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Are Salivary Gland Ultrasonography Scores Associated with Salivary Flow Rates and Oral Health-related Quality of Life in Sjögren Syndrome?

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ABSTRACT. ***Objective***. Major salivary gland ultrasonography (SGUS) is a widely used imaging technique to evaluate salivary gland involvement in primary Sjögren syndrome (pSS). The aim of this study was to evaluate the relationship between SGUS, salivary flow rate (SFR) as an objective measure of the gland function, and oral health-related quality of life (OHRQOL) as a patient-reported outcome measure (PROM) in a pSS cohort.
Methods. Sixty-six patients with pSS were examined by SGUS according to Hocevar and Milic scoring systems. Patients with inhomogeneity/hypoechoic areas with scores ≥ 2 in parotid and submandibular glands were classified separately as "severe glandular involvement." Further, oral health, SFR, and Oral Health Impact Profile-14 (OHIP-14) for OHRQOL were assessed.
Results. Both total Hocevar and Milic scores were higher in 21 pSS patients with low unstimulated whole salivary flow rate (U-WSFR) than 45 pSS patients without low U-WSFR ($P = 0.001$ and $P < 0.0001$, respectively). Increased scores of homogeneity, hypoechoic areas and glandular border visibility were observed in patients with low U-WSFR ($P < 0.05$). Among these variables, homogeneity score was found to be an independent risk factor for low U-WSFR in pSS according to logistic regression analysis (OR 1.586, $P = 0.001$). Moreover, a higher OHIP-14 score was observed in severe parotid involvement compared to nonsevere cases (23.26 ± 21.19 vs 8.32 ± 13.82, $P = 0.004$).
Conclusion. High Milic and Hocevar SGUS scores are associated with reduced SFR and poor OHRQOL as a PROM. The inhomogeneity component of the SGUS score is associated with low U-WSFR and is an indicator of severely affected gland function.

Key Indexing Terms: salivary glands, Sjögren syndrome, ultrasonography

Sjögren syndrome (SS) is characterized by autoimmune inflammation and destruction of exocrine salivary and lacrimal glands, leading to common symptoms such as dryness of the eyes and mouth[1]. Major salivary gland ultrasonography (SGUS) is a noninvasive imaging method to evaluate salivary gland involvement. There is an increasing amount of data showing US to be a specific and sensitive alternative to sialography and scintigraphy[2,3].

The objective oral signs of salivary gland dysfunction are listed in sets of 2002 American-European Consensus Group (AECG) classification criteria for primary SS (pSS) as either decreased unstimulated whole salivary flow rate (U-WSFR), an abnormal result on parotid sialography, or an abnormal result on salivary scintigraphy[4]. In 2016, new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for pSS were developed and, with the exclusion of sialography and salivary gland scintigraphy, the available methods for evaluation of pSS orally include minor salivary gland biopsy and U-WSFR[5]. However, SGUS was not included in the recent classification criteria, despite some studies having indicated that SGUS has comparable sensitivity and specificity to scintigraphy, sialography, and other imaging techniques for the classification of patients as having pSS. Until now, few studies have tested its reliability, but there has been no international consensus on SGUS elementary definitions and scores[6,7,8]. Recently, the OMERACT Ultrasound Working Group developed new definitions aiming for a novel semiquantitative US score for pSS patients with "good" interreader reliability and "excellent" intrareader reliability[9].

Salivary flow rate (SFR) is an easy and noninvasive method to determine functions of salivary glands[10,11]. Saliva has a crucial role in cleaning the oral cavity, swallowing food, protecting oral tissues, and providing moisture to facilitate speech[12]. Therefore, hypofunction of the salivary glands causes a difficulty in speech,

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eating, and swallowing, as well as halitosis, oral infections, altered taste, and poor oral health-related quality of life (OHRQOL)[13]. Yet, available studies for validation are limited between SFR and SGUS in patients with pSS.

Therefore, the aim of this study was to evaluate the relationship among SGUS, U-WSFR as an objective criteria of gland function, and OHRQOL as a patient-reported outcome measure (PROM) in a pSS cohort.

MATERIALS AND METHODS

Sixty-six patients (F/M: 65/1; mean age: 51 ± 12 yrs) with established pSS were included in this cross-sectional study. The main demographic and clinical findings are listed in Table 1. All patients were followed up in the rheumatology outpatient clinic at Marmara University Hospital, Istanbul. The patients were consecutively enrolled in the study from January 2017 to March 2018. Exclusion criteria were hepatitis B or C infections, sarcoidosis, and other connective tissue diseases. All included patients fulfilled the 2002 AECG classification criteria for pSS[4] and gave written informed consent to participate. The study was approved by the local ethics committee at Marmara University Medical Faculty (09.2016.329). In the study protocol, the same investigators evaluated oral health (GM) and SGUS images (NI) in a blinded fashion.

Major salivary gland ultrasonography. SGUS (bilateral parotid and submandibular glands) was performed with MyLab 70 ultrasound machine (Esaote) equipped with an 18-6 MHz linear array transducer. All patients were examined in the supine position, with extension of the neck. The parotid glands were scanned in both the longitudinal and transverse planes, whereas the submandibular glands were scanned only in the longitudinal plane. Stored SGUS images of 4 glands were evaluated by using 2 semiquantitative scoring systems. An experienced ultrasonographer (NI) who was blinded to the patients' data performed all US examinations. The patients were clinically examined by another physician.

Hocevar scoring system (0–48 points) includes 5 variables for each of the 4 glands[14]: parenchymal echogenicity (0–1 point), homogeneity (0–3 points), presence of hypoechoic areas (0–3 points), hyperechoic foci (0–3 points), and visibility of glandular borders (0–3 points; Figure 1). Milic scoring system (0–12 points) uses 1 variable for each of the 4 glands[15] and is graded from 0 to 3 for parenchymal inhomogeneity.

In addition, 1 parotid and 1 submandibular gland, either the left or the right side, were scored together. Patients with inhomogeneity/ hypoechoic areas with scores ≥ 2 in parotid and submandibular glands were classified as severe parotid or severe submandibular involvements, respectively. The ultrasonographer (NI) previously showed excellent intraobserver reliability on the continuous data for both total Hocevar and Milic scores[16].

Unstimulated and stimulated whole salivary flow rates. All measurements were performed in the morning (9:00–11:00 AM). Patients refrained from

Table 1. Demographics and clinical characteristics of patients with pSS.

	All Patients n = 66	Low U-WSFR(+), ≤ 0.1 mL/m, n = 21	Low U-WSFR (–), > 0.1 mL/m, n = 45
Clinical characteristics			
Sicca symptoms	62 (93.9)	21 (100)	41(91.1)
Arthralgia	55 (83.3)	17 (80.9)	38 (84.4)
Recurrent parotiditis	16 (24.2)	5 (23.8)	11 (24.4)
Raynaud phenomenon	11 (16.6)	4 (19.04)	7 (15.5)
Peripheral neuropathy	4 (6.0)	2 (9.5)	2 (4.4)
Leukocytoclastic vasculitis	3 (4.5)	2 (9.5)	1 (2.2)
Interstitial lung disease	2 (3.0)	1 (4.8)	1 (2.2)
Newborn with cardiac heart block	2 (3.0)	0 (0)	2 (4.4)
Schirmer test < 5/5 mm (n = 36)	30/36 (83.3)	9/12 (75)	21/24 (87.5)
Laboratory characteristics			
Anti-Ro	21 (31.8)	11 (52.3)	20 (44.4)
Anti-La	18 (27.2)	6 (28.6)	8 (17.7)
Anti-Ro and anti-La	18 (27.2)	6 (28.6)	8 (17.7)
RF (17/55)	17 (25.8)	6 (28.6)	11 (24.4)
Acute-phase response			
ESR, mm/h	31.3 ± 18.7	34.4 ± 20.7	30.0 ± 17.9
CRP, mg/dl	4. 8 ± 6.1	3.9 ± 4.0	5.1 ± 6.9
Treatment			
Hydroxychloroquine	60 (90.9)	18 (85.7)	42 (93.3)
Prednisolone	20 (30.3)	6 (28.6)	14 (31.1)
Dosage, mg/day, mean ± SD	5.6 ± 1.8	5.6 ± 2.2	5.6 ± 1.7
Duration, yrs, mean ± SD	2.2 ± 2.0	1.8 ± 0.9	2.4 ± 2.4
Methotrexate	20 (30.3)	6 (28.6)	14 (31.1)
Dosage, mg/week, mean ± SD	14.4 ± 2.4	14.0 ± 2.2	14.6 ± 2.6
Duration, yrs, mean ± SD	2.5 ± 2.4	2.1 ± 1.3	2.6 ± 2.8
Azathioprine	5 (7.5)	2 (9.5)	3 (6.5)
Rituximab	1 (1.5)	0 (0)	1 (2.2)

Values are n (%) unless otherwise specified. pSS: primary Sjögren syndrome; U-WSFR: unstimulated whole salivary flow rate.

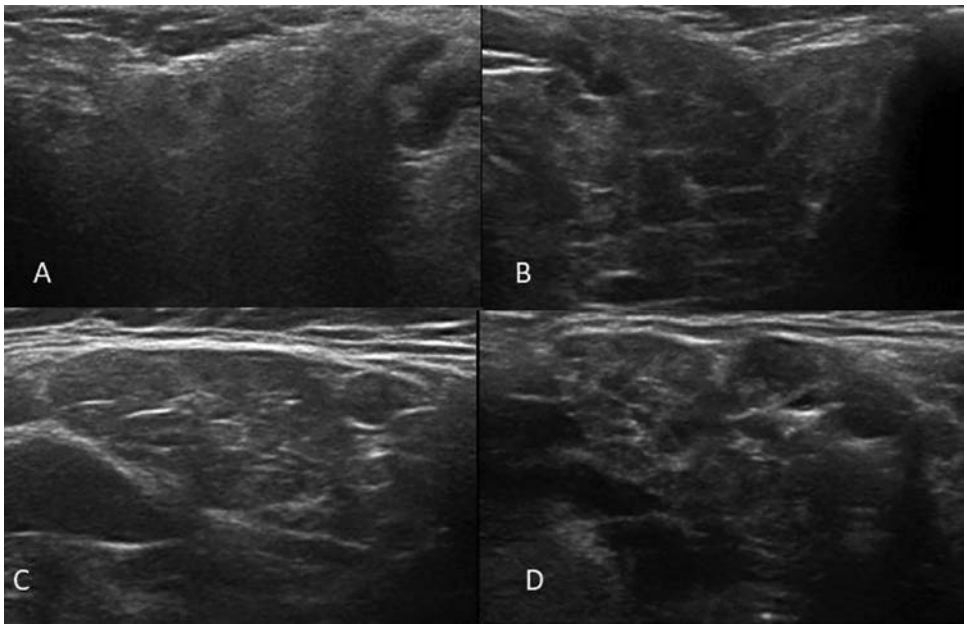

Figure 1. Representative images illustrating each of the variables analyzed in the salivary gland ultrasonography of patients with pSS. (A) Parotid gland with mild inhomogeneity with hypoechoic areas. (B) Parotid gland with confluent hypoechoic areas, multiple cysts, and poorly defined borders as well. (C) Submandibular gland with hypoechoic areas and prominent hyperechoic bands. (D) Submandibular gland with grossly inhomogenous appearance with hypoechoic areas and hyperechoic bands as well as poorly defined borders. pSS: primary Sjögren syndrome

eating, drinking, or smoking for a minimum of 2 h before saliva collection. They were asked to lean forward and spit their saliva for 15 min into a graduated test tube. Then, U-WSFR was calculated as milliliters per minute (mL/min) in laboratory conditions (FTO). In the second step, patients chewed a piece of paraffin until it became soft and swallowed their saliva before the collection. Then, patients spit their saliva into a tube at short intervals and kept chewing. Stimulated whole saliva samples of patients were collected during the 5-min chewing period. The volumes ≤ 0.1 mL/min for U-WSFR and ≤ 0.7 mL/min for stimulated whole SFR (S-WSFR) suggested salivary hypofunction[5,17,18], with the term "low U-WSFR" used for volumes < 0.1 mL/min of U-WSFR.

Oral health and oral health-related quality of life. Oral health was assessed by various indices, including: plaque index (PI), gingival index (GI), bleeding on probing (BOP), periodontal pocket depth (PPD), clinical attachment level (CAL), presence of dental caries, the number of natural teeth, and frequency of tooth brushing[19].

OHRQOL as a PROM was evaluated by using the Turkish version of the Oral Health Impact Profile (OHIP-14). OHIP-14 scores ranged from 0 to 56 points[20], with higher scores indicating poorer OHRQOL status.

Statistical analysis. Statistical analysis was performed using IBM SPSS 16.0 (IBM Corp.). Data were presented as mean ± SD for continuous variables or percentages for the categorical variables. SGUS scores were compared by using Mann–Whitney U test in patients with and without low U-WSFR due to non-normal distribution of data according to the Kolmogorov–Smirnov test (P < 0.0001). In addition, Mann–Whitney U test and Spearman correlation test were utilized to evaluate the association between SGUS scores with the oral health indices and OHIP-14.

For diagnostic accuracy of SGUS scores to predict low U-WSFR, areas under the curve (AUC) were calculated using receiver-operating characteristic (ROC) curve analysis and presented with 95% CI. AUC was interpreted as not discriminative (< 0.5), poor (≥ 0.5 to < 0.7), fair (≥ 0.7 to < 0.8), good (≥ 0.8 to < 0.9) or excellent (≥ 0.9–1.0).

Binary logistic regression analysis was also used to evaluate the relationships between low U-WSFR and SGUS variables for scores of hypoechogenic areas, homogeneity, and border visibility. In binary regression analysis, having low U-WSFR as a dependent variable was coded as "1," with all others being "0". Hypoechogenic areas, homogeneity, and border visibility were used as continuous data in the analysis, whereas P < 0.05 were considered as significant.

RESULTS

Sixty-six patients with pSS that had a mean disease duration of 7.2 ± 4.8 years and mean follow-up periods of 60 ± 49 months were enrolled in the study. Low U-WSFR (≤ 0.1 mL/min) was present in 21 of these patients (31%) and reduced S-WSFR (≤ 0.7 mL/min) level was determined at the same rate. The total SGUS scores of the 4 glands, the unilateral combination of parotid and submandibular glands, as well as the separate major salivary glands according to Hocevar and Milic scoring systems, were higher in patients with low U-WSFR (P < 0.05), as summarized in Table 2.

Total AUC scores for Hocevar (0.762) and Milic (0.790), along with unilateral scoring of parotid and submandibular glands for Hocevar [0.769 (right) and 0.749 (left)] and Milic [0.788 (right) and 0.775 (left)], were adequate to indicate low U-WSFR (Table 2). Both unilateral right and left SGUS scores for parotid and submandibular glands seem to have similar AUC to the total scores of the 4 glands.

The individual components of the Hocevar score (i.e., homogeneity and hypoechoic areas) and glandular border visibility scores were higher in patients with low U-WSFR (Table 2). The AUC was also adequate for scores of homogeneity, hypoechoic areas, and glandular border visibility to indicate low U-WSFR

Table 2. SGUS scores and ROC curve analysis in patients with pSS according to unstimulated whole salivary flow rate (U-WSFR).

	Low U-WSFR (+), ≤ 0.1 mL/m, n = 21	Low U-WSFR (–), > 0.1 mL/m, n = 45	*P*	AUC in ROC Analysis
Hocevar score (total)	24.6 ± 9.1	15.4 ± 8.7	**0.001**	0.762
Parotid (R+L)	11.7 ± 6.6	6.9 ± 5.1	**0.010**	0.697
Submandibular (R+L)	13.0 ± 3.9	8.7 ± 4.7	**0.001**	0.743
Parotid and Submandibular (L)	12.1 ± 4.7	7.8 ± 4.4	**< 0.0001**	0.749
Parotid and Submandibular (R)	12.6 ± 4.7	7.8 ± 4.5	**0.001**	0.769
Milic score (total)	7.4 ± 2.2	4.8 ± 2.4	**< 0.0001**	0.790
Parotid (R+L)	3.5 ± 1.6	2.0 ± 1.4	**0.001**	0.744
Submandibular (R+L)	3.9 ± 1.2	2.9 ± 1.4	**0.002**	0.714
Parotid and Submandibular (L)	3.7 ± 1.2	2.4 ± 1.2	**< 0.0001**	0.775
Parotid and Submandibular (R)	3.7 ± 1.1	2.4 ± 1.1	**< 0.0001**	0.788
SGUS variables				
Parenchymal echogenicity	3.1 ± 1.5	2.4 ± 1.7	0.126	0.607
Homogeneity	7.3 ± 2.2	5.0 ± 2.3	**< 0.0001**	0.768
Hypoechoic areas	5.7 ± 2.7	2.9 ± 2.7	**< 0.0001**	0.767
Hyperechogenic foci	4.1 ± 1.7	3.3 ± 1.9	0.103	0.622
Glandular border visibility	4.4 ± 2.9	2.0 ± 2.5	**0.001**	0.745

Values in bold are statistically significant. AUC: area under the curve; L: left; R: right; ROC: receiver-operating characteristic; SGUS: major salivary gland ultrasonography.

(Table 2, Figure 2). The ROC analyses of S-WSFR were found to be similar to those of U-WSFR (AUC for S-WSFR was 0.697–0.790 for scores of Hocevar and subgroups; 0.714–0.784 for scores of Milic and subgroups; and 0.600–0.763 for SGUS variables).

Among these, homogeneity score was found to be an independent variable for low U-WSFR in patients with pSS according to binary logistic regression analysis (OR 1.586; $P = 0.001$; Table 3).

The mean score of OHIP-14 as a PROM was 21.57 ± 15.5 in patients with pSS, while it was higher in patients with low U-WSFR (33.6 ± 16.3 vs 15.97 ± 11.6, $P < 0.001$) and correlated with U-WSFR (r –0.52, $P < 0.001$) and S-WSFR (r –0.37, $P = 0.002$). Moreover, severe parotid involvement (23.26 ± 21.19) manifested an increase in OHIP-14 score in comparison to nonsevere cases (8.32 ± 13.82, $P = 0.004$). However, no similar disposition was found with the severe submandibular involvement ($P = 0.79$). In patients with pSS, no significant difference was observed between SGUS scores and the oral health indices, including scores of PI, GI, BOP, PPD, and CAL, and number of teeth and caries. On the other hand, the frequency of tooth brushing correlated with both Hocevar

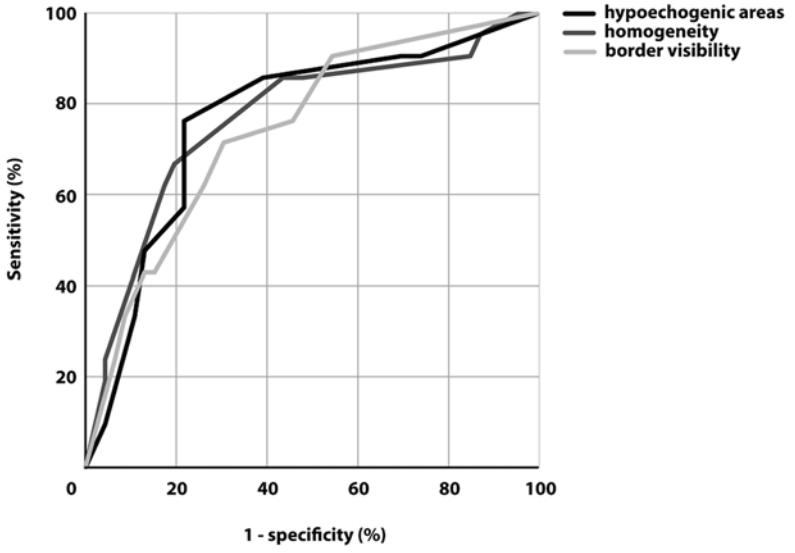

Figure 2. ROC analysis of hypoechoic areas, homogeneity, and glandular border visibility for low U-WSFR in patients with pSS. pSS: primary Sjögren syndrome; ROC: receiver-operating characteristic; U-WSFR: unstimulated whole salivary flow rate.

Table 3. The independent variable for low unstimulated whole salivary flow rate in patients with pSS according to binary logistic regression analysis.

	B[a]	SE	Wald[b]	Df	*P*	OR	95% CI for OR	
							Lower	Upper
Homogeneity	0.461	0.144	10.317	1	**0.001**	1.586	1.197	2.102
Constant	−3.630	0.985	13.577	1	**< 0.0001**			

Values in bold are statistically significant. [a] Regression coefficient. [b] Wald statistics. Df: degree of freedom; pSS: primary Sjögren syndrome; SE: standard error.

(r 0.3, $P = 0.012$) and Milic scoring systems (r 0.3, $P = 0.036$; data not shown).

DISCUSSION

In our study, both total and unilateral combinations of parotid and submandibular SGUS scores were found to be high in patients with low U-WSFR. This suggests that there might be an association between functional status of the glands and SGUS changes. Evaluating US variables separately, we found that homogeneity, hypoechoic areas, and glandular border visibility were associated with low U-WSFR. Among these, homogeneity was found to be an independent variable in the indication of low U-WSFR.

Previous studies have shown that an increase in SGUS scores is associated with a decrease in U-WSFR[21,22] and S-WSFR[23,24]. Using a scoring system that essentially focused on salivary gland inhomogeneity, Baldini, *et al*, demonstrated that changes in the salivary gland parenchymal echostructure appeared relatively early in the course of the disease[25]. In addition, the SGUS score was significantly correlated with both the U-WSFR and the minor salivary gland biopsy focus score. Therefore, SGUS seems to reflect the dysfunction of the salivary glands and even inflammation of the disease. In parallel with these data and despite the different scoring systems adopted, all available studies highlighted parenchymal gland inhomogeneity as the single most important feature for differentiating pSS from other salivary gland diseases[26]. Currently, there are few studies available comparing the histology specifically with the US hypoechogenic/inhomogeneous areas of the major salivary glands[27,28,29]. Therefore, it is possible that such areas may occur due to atrophy of the gland resulting from a chronic autoimmune inflammatory process in pSS[21,23]. Our study suggests that homogeneity, hypoechoic areas, and glandular border visibility are associated with low U-WSFR and also S-WSFR. Moreover, since homogeneity was found to be an independent variable in the indication of low U-WSFR, the US homogeneity score may be used to determine poor functional status of salivary glands in clinical practice.

Previously, the evaluation of the combination of unilateral parotid and submandibular glands was adequate to predict ACR/EULAR classification for patients with pSS (AUC > 0.8)[30]. Our study also demonstrates that scoring of the combined unilateral parotid and submandibular glands was sufficient to predict low U-WSFR (AUC > 0.7). Thus, scoring of only 1 side not only predicts ACR/EULAR classification but also predicts the functional status of the salivary glands. Further, there is no difference in scoring the left or right side of the glands.

Another key result of the present study is the poor OHRQOL observed in patients with low U-WSFR, which also appeared to be associated with severe parotid involvement in pSS. The US assessment of the parotid glands was found to be a determinant for poor OHRQOL. Poor OHIP-14 scores reflected decreases in SFR due to destruction of salivary glands limiting the functional and protective properties of saliva in the oral mucosa. In Sjögren syndrome, the hyposalivation is commonly seen since salivary glands, as exocrine glands, are mainly affected by disease pathogenesis[31]. Since the OHIP-14 score is affected by SFR[32], OHIP-14 is thought to be a valid and reliable instrument to assess the OHRQOL[33]. Moreover, poor OHIP-14 score is found in patients with xerostomia[34]. Another study[35] investigated the relationship between OHRQOL and SGUS, revealing that US scores ≥ 17 had significantly worse periodontal health (higher OHIP-14 questionnaire scores; mean scores 14.8 vs 3.2, $P = 0.007$). Therefore, sonographic diagnosis of pSS may potentially help to identify the patients who need routine assessment and management of their oral health. In contrast, no significant difference was found between salivary gland sonographic changes and the oral health indices in our study, which may be a result of increased frequency of tooth brushing and could be correlated with both SGUS scoring systems.

Our study had several limitations. First, it was a single-center and cross-sectional study with a relatively small number of patients with pSS. Second, there was only a single investigator who performed and scored the SGUS. Third, the minor salivary gland biopsy was only performed if the participants did not fulfill the AECG criteria; therefore, histopathology data was not sufficient to compare U-WSFR, OHRQOL, and SGUS findings. Finally, SFR of major glands were not evaluated separately in the study protocol.

The SGUS is a simple, noninvasive, and efficient method for the evaluation of salivary glands with different scores in patients with pSS. SGUS scores of the sums of 4 glands, as well as unilateral parotid and submandibular glands, are sufficient to predict low U-WSFR in patients with pSS evaluated by Hocevar and Milic scoring systems. SGUS scores are correlated with both low U-WSFR and poor OHRQOL as a PROM. Among US variables, homogeneity of salivary glands is an independent variable for the low U-WSFR in clinical practice.

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