Are Salivary Gland Ultrasonography Scores Associated with Salivary Flow Rates and Oral Health Related Quality of Life in Sjögren's syndrome?

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Abstract

***Aim**:* Ultrasonography of major salivary glands (SGUS) is a widely used imaging technique to evaluate salivary gland involvement in primary Sjögren's 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. Furthermore, 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 non-severe ones (23.26 ± 21.19 vs 8.32 ± 13.82, $p=0.004$).

***Conclusion**:* High Milic and Hocevar SGUS scores are associated with reduced SFRs and poor OHRQoL as a PROM. US inhomogeneity of salivary glands is associated with low U-WSFR and is a good indicator of severely affected gland function.

Introduction

Sjögren's syndrome is characterized by autoimmune inflammation and destruction of exocrine salivary and lacrimal glands, leading to common symptoms of dryness of eyes and mouth (1). Ultrasonography of major salivary glands (SGUS) is a non-invasive 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 given in sets (4) of 2002 American-European Consensus Group (AECG) classification criteria for primary Sjögren's syndrome (pSS) as either decreased unstimulated whole salivary flow rate (U-WSFR), an abnormal result on parotid sialography or an abnormal result on salivary scintigraphy. In 2016, new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for pSS were developed 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 have indicated that SGUS has comparable sensitivity and specificity to scintigraphy, sialography and other imaging techniques for the classification of patients as pSS. Uptill now, few studies have tested its reliability but there has been no international consensus existing on SGUS elementary definitions and scores (6-8). Recently, OMERACT ultrasound working group has developed new definitions aiming for a novel semiquantitative US score with a good and excellent interreader and intrareader reliability in pSS patients (9).

Salivary flow rate (SFR) is an easy and non-invasive method to determine functions of salivary glands (10,11). Saliva has a crucial role in cleaning the oral cavity, swallowing food, protecting oral tissues, providing moisture to facilitate speech (12). Therefore, hypofunction of the salivary glands causes a difficulty in speech, eating and swallowing, halitosis, oral infections as well as 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 years) 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 of 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, oral health (GM) and SGUS images (NI) were evaluated by the same investigators in a blinded fashion.

Major Salivary gland Ultrasonography

Major salivary glands (bilateral parotid and submandibular glands) ultrasonography was performed with My Lab 70 US machine (Esaote, Italy) 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, while the submandibular glands were scanned only in the longitudinal plane. Stored SGUS images of 4 glands were evaluated by using two semiquantitative scoring systems. An experienced ultrasonographer (NI) who was blinded to the patients' data performed all ultrasonographic examinations. The patients were clinically examined by another physician.

Hocevar scoring system (0-48 points) includes five parameters for each 4 glands (14);

- Parenchymal echogenicity (from 0 to 1 point),

- Homogeneity, presence of hypoechoic areas, hyperechoic foci and visibility of glandular borders (from 0 to 3 points) (Figure 1).

Milic scoring system (0-12 points) uses one parameter for each 4 glands (15);

- Graded from 0 to 3 for parenchymal inhomogeneity.

In addition, one parotid and one submandibular gland, either the left or the right side, scored together. Furthermore, 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 to 11 a.m.). Patients refrained from eating, drinking or smoking for a minimum of 2 hours before saliva collection. They were asked to lean forward and spit their saliva for 15 minutes into a graduated test tube. Then, U-WSFR was calculated as millilitres per minute (ml/min) in laboratory conditions (FTO). In the second step, patients chew a piece of paraffin until it becomes soft and swallows their saliva before the collection. Then, patients spit their saliva into a tube at short intervals and keep chewing. Stimulated whole saliva samples of patients are collected during 5-minute chewing period. The volumes ≤0.1 ml/min for U-WSFR and ≤0.7 ml/min for stimulated whole salivary flow rate (S-WSFR) suggested salivary hypofunction (5,17,18) and the term low U-WSFR was used for volumes less than 0.1 ml/min of U-WSFR.

Oral Health and Oral Health-Related Quality of Life (OHRQoL)

Oral health was assessed by various indices, e.g., 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 or frequency of tooth brushing (19).

OHRQoL as a patient reported outcome measure (PROM) was evaluated by using the Turkish version of oral health impact profile (OHIP-14). Scores of OHIP-14 ranged from “0” to “56” points (20). Higher scores indicate poorer OHRQoL status.

Statistical analysis

Statistical analysis was calculated by using IBM SPSS 16.0 (IL, USA). Data were presented as mean ± standard deviation for continuous variables or percentages of 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 Kolmogorow-Smirnov test ($p<0.0001$). In addition, Mann Whitney U test and Spearmen's correlation test was 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 by using receiver operating characteristic (ROC) analysis and presented with 95% confidence intervals. AUC was interpreted as not discriminative (<0.5), poor (≥0.5-0.7), fair (≥0.7-0.8), good (≥0.8-0.9) or excellent (≥0.9-1.0).

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

Results

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

Among the individual components of the Hocevar score, i.e., homogeneity and hypoechoic areas, as well as 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, Figure 2). The ROC analyses of S-WSFR were found to be similar to those of U-WSFR (AUC for S-WSFR from

0.697 to 0.790 for scores of Hocevar and subgroups; from 0.714 to 0.784 for scores of Milic and subgroups; from 0.600 to 0.763 for SGUS parameters).

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).

Mean score of OHIP-14 as a PROM was 21.57±15.5 in the pSS patients, while it was higher in patients with low U-WSFR (33.6±16.3 vs 15.97±11.6, p=0.000) 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 non-severe ones (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, CAL and number of teeth and caries. On the other hand, the frequency of tooth brushing correlated with both Hocevar (r:0.3, p=0.012) and Milic scoring systems (r:0.3, p= 0.036).

Discussion

In the present study, both total and unilateral combination 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 parameters separately, homogeneity, hypoechoic areas and glandular border visibility were associated with low U-WSFR. Among these, homogeneity was found to be an independent variable to indicate 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 (22-24). Using a scoring system that basically 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 in spite of 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 (27-29). Therefore, it remains tempting to speculate whether such areas may be 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, the homogeneity was found to be an independent variable to indicate low U-WSFR. Therefore, the US homogeneity score may be used to determine poor functional status of salivary glands in clinical practice.

Previously, evaluation of combination of unilateral parotid and submandibular glands apparently adequate to predict ACR-EULAR classification for pSS patients (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 one side not only predicts ACR-EULAR classification but also predicts the functional status of the salivary glands. Furthermore, there is no difference to score left or right side of the glands.

Another key result of the present study is poor OHRQoL observed in patients with low U-WSFR. It 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's syndrome, the hyposalivation is commonly seen since salivary glands as exocrine glands are mainly affected by disease pathogenesis (31). Since OHIP-14 score is affected by salivary flow rate (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 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. On the other hand, no significant difference was determined between salivary gland sonographic changes and the oral health indices in our study, which may probably as a result of increased frequency of tooth brushing, be correlated with both SGUS scoring systems.

Our study had some obvious limitations. Firstly, it was a single-center and cross-sectional study with a relatively small number of pSS patients. Secondly, there was only a single investigator who performed and scored the SGUS. Thirdly, 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, salivary flow rates of major glands were not evaluated separately in the study protocol.

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

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Table-1: Demographics and Clinical Characteristics of pSS patients

	All patients n=66	**Low Unstimulated Whole Salivary Flow Rate (+) U-WSFR ≤0.1ml/m n=21**	**Low Unstimulated Whole Salivary Flow Rate (-) U-WSFR >0.1 ml/m n=45**
Clinical characteristics n (%)			
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 (16,4)	4 (19.04)	7 (15.5)
Peripheral Neuropathy	4 (6.0)	2 (9.5)	2 (4.4)
Leucocytoclastic 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 n (%)			
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 n (%)	60 (90.9)	18 (85.7)	42 (93.3)
Prednisolone n(%)	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 (years), mean ±SD	2.2±2.0	1.8±0.9	2.4±2.4
Methotrexate n(%)	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 (years), mean ±SD	2.5±2.4	2.1±1.3	2.6±2.8
Azathioprine n (%)	5(7.5)	2 (9.5)	3 (6.5)
Rituximab n (%)	1 (1.5)	0 (0)	1(2.2)

Table-2: SGUS Scores and ROC Curve Analysis in pSS patients According to Unstimulated Whole Salivary Flow Rate

	Low Unstimulated Whole Salivary Flow Rate (+) **U-WSFR ≤0.1 ml/m**	**Low Unstimulated Whole Salivary Flow Rate (-)** **U-WSFR >0.1 ml/m**	***p***	***AUC in ROC analysis***
	n=21	**n=45**		
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 parameters				
-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 visibilite	4.4±2.9	2.0±2.5	**0.001**	0.745

Table 3: The Independent Variable for Low Unstimulated Whole Salivary Flow Rate in Patients with pSS According to Binary Logistic Regression Analysis

	B[a]	Std Error	Wald[b]	Df[c]	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**			

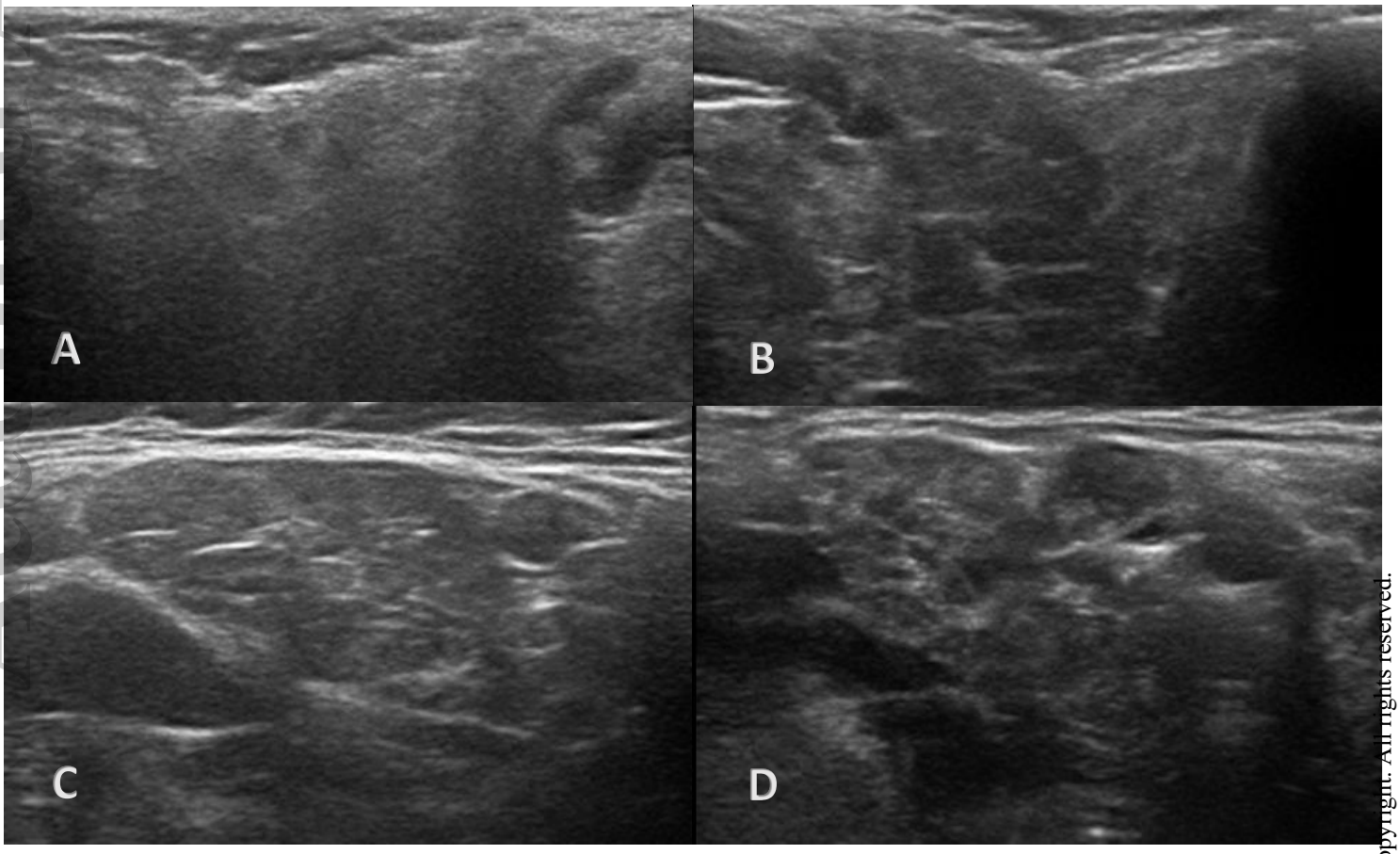
a: Regression coefficient

b: Wald statistics

c: Degree of freedom

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, multipl 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



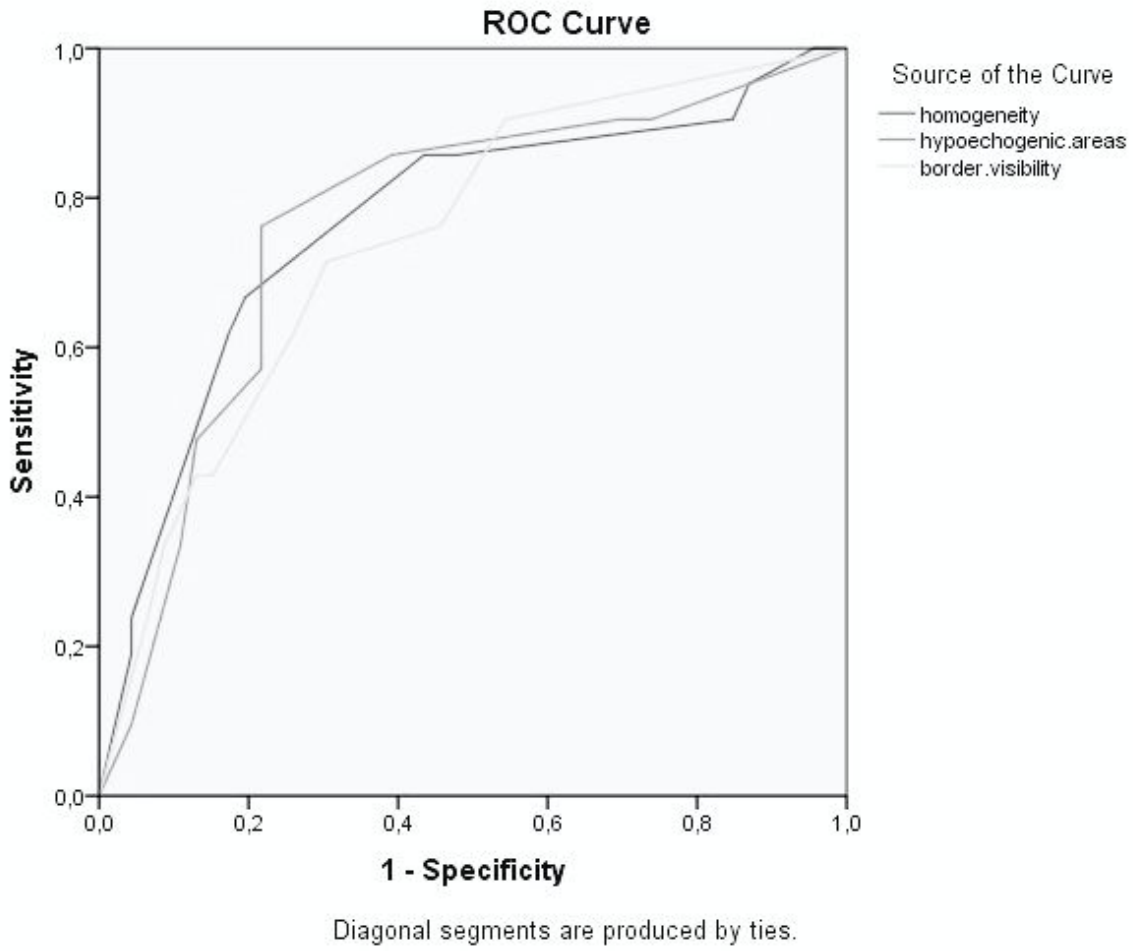


Figure 2: ROC Analysis of Homogeneity, Hyperechoic areas and Border visibility for Low U-WSFR in Patients with pSS