Shear-Wave Elastography Evaluation of Major Salivary Glands in Primary Sjögren's Syndrome

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Abstract

Objectives: Salivary glands ultrasonography has recently been shown to be useful in the diagnosis of Primary Sjögren's Syndrome (pSS). Shear-wave elastography (SWE) is a promising tool for the quantitative assessment of tissues stiffness, but studies evaluating its role in pSS diagnosis are limited. This study aimed at investigating the diagnostic performance of SWE in pSS.

Materials and Methods: Cross-sectional study including patients fulfilling the 2016 ACR/EULAR classification criteria for pSS and healthy subjects. The four major salivary glands were assessed using SGUS. B-mode scans were rated using the *Hočevar* score, and shear-wave velocity (SWV) values were obtained using SWE. Intraclass-correlation coefficient (ICC) estimates were used to assess reliability. Cut-off values for differentiating pSS patients from healthy subjects were calculated using Receiver-Operating Characteristics (ROC) curves.

Results: We included 50 pSS and 25 healthy subjects. Inter-rater reliability of SWE was moderate (ICC=0.64) and intra-rater reliability was moderate to good (ICC= 0.73 to 0.83). Total SWV (2.09 m/s (0.32); p<0.001), parotid SWV (2.25 m/s (0.40)) and submandibular SWV (1.92 m/s (0.38)) were significantly higher in pSS patients. Total and parotid SWV presented good diagnostic performance for pSS diagnosis (AUROC= 0.80 and 0.81, respectively). The *Hočevar* score demonstrated excellent diagnostic performance (AUROC= 0.98) and combining it with total SWV did not result in statistically significant improvement (*p*=0.301).

Conclusions: SWE may contribute to the diagnosis of pSS. Large prospective studies including *sicca* and secondary SS patients, as well as the standardisation of SWE protocols, are warranted to assess the role of SWE in pSS management.

Keywords: Salivary glands ultrasonography; shear-wave elastography; Primary Sjögren's Syndrome.

Introduction

Primary Sjogren's Syndrome (pSS) is a systemic autoimmune disease characterised by lymphocytic infiltration and damage of exocrine glands, including the lacrimal and salivary glands[1]. The diagnosis of pSS is based on a combination of clinical features, such as xerostomia and xerophthalmia, and laboratory, histological and imaging findings.

In parallel with the established usefulness of salivary gland scintigraphy and minor salivary gland biopsy[2], salivary glands ultrasonography (SGUS) has emerged as a non-invasive technique for studying pSS. SGUS detects characteristic salivary gland echostructure abnormalities, relevant to the early diagnosis of pSS[3]. B-mode SGUS has been shown to have better diagnostic

accuracy than sialography and sialoscintigraphy in this condition[4,5]. The addition of B-mode SGUS scores also improved the diagnostic performance of the 2002 American–European Consensus Group (AECG) and the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for pSS[6,7]. However, up to the present time, they have not yet been integrated into pSS classification criteria. SGUS is well accepted by patients, and ultrasound devices are widely available to rheumatologists in European countries[8,9].

Several scoring systems have been used to classify SGUS findings, leading to significant heterogeneity between study reports[10,11]. Recently, the OMERACT group developed a consensus B-mode score [12] attempting to homogenise procedures and results in future studies. Notwithstanding, B-mode SGUS sensitivity and specificity vary significantly between studies as they are operator and device-dependent[13], thus leaving room for improvement.

Elastography is a novel ultrasound modality assessing tissue stiffness, which can be integrated into ultrasound devices. In particular, shear-wave elastography (SWE) provides a quantitative estimation of the stiffness of a specific region of interest (ROI) of the examined tissue. SWE is less operator-dependent than previous elastography modalities, as it does not rely on external operator compression[14]. Recently, researchers have shown that SWE has good reliability (intraclass correlation coefficients (ICC) often >0.75) and convergent validity against modified Rodnan skin score (mRSS) for skin assessment in systemic sclerosis[15,16]. It is also a validated method to evaluate fibrosis in the Achilles tendons, liver, and other organs[17].

Progressive salivary gland fibrosis may lead to increased tissue stiffness[18], which suggests that SWE may be helpful for evaluating major salivary gland involvement in pSS. However, this hypothesis has been scarcely investigated[19–21].

This study was designed to clarify the usefulness of SWE in pSS by determining its reliability, diagnostic performance, and correlation with B-mode findings.

Materials and methods

Study design and patients

We conducted a cross-sectional study based on a cohort of pSS patients regularly followed-up at a tertiary Rheumatology clinic (Centro Hospitalar e Universitário de Coimbra, Portugal). Consecutive patients with pSS were included, all satisfying the 2016 ACR/EULAR classification criteria for pSS. Patients with concomitant autoimmune diseases, C hepatitis, HIV, history of sialolithiasis, parotid duct stenosis, major salivary gland lymphoma and patients treated with sicca symptoms-inducing drugs were excluded. A group of healthy subjects with

similar gender and age distribution was included as a control group, recruited among the hospital staff, patients' family members and university students. The latter subjects would be excluded in case of *sicca* symptoms, autoimmune disease of any nature, or treatments known to induce *sicca* syndrome. All participants provided written informed consent before any study procedure in accordance with the Declaration of Helsinki. Ethics approval was obtained by the local Ethics Committee (protocol number CHUC-102-16).

Patients' assessments

Demographic and clinical data including age, gender, disease duration, immunological profile, major salivary scintigraphy results and Schirmer's test, were retrieved from patients' charts and registered.

A standardised ultrasound (US) evaluation was performed for each participant, in a single visit. The four major salivary glands (parotid and submandibular glands, bilaterally) were assessed using B-mode and SWE modalities (Figure 1), both performed on the same day, with a maximal interval of one hour between the two evaluations. First, B-mode scans were acquired. Then, shear-wave mode was activated, and the SWE output simultaneously displayed a color-coded tissue stiffness map and shear-wave velocity values (in m/s, up to 10 m/s) in each image. A Siemens ACUSON S-2000TM (Siemens Healthcare) US device equipped with an 18 MHz (for B-mode) and a 9 MHz (for SWE) linear transducers were used for imaging and data acquisition. All participants were evaluated in a sitting position with hyperextension of the neck. All measurements were obtained between 9 am and 5 pm under stable instrumental and environmental conditions, with a room temperature between 20-22ºC.

B-mode SGUS evaluation

SGUS was first performed on the four glands in B mode. Longitudinal and transverse scans were acquired, according to the 2017 EULAR standardised procedures for ultrasound imaging in rheumatology[22]. Transverse and longitudinal scans of the parotid glands were obtained by one of three independent operators (operators 1, 2 or 3), randomly assigned. For the submandibular glands, a single longitudinal scan was acquired. All operators had more than five years of experience in ultrasound and were blinded to clinical information.

Ultrasonographic findings were classified according to the score described by *Hočevar et al.* [23] graded as follows: (i) Parenchymal echogenicity: grade 0- homogeneous gland; grade 1- mild inhomogeneity; grade 2- evident inhomogeneity; grade 3- grossly inhomogeneous gland; (ii) Presence of hypoechogenic areas: grade 0- absent; grade 1 - a few, scattered; grade 2 - several; grade 3- numerous; (iii) Hyperechogenic reflections in the parotid glands: grade 0-

absent; grade 1 - a few, scattered; grade 2 - several; grade 3- numerous; (iv) Hyperechogenic reflections in the submandibular glands: grade 0- absent; grade 1- present; (v) Clearness of salivary gland borders: grade 0- clear, regular defined borders; grade 1 - partly defined borders; grade 2- ill-defined borders; grade 3 - borders not visible. A score was obtained for each major salivary gland, bilaterally. Total *Hočevar* score was calculated by the sum of the scores obtained in each of the four glands (range 0-48).

Shear-wave elastography evaluation

For SWE imaging acquisition, longitudinal and transverse SWE elastograms were obtained in the parotid glands. For the submandibular glands, a single longitudinal scan was acquired. A ROI was obtained by identifying the glandular area using the underlying grey scale scan. Then, shear-wave velocity (SWV) values (in meters per second; m/s) were obtained in three peripheral and three central areas of each major salivary gland (six measures per gland): left parotid SWV, right parotid SWV, left submandibular SWV and right submandibular SWV. Parotid SWV was represented by the mean SWV value of the two parotid glands. Submandibular SWV was obtained by calculating the mean SWV value obtained in the two submandibular glands. SWE was performed by one of two independent operators (operators 4 and 5), both having more than five years of experience in elastography.

Reliability assessments

Inter-rater reliability was assessed in the first ten pSS patients regarding B-mode (operators 1, 2 and 3) and SWE (operators 4 and 5). As a moderate to good reliability for both US modalities was verified, all the remaining participants were independently examined by solely one of the three B-mode operators and one of the two SWE operators. For intra-rater reliability, each operator performed a second blinded B-mode/SWE examination one month after the initial assessment.

Primary and secondary outcomes

The primary outcome was the diagnostic performance of total SWV assessed by the area under the Receiver Operating Characteristics curve (AUROC). Total SWV was obtained by calculating the mean of the SWV values obtained in the four glands.

The secondary outcomes were: (i) The diagnostic performance of parotid SWV, assessed by AUROC; (ii) The diagnostic performance of submandibular SWV, assessed by the AUROC; (iii) The diagnostic performance of total *Hočevar* score, assessed by the AUROC; (iv) The diagnostic

performance of combined total *Hočevar* score and total SWV, as described below, assessed by the AUROC.

Statistical analysis

Descriptive statistics comprising demographic and clinical data of the included patients were obtained. Categorical data were presented as absolute counts and frequencies. For continuous variables, mean with standard deviation (SD) and median with interquartile range (IQR) were applied, as appropriate.

Inter and intra-rater reliability were assessed using intraclass-correlation coefficient (ICC) estimates and their 95% confidence intervals (CI). For inter-rater reliability analysis, two-way mixed-effects models, single measurements, absolute agreement were applied. The reader was defined as fixed, as we were interested in the readers of the present study and did not want to generalise the results.

Comparison of *Hočevar* scores and SWV values between pSS and healthy subjects was performed using Student's t-test and chi-square test. Correlations between SWV values variables, and between total SWV and disease duration, were assessed using Pearson's correlation coefficient. The sensitivity, specificity, and cut-off values for differentiating pSS patients from healthy subjects for total, parotid and submandibular SWV were calculated using ROC curves. A ROC analysis was carried out to compare the diagnostic performances of total SWV, parotid SWV, and submandibular SWV.

Multivariate logistic regression using total *Hočevar* score and total SWV as covariates was performed to determine the probability of diagnosing pSS using the combination of the two methods. By definition of the logistic regression, a diagnosis of pSS was reported when this probability was above 50%. Then, the diagnostic performance of the combination was determined using ROC curves. The diagnostic performance of the assessed techniques using AUROC was interpreted as follows: AUROC: <0.50 – none; ≥0.50 to 0.70 – weak; ≥ 0.70 to 0.80 – acceptable; ≥ 0.8-0.9: good and ≥ 0.90 – excellent discriminatory power [24].

A value of $p<0.05$ was considered significant. The analyses were performed using IBM SPSS Statistics for Windows, version 26.0. Armonk, NY: IBM Corp.

Results

We included 75 participants, 50 pSS patients (mean (SD) age: 56.2 (13.7); 98.0% females) and 25 healthy subjects (mean (SD) age: 53.5 (9.2); 96.0% females). The patient's clinical and laboratory descriptive data are presented in Table I.

Reliability analysis

For B-mode modality, inter-rater reliability was good between operators 1 and 2 (ICC=0.86; [95% CI 0.46 to 0.97]) and operators 1 and 3 (ICC= 0.78; [95% CI 0.06 to 0.97] and excellent between operators 2 and 3 (ICC=0.95; [95% CI 0.62 to 1.00]). Intra-rater reliability was excellent for operator 1 (ICC=0.95; [95% CI 0.46 to 1.00]), operator 2 (ICC= 0.97; [95% CI 0.65 to 1.00]) and 3 (ICC= 0.98; [95% CI 0.40 to 0.99]).

For SWE, inter-rater reliability was moderate (ICC=0.64; [95% CI – 0.05 to 0.92]) and intra-rater reliability was good for operator 4 (ICC=0.83; [95% CI -0.58 to 1.00] and moderate for operator 5 (ICC 0.73; [95% CI -0.72 to 0.99].

B-mode SGUS scores

The results of the *Hočevar* score obtained in the four major salivary glands of all participants are presented in Table II. Total *Hočevar* score was significantly higher in patients than in healthy subjects, and the same was observed in each of the four glands individually.

Shear-wave elastography values

The SWV values obtained for all participants in the four major salivary glands are described in Table II. The mean SWV was significantly higher in pSS patients than in healthy subjects in each of the four glands. The same was observed with the average total measure.

Left and right parotid SWV (r=0.56; p<0.001) and left and right submandibular SWV (r=0.54; p<0.001) correlated moderately. Parotid and submandibular SWV correlated poorly (r=0.43; p<0.001).

No statistically significant correlation was found between total SWV and disease duration (p>0.05).

Correlation between SWE and B-mode

There was a weak positive correlation between total SWV and total *Hočevar* score and also between SWV and *Hočevar* score in the left parotid (r=0.42; p<0.001), right parotid (r=0.36; p<0.001) and right submandibular gland (r=0.30; p=0.011). This correlation was not statistically significant in the left submandibular gland (p=0.863).

Diagnostic performance of SWE and B-mode

Total SWV (AUROC=0.80; 95% CI [0.69-0.90]) and parotid SWV (AUROC=0.81; 95% CI [0.71-0.91]) showed good discriminatory power for pSS diagnosis; no statistically significant differences were found between the two measures (p=0.696). Both were significantly greater

than AUROC for submandibular SWV (AUROC=0.68; 95% CI [0.55-0.82]), $p<0.05$ (Figure 2). The cut-offs of 1.95 m/s, 1.96 m/s and 1.60 m/s for total, parotid and submandibular SWV values differentiated pSS patients from healthy subjects with sensitivities of 65.3%, 77.6% and 79.2% and specificities of 80.0%, 68.0% and 64.0%, respectively. Total *Hočevar* score presented excellent diagnostic performance for differentiating patients from healthy subjects (AUROC=0.97; 95% CI [0.93-1.00]).

The combination of total SWV and total Hočevar score demonstrated excellent diagnostic performance for pSS diagnosis (AUROC= 0.98; 95 % CI [0.95-1.00]). It was slightly higher than the diagnostic performance of single total Hočevar, however, without reaching statistical significance (p=0.301).

Discussion

This study demonstrated a good performance of SWE for the diagnosis of pSS, using total SWV (AUROC=0.80) or parotid SWV (AUROC=0.81). The best diagnostic performances were obtained for the cut-offs of 1.95 m/s for total SWV and 1.96 m/s for parotid SWV. Total, parotid, and submandibular SWV values showed weakly positive correlations with their correspondent Hočevar scores, indicating that these techniques might address different tissue properties. We also found no statistically significant association between total SWV and disease duration, results that are comparable to previous findings[19,25–27] and suggest that the rate of disease progression in pSS may differ between patients.

We found that parotid SWV is as accurate as total SWV for pSS diagnosis, and both performed better than submandibular SWV. The superior usefulness of parotid SWV has been demonstrated by other authors using different elastography techniques[28]. Despite the hypothesis, raised by some studies, of a greater extent of involvement of the parotid gland comparing to the submandibular glands in pSS[29,30], we should also notice that a correct visualisation of the submandibular glands using SGUS is technically more difficult due to the greater depth of these glands and the blurring induced by the surrounding structures, which may lead to less accurate evaluations[31]. Although in different degrees, pSS would be expected to involve the four major salivary glands[32]. Therefore, SWE should be performed on the four glands - as in B-mode SGUS procedures - due to the importance of excluding other potential diagnoses.

SWE did not outperform or add to the excellent diagnostic performance of the Hočevar score. Intra- and inter-rater reliability of SWE (0.73-0.83 and 0.64) were also lower than

observed with B-Mode (0.95-0.98 and 0.78-0.95, respectively), suggesting an opportunity for technical improvement.

Few previous cross-sectional studies have evaluated the use of SWE for pSS diagnosis[19–21]. All indicated that SWE has better diagnostic performances than the previously used compression-dependent strain imaging techniques[32]. Strain elastography was applied in a few studies published between 2014 and 2019 and showed inconsistent results[28,33,34]. More recently, using a single operator, *Arslan et al.*[19] reported a higher sensitivity and specificity of SWE for pSS diagnosis than the observed in our study, for both the parotid (cut-off 2.48 m/s, Se. 82.1%, Sp. 91.7%) and the submandibular glands (cut-off 2.59 m/s, Se. 79.2%, Sp. 90%). These cut-off values were much higher than we observed. However, interpreting these different results must take into account that a diverse ultrasound device was used (Toshiba Aplio 500) and a different method to quantify stiffness was applied (automatic whole ROI SWV value).

Likewise, *Bădărînză et al.*[20] *and Moisoiu et al.*[21] reported tissue stiffness measured in kilopascals and used a different ultrasound machine and SWE software, thus precluding comparisons with our results. In all three studies, SWV values were significantly higher in pSS patients than in healthy subjects, favouring the hypothesis that parenchymal changes result in increased tissue stiffness[35,36] and underlining the potential value of this technique. These observations emphasise the need to standardise the procedures for image acquisition and analysis as a mean to assess the full potential value of SWE in pSS.

Our study has several strengths. Using SWE reduces operator bias because it does not rely on tissue compression and allows for multiple SWV readings within a ROI of the gland, using the overlying B-mode visualization[14]. This aspect may be of utmost importance, as major salivary glands can be difficult to locate, especially when they present structural changes as in pSS patients. Additionally, we have provided, for the first time, data on inter and intra-rater reliability of SWE applied to salivary gland assessment in pSS, showing moderate to good reliability coefficient values.

The main limitations of our study comprise the relatively small sample size and the inclusion of only healthy non-*sicca* subjects as controls. Also, as this study is based on a clinical outpatient cohort, only “overt stage” disease pSS patients were included, therefore precluding the analysis of the elastographic findings in different stages of the disease, including preclinical and asymptomatic stages[37]. Additionally, B-mode SGUS findings could not be reported using the new OMERACT consensus score[12], unavailable at the time this study was initiated. We used the score described by *Hočevar et al.* as it is a complex score that includes most US changes typical of pSS. However, it has a limited ability to adequately rate severely fibrotic glands with no longer distinguishable hyperechoic bands[23]. This aspect might be one of the reasons why SWV showed

a weak correlation with B-mode findings. The location of specific ROIs within the gland included the systematic obtention of SWV values from peripheral and central areas for all patients, randomly including hyperechoic and hypoechoic areas, and resulting in a single medium SWV measure for each patient. However, this method of SWV evaluation is operator dependent and may have contributed to lower reliability indices and poorer correlation with B-mode. The excellent performance of the Hočevar score in distinguishing pSS patients and controls, and its high reliability values in our study, might question whether there is a need to improve the diagnostic performance of SGUS using an additional technique. We were unable to improve total Hočevar score performance by combining it with total SWV.

Despite this, we believe that we should continue to strive for improvement in SWE assessment for three main reasons: (i) The performance of SGUS as reported by Hočevar et al.[11] and other authors using different scores[6,38] is usually lower, indicating that better diagnostic accuracies could be obtained by adding a complementary imaging method; (ii) There is a potential role of elastography in the detection of pSS serious complications as parotid lymphoma; this has been demonstrated by the excellent sensitivity and specificity obtained for the SWE cut-off of 11.2 kPa for the identification of parotid MALT lymphoma in the study conducted by Bădărînză et al.[20]; (iii) B-mode evaluation and elastography of the major salivary glands might represent complementary techniques as they assess different properties and characteristics of the glandular tissue; in addition, little is known about their relative importance for managing pSS.

Conclusion

SWE may represent a valuable tool in pSS diagnosis as it demonstrated a good discriminative power in this cross-sectional study including healthy subjects as controls. Future studies should aim at procedures standardisation and the inclusion of larger samples with patients with *sicca* syndrome and secondary SS, ideally in a prospective design.

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Tables and Figures

Table I. General clinical and laboratory characteristics of Primary Sjögren's Syndrome patients.

Patient's characteristics	
Females, %	98.0
Age[a]	56.2 (13.7)
Disease duration since diagnosis, years[a]	12.20 (7.27)
	Positives/Total
Xerostomia	48/50
Xerophthalmia	50/50
Extraglandular involvement	24/50
Anti-SSA-60 positivity	47/50
Anti-SSB positivity	26/50
Minor salivary gland biopsy positivity[b]	12/19
Abnormal salivary gland scintigraphy[c]	19/21
Schirmer's test positivity	42/50
Current medications	
Prednisolone≥1 mg/day	5/50
Hydroxychloroquine	19/50
Methotrexate	3/50
Azathioprine	3/50
Nonsteroidal anti-inflammatory drugs	15/50
Pilocarpine	14/50

[a]mean (standard deviation); [b]all samples presented some degree of lymphocytic sialoadenitis, 12 of them satisfying the pathological criterion (focus score ≥ 1 per 4 mm^2 of tissue);[c] abnormal parotid and/or submandibular glands function and/or response to the stimulus.

Table II. B-mode and shear-wave elastography findings in the four major salivary glands at protocolised evaluation.

	pSS (N=50)	Healthy subjects (N=25)	*p* value
***Hočevar et al.* (range 0-48)**			
Total, mean (SD)	22.24(8.76)	3.72 (3.46)	<0.001
Left parotid gland, mean (SD)	6.14 (2.45)	0.92 (1.26)	<0.001
Right parotid gland, mean (SD)	5.68 (2.43)	0.68 (0.85)	<0.001
Left submandibular gland, mean (SD)	5.68 (2.27)	1.28 (1.31)	<0.001
Right submandibular gland, mean (SD)	5.76 (2.29)	0.84 (1.07)	<0.001
Shear-wave velocity (m/s)			
Total, mean (SD)	2.09 (0.32)	1.74 (0.24)	<0.001
Left parotid gland, mean (SD)	2.24 (0.40)	1.83 (0.30)	<0.001
Right parotid gland, mean (SD)	2.25 (0.53)	1.83 (0.31)	<0.001
Parotid glands, mean (SD)	2.25 (0.40)	1.83 (0.26)	<0.001
Left submandibular gland, mean (SD)	1.94 (0.45)	1.70 (0.32)	0.020
Right submandibular gland, mean (SD)	1.90 (0.45)	1.61 (0.32)	0.005
Submandibular glands, mean (SD)	1.92 (0.38)	1.66 (0.30)	0.019

pSS- Primary Sjögren's Syndrome.

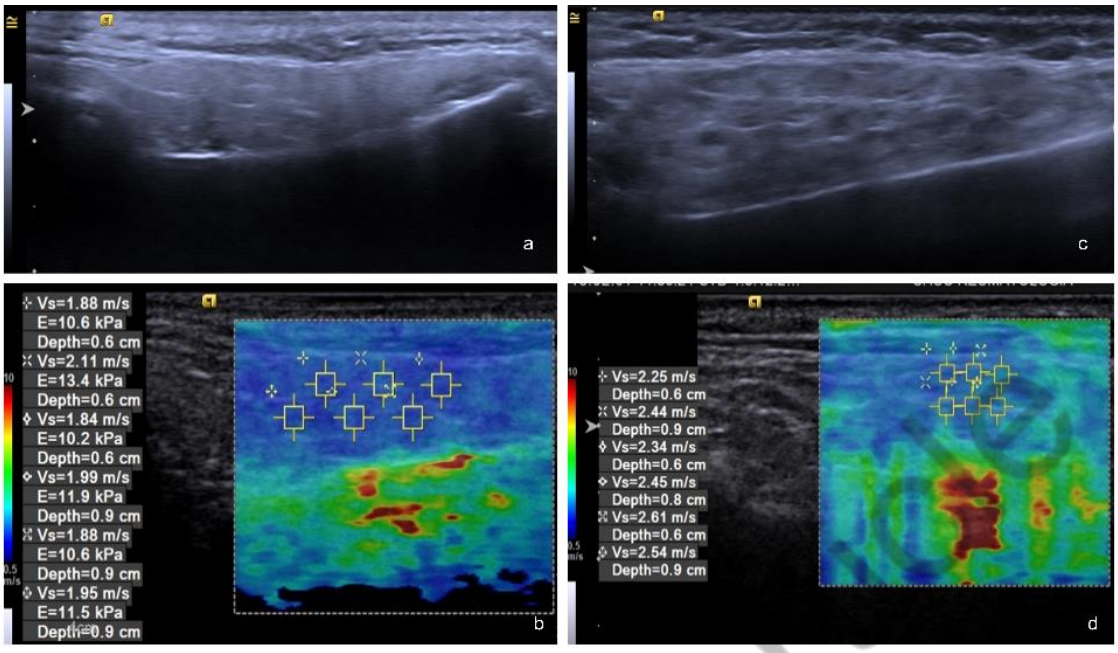

Fig. 1. B-mode longitudinal scan and correspondent colour elastogram of the left parotid gland of a healthy subject (a and b) and a Primary Sjögren's Syndrome (pSS) patient (c and d). Greater parenchymal inhomogeneity and hypoechoic areas are visible on the B-mode scan of the pSS patient (c), with corresponding higher shear-wave velocity values (presented on the left side in meters/second; d). On colour elastogram, red, green/yellow, and blue indicate high, intermediate, and low stiffness, respectively.

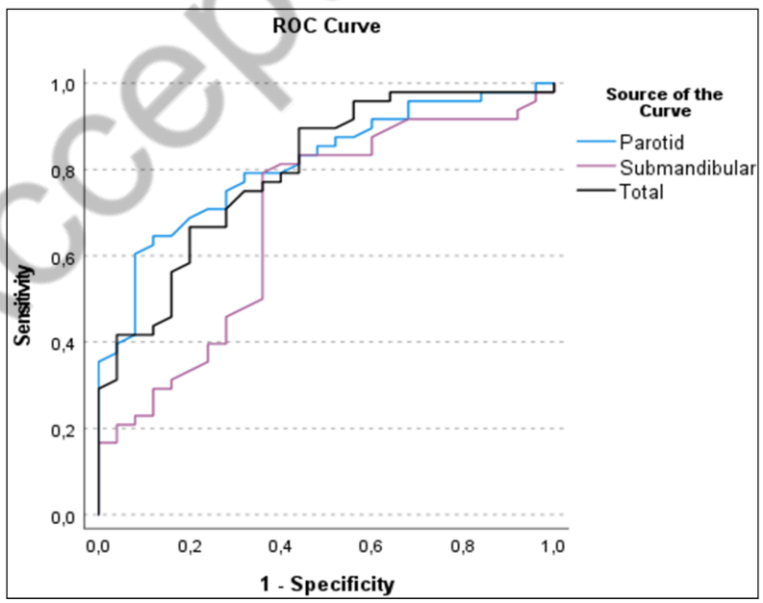

Fig. 2. Receiver Operating Characteristics analysis for parotid, submandibular and total shear-wave velocity.

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