	0.065	5.2 $\pm$ 2.9	4.5 $\pm$ 2.9	0.2
-pain	4.6 $\pm$ 3	4.9 $\pm$ 3.1	4.3 $\pm$ 2.8	0.2	4.9 $\pm$ 3.1	4.2 $\pm$ 2.9	0.2
ESSDAI-total	2.8 $\pm$ 4.1	3.0 $\pm$ 4.2	2.5 $\pm$ 4.1	0.8	2.9 $\pm$ 4.1	2.6 $\pm$ 4.3	0.9

The duration of follow-up period was  $61 \pm 53$  months. Clinical and laboratory characteristics of the patients were summarised in Table I. The patients were mainly classified as pSS according to clinical and serological domains of the 2002 AECG criteria, only 14 (17%) patients had minor salivary gland biopsy with 50% positivity.

For the determination of relationship between SGUS findings to clinical and laboratory variables, patients were divided into two groups according to the SGUS scores cut-off values: SGUS scores of  $< 17$  ( $n=39$ ) or  $\geq 17$  ( $n=46$ ) for Hocevar and scores  $< 6$  ( $n=34$ ) or  $\geq 6$  ( $n=51$ ) for Milic were given in Table II. Of the activity scores, only ESSPRI-dryness component was higher in patients with Hocevar score  $\geq 17$ . Scores

of global and clinical ESSDAI, ESSPRI and other components of ESSPRI were not significantly higher in patients with scores of above the cut-off values for Hocevar and Milic. Although patients with  $\geq 17$  scores of Hocevar tended to have higher ESSPRI total and ESSPRI fatigue, it was not statistically significant (Table II). ESSDAI was also not found to be correlated with SGUS scores in patients with positivity of antiRo/antiLa.

The twenty-nine patients who suffered from systemic involvement (peripheral neuropathy or leucocytoclastic vasculitis or interstitial lung disease or lymphadenopathy or arthritis) (cumulative/ever) had more frequently higher SGUS scores according to both Hocevar (72.4% vs. 44.6%,  $p=0.013$ ) and Milic

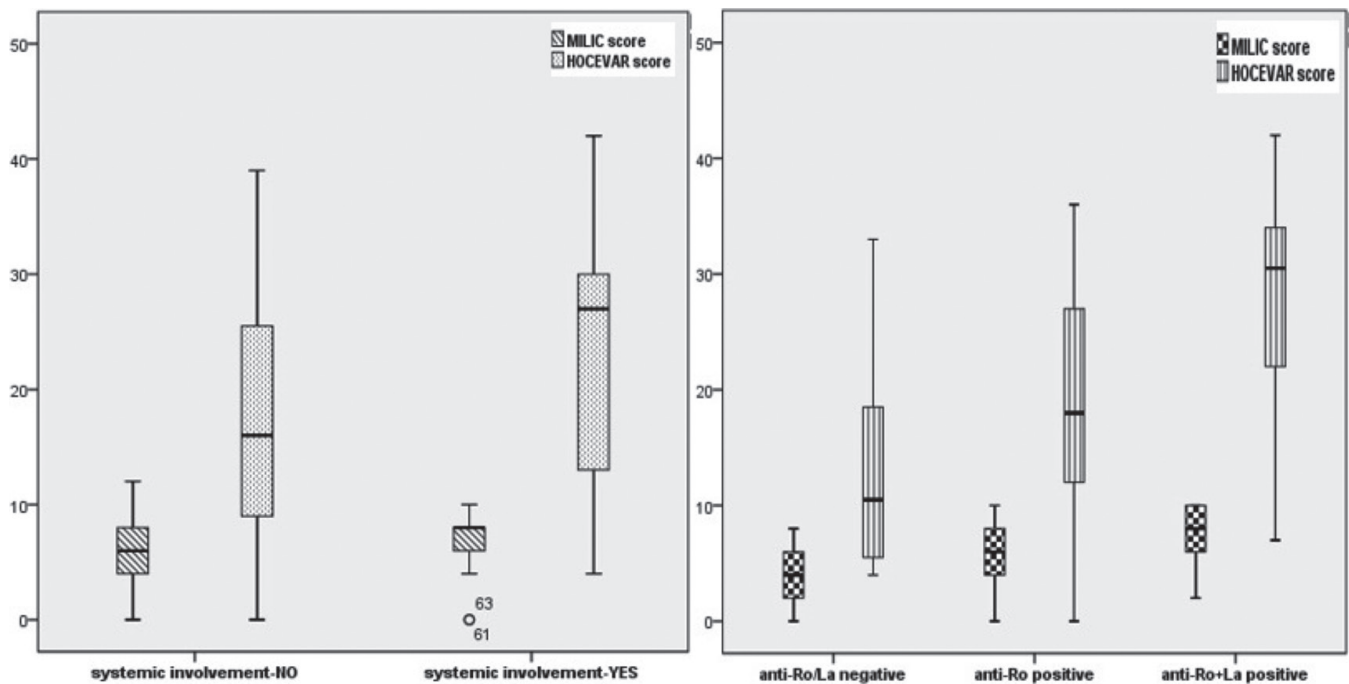


Fig. 2. The rate of systemic involvement and seropositivity according to the higher scores of SGUS.

(75.9 vs. 51.8%,  $p=0.026$ ). Anti-Ro/La or anti-Ro/La positive patients were found to have higher Hocevar ( $27.2\pm 9.8$  vs.  $2.6\pm 8.1$  for anti-Ro/La or  $19.6\pm 9.7$  vs.  $12.6\pm 8.1$   $p<0.001$  for anti-Ro) and Milic scores ( $7.7\pm 2.5$  vs.  $4.0\pm 2.3$  for anti-Ro/La or  $6.2\pm 2.5$  vs.  $4.0\pm 2.3$   $p<0.001$  for anti-Ro) than anti-Ro/La negatives (Fig. 2). U-WSFR levels were lower in patients with scores above the cut-off values for Hocevar and Milic ( $0.62\pm 0.71$  ml/min vs.  $1.05\pm 0.80$ ,  $p=0.005$  and  $0.65\pm 0.71$  ml/min vs.  $1.1\pm 0.8$ ,  $p=0.005$ ).

Thirty-eight (44%) and 41(48%) patients, respectively, were classified as having severe parotid or severe submandibular involvements. The patients with any type of systemic involvement had more frequently severe parotid ( $65.5$  vs.  $33.9\%$ ,  $p=0.005$ ) or severe submandibular gland involvements ( $75.9$  vs.  $51.8\%$ ,  $p=0.026$ ) according to SGUS (inhomogeneity/ hypochoic areas scores  $\geq 2$ ). In addition, positivity of anti-Ro or anti-Ro/La were also more common in patients with severe parotid or severe submandibular gland involvements ( $82\%$  vs.  $41\%$ ,  $p=0.001$  and  $46\%$  vs.  $15\%$ ,  $p=0.006$  for parotid and  $80\%$  vs.  $29\%$ ,  $p<0.001$  and  $44\%$  vs.  $7\%$ ,  $p=0.001$  for submandibular gland, respectively). U-WSFR was lower in patients with

severe parotid or severe submandibular gland involvement ( $0.6\pm 0.8$  ml/min vs.  $1.0\pm 0.8$ ,  $p=0.003$  and  $0.6\pm 0.6$  ml/min vs.  $1.2\pm 0.9$ ,  $p=0.005$ ).

The odds ratios (OR) were 3.5 (95% CI, 1.4–9.5) for severe parotid and 2.9 (95% CI, 1.1–8.0) for severe submandibular gland involvements for the association of the systemic features in this pSS cohort. Severe US parotid involvement occurring in 38 patients was found to have 66% sensitivity and 66% specificity for systemic involvement, while severe submandibular gland involvement occurring in 41 patients had 76% sensitivity and 48% specificity for systemic involvement.

### Discussion

This study revealed that structural damage of the salivary glands, as assessed by grey scale US is significantly associated with patient-reported severity of dryness, presence of extraglandular manifestations and anti-Ro/La in this pSS cohort. Systemic disease activity as measured by ESSDAI and ESSPRI was not shown to be related to scoring of SGUS according to both Hocevar and Milic systems besides association with dryness component of ESSPRI and  $\geq 17$  scores of Hocevar.

In one study (10), the relationship be-

tween SGUS and disease activity in pSS was showing ESSDAI levels to be higher in patients with abnormal SGUS according to parenchymal heterogeneity score of 2-3 in Hocevar system ( $8.1$  vs.  $3.4$ ,  $p<0.001$ ). The high prevalence of systemic involvement in that cohort may have possibly lead to a significant difference related to disease activity between US groups. Another study (11), showed that patients with US scores of 3 or 4, graded according to echostructure of glands on a scale of 1-4 (19), had more frequently ESSDAI  $\geq 5$  ( $34$  vs.  $13\%$ ,  $p=0.064$ ). Another study could not detect any difference related to disease activity by ESSDAI between the patients who were grouped according to cut-off value of 14 for Hocevar score (20). Similarly, we did not observe any relationship between ESSDAI and ESSPRI components with US scores, except ESSPRI dryness component which was prominent in patients with scores of above the cut-off values for Hocevar. In accordance with Hammenfors *et al.* (21), we found that patient-reported severity of dryness, fatigue and serological alterations were associated with more severe parenchymal findings on SGUS. Furthermore, in TRACTISS and TEARS randomised controlled trials evaluating RTX treatment in pSS

and including glandular assessment, did not report any relationship between ESSDAI, glandular activity or ESSPRI scores and SGUS changes (22, 23). In a recent review, Baldini *et al.* suggested that, improvement in differentiating between glandular inflammatory/lymphoproliferative activity and damage, as evaluated by SGUS, is of primary importance to increase the value of this imaging tool in pSS (24).

The patients with systemic involvement were shown to have more frequent severe SGUS findings in the study of Theander *et al.* (10), comparable to our results. In addition, the patients with any systemic involvement in our cohort had more severe parotid and submandibular gland involvements. In the literature some studies found distinctive ultrasonographic features that were predominant in submandibular glands in pSS patients (21, 25), another study showed the changes were evident in parotids (26). Recently, it was suggested that one parotid and one submandibular gland either the left or the right side should be scored together as the severity of SGUS findings in the parotid and submandibular gland may differ (27). The ORs to predict the systemic involvement in our pSS cohort were found to be higher for severe parotid than for severe submandibular gland involvements (OR 3.5 (%95CI 1.4-9.5) and 2.9 (%95CI 1.1-8.0)). Furthermore severe parotid involvement showed a low sensitivity but high specificity for pSS systemic involvement than severe submandibular gland involvement (66% vs. 76% and 66% vs. 48%) in our cohort. In accordance with these studies, severe parotid sintigraphic findings were found more frequent in patients who have more severe disease with anti-Ro or anti-La positivity (28).

In our patients, anti-Ro or anti-La positivity was more common in patients with severe parotid or submandibular gland involvement. These patients also were found to have higher Hocevar and Milic scores than anti-Ro/La negatives in our cohort compatible with the studies demonstrating high seropositivity in concordant with severe US findings (10, 11). Lee *et al.* (20),

also demonstrated positivity of anti-Ro/La independently associated with SGUS scores in the multivariate analysis ( $\beta=6.060$ ,  $p=0.001$ ). Ramos-Casals *et al.* (28) demonstrated anti-Ro or anti-La positivity were frequent in patients with severe parotid sintigraphic findings supporting the association of seropositivity with glandular destruction in pSS.

We demonstrated lower U-WSFR in patients with high total scores of SGUS compatible with the other SGUS studies in pSS (11, 29). Both severe parotid and severe submandibular gland involvement were found in patients with lower U-WSFR.

Our study has some limitations. This was a single-centre study and the cross-sectional design did not allow to observe the progress of US changes individually in pSS patients. A single ultrasonographer performed the SGUS to score the severity of salivary gland involvement however intrarater reliability score of the US assessment was high for both continuous and binary variables. Patients were recruited to the study according to 2002 AECG criteria, so a biopsy was performed only if the criteria was not fulfilled. Therefore the histopathological data of minor salivary glands was not included and compared to US findings.

### Conclusion

The associations observed in this study between SGUS, patient-reported severity of dryness, extraglandular involvement and autoantibodies point out the significantly high value of SGUS as a tool to assess salivary gland involvement in pSS. The patients with high SGUS scores, especially in parotid glands, need to be followed up more closely as they are at increased risk of poor outcome.

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