Value of conventional ultrasound and shear wave elastography in assessing disease activity and prognosis in female patients with Sjögren's syndrome

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Abstract

Objective

This study aimed to assess the diagnostic value of labial salivary gland changes in female patients with Sjögren's syndrome (SS) having different European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and serological markers using conventional ultrasound and shear wave elastography (SWE).

Methods

A total of 82 female inpatients diagnosed with SS were retrospectively examined at the First Affiliated Hospital of Soochow University from July 2020 to December 2021. The patients were divided into two groups based on the ESSDAI score: remission group (ESSDAI <5) and active group (ESSDAI ≥5). The prognosis of patients was assessed using serological markers. The ultrasound examination of bilateral labial glands was performed in all patients to analyse the quantity and area of the largest single labial gland per unit detection range (Smax). The SWE of labial glands was performed in different groups.

Results

The Smax and quantity of labial glands on both sides were correlated with patient age in 82 female patients with SS. Emin, Emean and Emax of the remission group based on ESSDAI were significantly lower than the active group ($p<0.001$), and the areas under the receiver operating characteristic (ROC) curve for these three in diagnosing were 0.720, 0.728 and 0.734, respectively. The differences in Emean, Emin and Emax values of labial glands between the two groups of immunoglobulin G (IgG) <16g/L and IgG ≥16g/L were statistically significant ($p<0.05$), and the area under the ROC curve (AUC) for the three values were 0.825, 0.830, and 0.815, respectively. There were statistically significant differences ($p<0.05$) in Emin, Emean, and Emax of labial glands between the hypocomplementaemic and non-hypocomplementaemic groups, and the AUC for the three values were 0.840, 0.843, and 0.819, respectively.

Conclusion

Conventional ultrasound and SWE of the labial gland can reflect the disease activity and prognosis of patients with SS, and more conveniently assess the progression in the patients and provide imaging evidence.

Key words

ESSDAI, hypocomplementaemia, IgG, shear wave elastography, Sjögren's syndrome

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Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease that occurs in middle-aged women. The pathological features are mainly lymphocyte infiltration of the exocrine glands and glandular secretion dysfunction (1), mostly manifested as the symptoms of ocular and oral dryness. European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) (1) is widely used clinically, and serological indicators (C3, C4, and IgG) are mainly applied to evaluate the prognosis of SS. However, ESSDAI is complex, and some parts of the tests are invasive, making an accurate assessment of the disease activity difficult. Ultrasound, as a noninvasive approach, plays an important role in assessing the disease activity and prognosis of patients with SS. Shear wave elastography (SWE) assesses tissue stiffness by measuring tissue deformation by compression, which is usually expressed as Young's modulus. Sound waves generated by the vibration of an acoustic source are reflected or absorbed in the propagation to produce acoustic radiation forces, which generate shear waves as the tissue particles vibrate laterally. The speed of shear wave propagation in a medium is related to the longitudinal modulus of biological tissue stiffness (3).

This study was performed to explore the application of conventional ultrasound and SWE in assessing the differences in the quantity, Smax, and stiffness of labial glands in female patients with SS having different ESSDAI scores and serological indices, thus simplifying the process of disease activity assessment and providing imaging information.

Methods

Clinical information

A total of 82 female patients with SS hospitalised at the The First Affiliated Hospital of Soochow University from July 2020 to December 2021 were enrolled, aged 15-74 years, with the average of 47.74±13.94 years. The study was conducted in accordance with the Declaration of Helsinki and the approval of the Ethics Committee of The First Affiliated Hospital of Soochow University. All patients met the SS diagnostic criteria established by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) in 2016 (4). The exclusion criteria were as follows: (a) history of head and neck radiation treatment, (b) history of hepatitis C infection, (c) acquired immune deficiency syndrome, (d) lymphoma, (e) sarcoidosis, (f) graft-versus-host disease, (g) IgG4-related disease, and (h) recent use of cholinergic drugs.

Instruments and methods

- Disease activity and prognosis

The inpatient data of 82 patients were retrospectively analysed. The ESSDAI scores were obtained for each patient. The patients were divided into two groups according to the 2002 European and American Consensus Panel (5): remission group (ESSDAI <5) and active group (ESSDAI ≥5).

The serological markers (C3, C4, and IgG) were collected. Patients with C3 <0.7 g/L and/or C4 <0.1 g/L were classified as hypocomplementaemia group and those who did not conform were classified as non-hypocomplementaemia group. According to IgG levels, the patients were classified into two groups: IgG <16 g/L and IgG ≥16 g/L (2).

- Ultrasonic examination

The examinations were performed randomly by two radiologists with two years of SWE imaging experience. Before the examination started, the examiners conducted the training and calibration to standardise the image acquisition. The ICCs were all greater than 0.80 for intra-observer argeement. The Supersonic Imagine Aixplorer diasonograph was applied, and a linear probe SLH20-6 with the frequency of 6–20MHz and an examination depth of 0.2 cm was selected. All patients were placed in a supine position, and the lower lip was divided into two parts, left and right, with the midline of the teeth as the body surface marker. The patients gently pulled the lower lip to expose bilateral sides of the lip during the examination. A disposable sterile probe cover was employed to prevent

contact between the mucosa and the probe to avoid cross-infection. The mucosa was examined, and the patients were subjected to a routine ultrasonic examination to determine the quantity of the labial glands in a probe (detection range: 27.3×8.7 mm^2, 234.98 mm^2). The detection mode was switched to the SWE mode, the probe was kept lightly on the mucosal surface, and the patient was asked to keep the lower lip in a relaxed position. After the SWE sampling frame was completely filled, the Q-Box was placed in the centre of the labial gland and the region of interest with a diameter of 1 mm (Fig. 1). All measurements were performed five times. The averages of the SWE values, including Emin, Emean, Emax, and Eratio, were obtained for statistical analysis.

- Minor salivary gland biopsy

After having scanned the labial glands, biopsy was performed under local anesthesia. After initial incision with surgical scalpel, blunt dissection was performed to expose and remove the labial glands. The sampled salivary glands were fixed in 10% buffer formalin and were submitted to the laboratory for examination. Lymphocytic aggregates comprised of ≥50 lymphocytes per 4mm^2 were designated as a lymphocytic focus. Histologic criteria requires a focus score (FS)≥1 (6) (Fig. 2).

Statistical analysis

The area of the largest individual labial gland within a probe (Smax) was outlined and measured using Image J. Statistical analyses were performed with SPSS 26.0 statistical software. According to distributions, the data were presented as the mean with standard deviation or median with interquartile range (IQR). The intra-rater argeement was investigated using the intraclass correlation coefficient (ICC). Spearman's test was used for correlation analysis. The Wilcoxon signed-rank sum test was used to compare the differences between the quantity, Smax, and SWE values of bilateral labial glands. The Mann-Whitney U-test was used to compare the differences between two independent groups. Receiver operating characteristic (ROC) curve analysis with area under the ROC curve (AUC) was used to determine the cut-off values with Medcalc 19.6. All statistical tests were conducted at the 5% significance level.

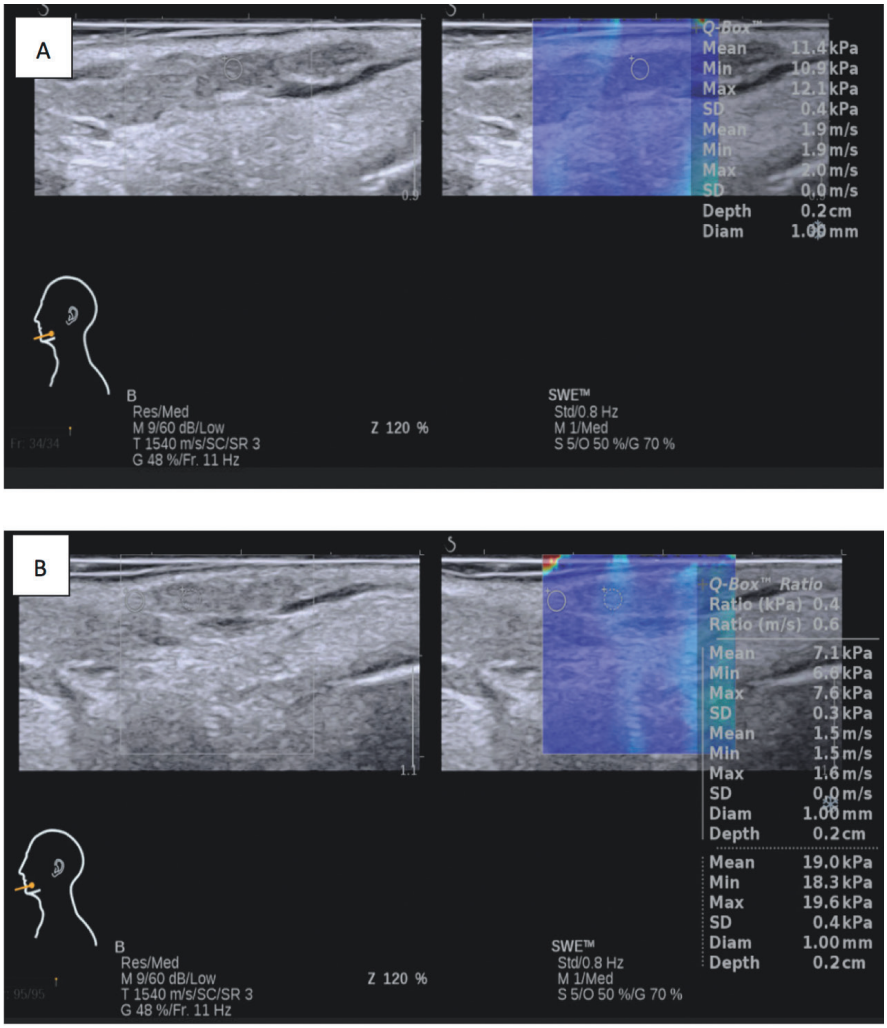

Fig. 1. Panel A: Emin, Emean, and Emax of the labial gland were 10.9kPa, 11.4kPa, and 12.1kPa, respectively. Panel B: Emin, Emean, and Emax of the labial gland were 6.6kPa, 7.1kPa, and 7.6kPa, respectively.

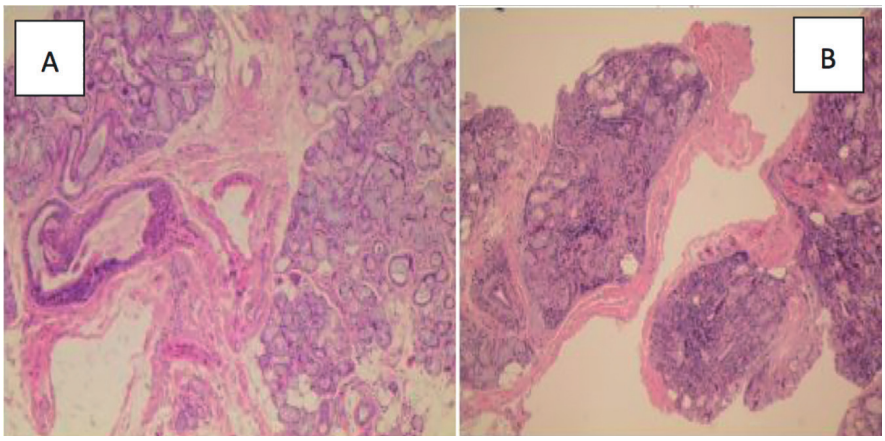

Fig. 2. Histopathological features of labial gland biopsy.
Panel A: No obvious lymphocytic foci were observed. Panel B: Focal lymphocytic sialadenitis with the focus score 6.

Table I. General characteristics of the patients.

Characteristics	SS patients (n=82)	
Age (years), mean±SD	47.74±13.94	
Disease duration (years), med (min-max)	1.00 (0.29,3.00)	
Number of women (%)	82/82 (100)	
Quantity of labial glands (/probe), med (min-max)		*p=0.988*
Right	2 (1, 3.25)	
Left	2 (1, 3)	
Smax (mm^2), med (min-max)		*p=0.690*
Right	3.93 (2.60, 5.71)	
Left	4.06 (2.58,5.61)	
Emin (kPa), med (min-max)		*p=0.513*
Right	10.35 (8.28,13.35)	
Left	10.30 (8.88,13.93)	
Emean (kPa), med (min-max)		*p=0.670*
Right	11.70 (9.00,14.60)	
Left	11.35 (9.65,14.85)	
Emax (kPa), med (min-max)		*p=1.000*
Right	13.30 (9.55,17.00)	
Left	12.45 (10.40,16.73)	
Eratio, med (min-max)		*p=0.621*
Right	1.0 (0.8,1.3)	
Left	1.0 (0.8,1.2)	
ESSDAI		
Remission group (n, %)	34 (41.5%)	
Active group (n, %)	48 (58.5%)	
IgG		
<16 (n, %)	45 (54.9%)	
≥16 (n, %)	37 (45.1%)	
Hypocomplementaemia		
Present	45 (54.9%)	
Absent	37 (45.1%)	

Emin: minimum elastic modulus; Emean: mean elastic modulus; Emax: maximum elastic modulus; Eratio: ratio of elastic modulus; ESSDAI: European League Against Rheumatism SS Disease Activity Index; S(max): the area of the largest single labial gland per unit detection range.

Table II. Correlation analysis between disease duration and age on ultrasonic characteristics of the labial gland.

Ultrasonic characteristics	Disease duration		Age	
	r	*p*	*r*	*p*
Emin	-0.049	0.662	-0.217	0.052
Emean	-0.049	0.844	-0.177	0.111
Emax	0.006	0.959	-0.171	0.124
Eratio	-0.066	0.579	0.032	0.786
Quantity	0.040	0.721	-0.502	<0.001
Smax	-0.074	0.508	-0.409	<0.001

Emin: minimum elastic modulus; Emean: mean elastic modulus; Emax: maximum elastic modulus; Eratio: ratio of elastic modulus; ESSDAI: European League Against Rheumatism SS Disease Activity Index; S(max): the area of the largest single labial gland per unit detection range.

Results

Comparison of patients' clinical data

We included 82 female patients with SS, mean age 47.74±13.94 years and the median disease duration 1.00 year (0.29, 3.00). 22 patients refused to conduct the labial gland biopsy. Table I shows the general characteristics of the patients with SS. No evidence existed for a statistically significant difference in the quantity, Smax, and SWE (Emin, Emean, Emax, and Eratio) of the bilateral labial glands (all $p>0.05$, Table I). Also, we did not find any correlation between age and SWE (Emin, Emean, Emax, and Eratio, all $p>0.05$, Table II) as well as with disease duration (all $p>0.05$). Compared with the elderly patient cohorts, the patients in the younger cohort had more and bigger labial glands ($p<0.05$, Table II).

Comparison of ultrasonic characteristics of the labial glands between groups with different ESSDAI scores

In the grouping of 82 patients with ESSDAI scores, 34 cases (41.5%) were in the remission group and 48 cases (58.5%) were in the active group. The Emin, Emean, and Emax values in the active group were higher than those in the remission group, and the differences were all statistically significant ($p<0.05$, Table III). The difference in Eratio between the two groups was not statistically significant ($p>0.05$, Table III). The differences in the quantity and Smax of labial glands were not statistically significant between the two groups ($p>0.05$, Table III).

The ROC curves were plotted with sensitivity as the vertical coordinate and 1-specificity as the horizontal coordinate; the AUC of Emin, Emean, and Emax were 0.720, 0.728, and 0.734, respectively. And the optimal cut-off values were 12.3kPa (sensitivity of 47.9%, specificity of 97.06%), 12.1kPa (sensitivity of 60.42%, specificity of 82.35%), and 13.1kPa (sensitivity of 66.67%, specificity of 79.41%), respectively (Fig. 3).

Comparison of ultrasonic characteristics of the labial glands with different serological indices between

- different IgG levels

According to the IgG level, 82 patients were divided into two groups of IgG <16 g/L and IgG ≥16 g/L. The Emin, Emean, and Emax in the former group were significantly lower than those in the latter group ($p<0.05$, Table IV). The difference in Eratio between the two groups was not statistically significant ($p>0.05$, Table IV). The differences in the quantity of labial glands and Smax

Table III. Comparison of ultrasonic characteristics of the labial gland in different ESSDAI score groups.

Ultrasonic characteristics	Remission group (n=34)	Active group (n=48)	Statistical quantities	*p-value*
Emin (kPa), mean ± SD	9.36±1.73	12.39±4.29	*t*=-3.384	0.001
Emean (kPa), med (min-max)	10.25 (9.23, 11.60)	13.25 (10.03,16.38)	*Z*=-3.502	<0.001
Emax (kPa), med (min-max)	11.05 (9.40,13.03)	14.45 (11.03,18.03)	*Z*=-3.596	<0.001
Eratio, med (min-max)	0.9 (0.8,1.2)	1.1 (0.9,1.4)	*Z*=-1.163	0.245
Quantity (/probe), med (min-max)	4 (2, 5)	3 (2, 4)	*Z*= -0.998	0.318
Smax (mm^2), med (min-max)	4.33 (2.46,5.90)	3.95 (2.89,5.54)	*Z*=-1.608	0.108

Emin: minimum elastic modulus; Emean: mean elastic modulus; Emax: maximum elastic modulus; Eratio: ratio of elastic modulus; ESSDAI: European League Against Rheumatism SS Disease Activity Index; S(max): the area of the largest single labial gland per unit detection range.

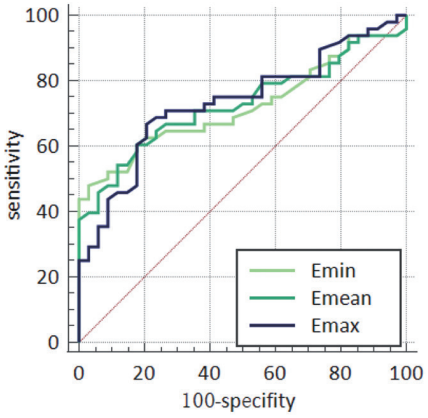

Fig. 3. ROC curves of SWE diagnostic for different ESSDAI scores.

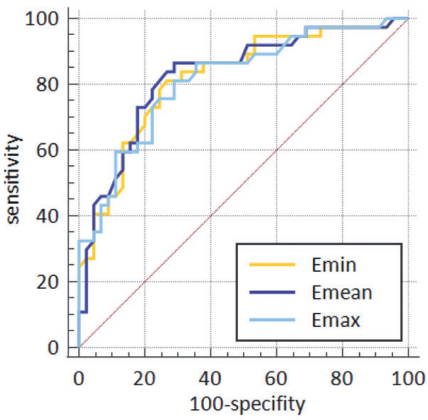

Fig. 4. ROC curves of SWE diagnosis at different IgG levels.

between the two groups were not statistically significant ($p>0.05$, Table IV). The ROC curves were plotted with sensitivity as the vertical coordinate and 1-specificity as the horizontal coordinate, and the AUC of Emin, Emean, and Emax were 0.825, 0.830, and 0.815, respectively, and the optimal cut-off values were 10.0 kPa (sensitivity of 81.08%, specificity of 73.33%), 10.7kPa (sensitivity of 86.49%, specificity of 71.1%), and 12.3kPa (sensitivity of 81.08 %, specificity of 71.11%) (Fig. 4).

- hypocomplementaemic and non-hypocomplementaemic groups

Among 82 patients with SS, 45.1% had hypocomplementaemia. The Emin, Emean, and Emax were significantly higher than those of 54.9% of patients with SS having the normal complement. The differences between the two groups were statistically significant ($p<0.05$, Table V). Eratio had no statistically significant difference between the two groups ($p>0.05$, Table V). Also, no statistically significant difference was observed in the quantity of labial glands and Smax between the two groups ($p>0.05$, Table V).

The ROC curves were plotted with sensitivity as the vertical coordinate and 1-specificity as the horizontal coordinate, and the AUC of Emin, Emean, and Emax were 0.840, 0.843, and 0.819, respectively. And the optimal cut-off values were 10.0kPa (sensitivity of 83.78%, specificity of 75.56%), 11.1kPa (sensitivity of 86.49%, specificity of 80.00%), and 12.3kPa (sensitivity of 86.49%, specificity of 75.56%), respectively (Fig. 5).

Table IV. Comparison of ultrasonic characteristics of the labial glands between different IgG levels.

Ultrasonic characteristics	<16g/L (n=45)	≥16g/L (n=37)	Statistical quantities	*p*-value
Emin (kPa), med (min-max)	9.20 (7.50, 10.35)	12.30 (10.40,16.00)	*Z*=-4.97	<0.001
Emean (kPa), med (min-max)	10.00 (8.50,11.30)	14.00 (11.75, 17.70)	*Z*= -5.08	<0.001
Emax (kPa), med (min-max)	11.00 (9.40,13.25)	15.60 (13.20,19.70)	*Z*=-4.89	<0.001
Eratio, med (min-max)	1.45 (0.95,1.88)	1.0 (0.9,1.35)	*Z*= -0.842	0.40
Quantity (/probe), mean ± SD	3.51 ± 0.97	3.39 ± 1.06	*t*=0.544	0.588
Smax (mm^2), med (min-max)	4.27 (2.66,6.09)	3.89 (2.55,5.25)	*Z*= -0.839	0.401

Emin: minimum elastic modulus; Emean: mean elastic modulus; Emax: maximum elastic modulus; Eratio: ratio of elastic modulus; ESSDAI: European League Against Rheumatism SS Disease Activity Index; S (max): the area of the largest single labial gland per unit detection range.

Discussion

Patients with SS suffer from progressive loss of glandular function due to lymphocyte infiltration of multiple exocrine glands. Some patients also have extra-glandular manifestations of other systems, such as Raynaud's phenomenon, arthritis, vasculitis, leukopenia, interstitial pneumonia and peripheral neuropathy, which may lead to different degrees of damage to related organs. The ESSDAI systematically evaluates the condition of patients with SS mainly from 12 domains, which ranges across four levels: no activity, low activity, moderate activity, and high activity. The total scores are calculated according to the corresponding weights. For patients with a single-system ESSDAI score ≥2 (moderate activity) or an overall ESSDAI score ≥5, systemic therapies, for instance, the use of glucocorticoids, immunosuppressive agents, intravenous immunoglobulins, and so on, need to be considered (7, 8). Therefore, an accurate assessment of disease activity can influence the selection of the treatment modality. Meanwhile, patients with higher ESSDAI scores are at a concomitantly higher risk of death (9). Millic *et al*. (10, 11) reported that patients with higher ESSDAI scores had higher ultrasound scores than those with lower scores, and the difference was statistically significant ($p<0.05$).

Table V. Comparison of ultrasonic characteristics of the labial gland between the hypocomplementaemic group and the non-hypocomplementaemic group.

Ultrasonic characteristics	Present (n=45)	Absent (n=37)	Statistical quantities	*p*-value
Emin (kPa), med (min-max)	9.20 (7.50, 10.10)	12.60 (10.55,15.50)	*Z*= -5.28	<0.001
Emean (kPa), med (min-max)	10.00 (8.75,11.00)	14.00 (12.30, 17.05)	*Z*= -5.32	<0.001
Emax (kPa), med (min-max)	10.90 (9.40,12.70)	15.60 (13.45,19.40)	*Z*=-4.94	<0.001
Eratio, med (min-max)	1.1 (0.90,1.85)	1.0 (0.90,1.25)	*Z*= -0.61	0.542
Quantity (/probe), mean ± SD	3.63 ± 1.05	3.25 ± 0.93	*t*=1.74	0.086
Smax (mm^2), med (min-max)	4.63 (2.66,6.38)	3.79 (2.55,4.97)	*Z*=-1.608	0.108

Emin: minimum elastic modulus; Emean: mean elastic modulus; Emax: maximum elastic modulus; Eratio: ratio of elastic modulus; ESSDAI: European League Against Rheumatism SS Disease Activity Index; S (max): the area of the largest single labial gland per unit detection range.

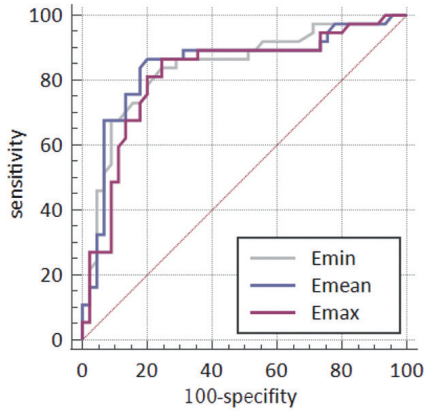

Fig. 5. ROC curves of SWE diagnosis in the hypocomplementaemic and non-hypocomplementaemic groups.

This suggested that ultrasound scores played a crucial role in the diagnosis of SS and in the evaluation of disease activity. However, ultrasound scores are highly subjective and vary among observers to some extent. Ultrasound was used in previous studies to assess the involvement of major glands, including the parotid and submandibular glands, while the pathological biopsy aimed at the labial glands. The subject in our cohort was the labial gland, and ultrasound imaging more intuitively reflected the histological changes in the labial gland affected by serological abnormalities.

In our study, 48 patients with SS had ESSDAI scores ≥5; SWE values (Emin, Emean, and Emax) in the labial gland were higher than in patients with ESSDAI <5. This was in line with the findings of Kimura-Hayama *et al*. (12), indicating that higher SWV in the parotid gland was found to be associated with higher ESSDAI scores and low C4 levels ($p<0.05$). Simultaneously, the influence of SS on salivary glands was synchronous with the influence on parotid, submandibular, and labial glands. This was probably because the altered salivary gland stiffness in patients with SS might be associated with increased chemokine (CXCL13) levels. Traianos *et al*. (13, 14) reported that CXCL13 was one of the major chemokines responsible for the initiation and maintenance of ectopic germinal center (GC) in the minor salivary gland and played a role in auto-reactive B-cell generation and expansion. Meanwhile, the serum CXCL13 level was significantly elevated in patients with SS having high ESSDAI scores, indicating that the disease activity was associated with elevated serum levels of biomarkers. In addition, Gottenberg *et al*. (15-17) reported an association of high ESSDAI scores with elevated levels of B-lymphocyte stimulator (BLys), suggesting that SS in the active phase had the presence of hyperactivated and proliferating B cells, leading to massive lymphocyte infiltration in the labial gland and altered glandular tissue structure with a hardened texture.

In our study, the presence of hypocomplementaemia and high levels of IgG in patients with SS were in connection with increased labial gland stiffness, with Emean being the most effective in distinguishing high levels of IgG with a cut-off value of 10.7 kPa and Emean being the most effective in assessing the presence of hypocomplementaemia with a cut-off value of 11.1 kPa. In this cohort, a significant difference was found in labial gland stiffness between the group with abnormal serological markers and the normal group. According to Martin *et al*. (18) high expression of IgG in the salivary glands of SS contributed to the continuous stimulation of the GC of RF-positive B cells, leading to the development of lymphoma. Ramos-Casals *et al*. (18) demonstrated a higher incidence of lymph node abnormalities in patients with SS and hypocomplementaemia than in the complement-normal group (18% *vs*. 5%, $p=0.01$). Previous studies also reported that lymphoma was a major cause of death in patients with SS (20, 21). Patients with multisystemic symptoms had a poor prognosis, and lymphoma was 10–44 times more likely to occur than in normal individuals. Severe parotid involvement, purpura, leukopenia, antibodies to the extractable nuclear antigen SSB, hyperimmunoglobulinaemia and hypocomplementaemia are risk factors for the development of lymphoma (22-25). Meanwhile, Brito-Zeron *et al*. (26) showed that SS with the presence of more than two prognosis-related adverse factors had a significantly lower survival rate and should be treated with more aggressive treatment options. Ultrasound, as a noninvasive method, could be used for the prognosis of patients before the appearance of adverse outcomes, in combination with serological indicators, prompting close follow-up by clinicians.

No correlation was observed between the duration of disease, age, and SWE of labial glands (Emin, Emean, Emax, and Eratio) in patients with SS in our study, which was in agreement with the findings of Theander *et al*. (11, 27). With age, the effect on the labial gland was remarkable in terms of area and quantity. Nevertheless, the results of this study did not correlate significantly, which might be related to the small sample size. The effect of disease duration on the salivary glands of patients with SS needs further exploration.

This study had some limitations. Firstly, the patients in this study were all female, and no study was conducted on the stiffness of labial glands between different sexes. Secondly, this study was a cross-sectional study, and the disease activity is a dynamic process. No secondary assessment of stiffness was conducted to compare the changes

before and after pharmacological intervention. In the end, the labial glands biopsy in our research was conducted to verify the pathological change resulting in the alteration of the hardness. In the following research, we hope we could find the correlation between pathological grading and ultrasonic imaging.

In conclusion, conventional ultrasound combined with SWE was significant for monitoring the disease activity of SS and assessing poor prognosis. SWE of the labial gland was associated with significantly higher ESSDAI scores in the active phase, high levels of IgG, and hypocomplementaemia. Compared with the ultrasound score, SWE was more objective. At the same time, the prognostic assessment was faster and simpler, and could be used as an effective adjunctive examination during the treatment of SS.

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