

## Research Article

# Combination of Salivary Gland Ultrasonography and Virtual Touch Quantification for Diagnosis of Sjögren's Syndrome: A Preliminary Study

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A total of 136 subjects (51 SS patients, 35 sicca syndrome patients without SS, and 50 healthy volunteers) were enrolled in this study. The mean SWV value for salivary glands of SS patients was statistically higher than that of controls ( $2.81 \pm 0.66$  m/s versus  $1.85 \pm 0.28$  m/s for parotid glands and  $2.29 \pm 0.34$  m/s versus  $1.82 \pm 0.25$  m/s for submandibular glands, resp.). Combining SWV values of parotid and submandibular glands gives a sensitivity of 88.2% (95% CI: 76.1–95.6%) and specificity of 96.0% (95% CI: 86.3–99.5%) at the cutoff point of 2.19 m/s, with an AUROC of 0.954 (95% CI: 0.893–0.986). In addition, combining SGUS score and SWV value yields a sensitivity of 98.0% (95% CI: 89.6–100%), specificity of 90.0% (95% CI: 78.2–96.7%), and AUROC of 0.962 (95% CI: 0.904–0.990). Classification tree considering the sequential use of SGUS score and SWV value achieved 92.1% accuracy for diagnosis of SS. Similarly, the ROC curve of combined SGUS scores and SWV values yields an AUROC of 0.954 (95% CI: 0.885–0.987), sensitivity of 97.1% (95% CI: 85.1–99.9%), and specificity of 92.2% (95% CI: 81.1–97.8%) for separating sicca syndrome patients (without SS) from SS patients. Combining SGUS and VTQ provides a promising tool for diagnosis of SS.

## 1. Introduction

Sjögren's syndrome (SS) is a common chronic autoimmune disease which affects mainly the exocrine glands with a typical focal lymphocytic infiltration, potentially leading to xerostomia and xerophthalmia [1]. SS is commonly found in patients with rheumatic disorders affecting the head and neck [2]. Currently, SS is diagnosed according to the criteria proposed by the American–European Consensus Group (AECG) in 2002 and American College of Rheumatology (ACR) in 2012 [3, 4]. An international consensus classification criterion for SS, approved by AECG and ACR, was recently published [5]. Labial salivary gland biopsy plays an important role in the diagnosis of SS. However, salivary gland biopsy is an invasive procedure associated with patient discomfort and the risk of complications, and disparity in minor salivary gland biopsy evaluation can lead to overestimation

of SS [6]. In recent years, salivary gland ultrasonography (SGUS) has been proposed as a convenient and noninvasive alternative to sialography, sialoscintigraphy, and magnetic resonance imaging for diagnosis and classification of primary and secondary SS [7–14]. Several comprehensive SGUS scoring systems for diagnosis of SS have been developed previously [15]. More recently, a simplified scoring system based on parenchyma ultrasound heterogeneity was proposed, which is relatively easy to use [16, 17]. However, these scoring systems are semiquantitative at best and somewhat subjective, which may lead to operator-dependent results. Therefore, there is still a need for noninvasive and objective methods for diagnosing SS salivary glands.

Shear wave velocity (SWV) imaging is an emerging ultrasound imaging modality which *quantitatively* evaluates tissue stiffness, a biomarker closely related to pathology. Typically, shear waves are generated in tissue by ultrasound

radiation force and the shear wave propagation velocity is measured and used alone or converted to Young's modulus for quantitative evaluation of tissue stiffness [18]. This imaging modality has shown good promise for liver fibrosis staging and cancer diagnosis [19]. A recent study indicates that SWV of parotid gland is a potentially useful parameter for diagnosis of primary SS [20]. However, combining SGUS score and salivary gland SWV value for SS classification has not been reported.

Because B-mode image texture and tissue stiffness represent different aspects of tissue characteristics, it is expected that the combination of both texture and stiffness information may improve the diagnostic performance. The aim of the present study is to investigate the value of combining simplified SGUS score and SWV value obtained with Virtual Touch Quantification (VTQ) in salivary glands for SS diagnosis.

## 2. Methods

**2.1. Patients and Healthy Controls.** This study was approved by the Human Research Ethics Committee of Shantou Central Hospital and Shantou University Medical College. Written, informed consent was obtained for all participants. Between January 2014 and February 2015, 51 consecutive SS patients (including primary and secondary SS) were enrolled in this study. Diagnosis of SS was made according to the AECG criteria, which includes a standardized clinical examination performed by an experienced rheumatologist (Yukai Wang), serological and laboratory tests, ocular tests, and salivary gland biopsy. During the same period of time, 50 healthy adult volunteers without SS were recruited as the control group and examined by SGUS and VTQ. All healthy volunteers had a normal medical history and physical examination; had no symptoms of xerostomia or keratoconjunctivitis sicca; had no sialoadenitis or mass lesions in salivary glands; and were not using medications. In addition, 35 sicca syndrome patients (without SS) were studied and compared with the SS patients.

**2.2. SGUS Score.** An Acuson S2000 ultrasound system (Siemens Medical Solutions, Mountain View, CA, USA) equipped with a linear 4–9 MHz probe was used in this study. When scanned, subjects were in a supine position and the neck extended and the head turned to the opposite side. The ultrasound transducer was gently coupled to the body surface with a sufficient amount of ultrasound gel. The bilateral parotid glands and submandibular glands were imaged. Parenchymal homogeneity was graded from 0 to 3 in accordance with the US scoring system described by Theander and Mandle and Hočvar et al. [16, 21]: score 0 = complete homogeneity, score 1 = mild inhomogeneity, score 2 = evident inhomogeneity, and score 3 = gross inhomogeneity. The final score was selected as the highest score among the 4 salivary glands [16]. All ultrasound acquisitions and scoring were performed by the same physician (Shaoqi Chen).

**2.3. Virtual Touch Quantification (VTQ).** Measurement of shear wave velocity was also obtained with the S2000 using

the VTQ function. The bilateral parotid glands and submandibular glands were identified under the guidance of real-time B-mode imaging. Six VTQ measurements were obtained in the central, peripheral, and subcapsular areas (2 measurements at each area) without visible vessels of each salivary gland during breathhold. Each VTQ measurement gave an estimate of shear wave velocity (SWV) in m/s. In order to reduce measurement variation, the highest and lowest SWV of all 6 measurements were eliminated and the remaining 4 measurements were averaged and used as the final value for each salivary gland. All VTQ measurements were performed by the same physician (Shaoqi Chen).

**2.4. Statistical Analysis.** Continuous variables were expressed as mean  $\pm$  standard deviation (SD). Comparison between SS and controls was performed by Fisher's exact chi-square test. The data were statistically analyzed using the SPSS software version 16 (IBM SPSS Statistics, Armonk, NY, USA). The optimal cutoff values were determined from a receiver operating characteristic curves (ROC) using MedCalc statistical software version 12.3.0. The sensitivity, specificity, and area under the ROC curve (AUROC) were used as diagnostic performance indicators. The optimal cutoff point was identified according to Youden tests. A classification and regression tree (CART) was used to determine whether separation between controls and SS patients could be improved by combining SGUS score and SWV value. Leave-one-out cross-validation (10-fold) was applied to determine classifier performance.

## 3. Results

The SS group included 51 patients (1 male and 50 female) with mean age of  $47.0 \pm 12.6$  years (range: 23–77 years). The control group included 50 healthy individuals (2 male and 48 female) with a mean age of  $45.3 \pm 12.2$  years (range: 20–71 years). There were 35 (5 male and 30 female) sicca syndrome patients (without SS) with a mean age of  $52.5 \pm 12.5$  years (range: 24–73 years). There was no statistically significant difference between the patient and control groups in terms of age and gender ( $P > 0.05$ ).

**3.1. Difference of SGUS Score between SS Patients and Healthy Controls.** Representative B-mode images with SGUS score of 0 through 3 are shown in Figure 1. The SS patients presented SGUS scores covering all 4 categories: 7.8% for score 0, 35.3% for score 1, 47.1% for score 2, and 9.8% for score 3. In contrast, score 0 accounted for 92% of the controls, and score 1 was detected in 8% of controls. The difference in SGUS scores between SS patients and controls was highly significant ( $P < 0.001$ ).

**3.2. Diagnostic Performance of SWV Value for Separating SS Patients and Healthy Controls.** Representative images of the parotid gland with VTQ measurements are shown in Figure 2. The mean SWV value for parotid glands of SS patients was statistically higher than that of controls ( $2.81 \pm 0.66$  m/s versus  $1.85 \pm 0.28$  m/s,  $P < 0.0001$ ). The ROC curve of SWV for separating parotid glands of SS patients from those

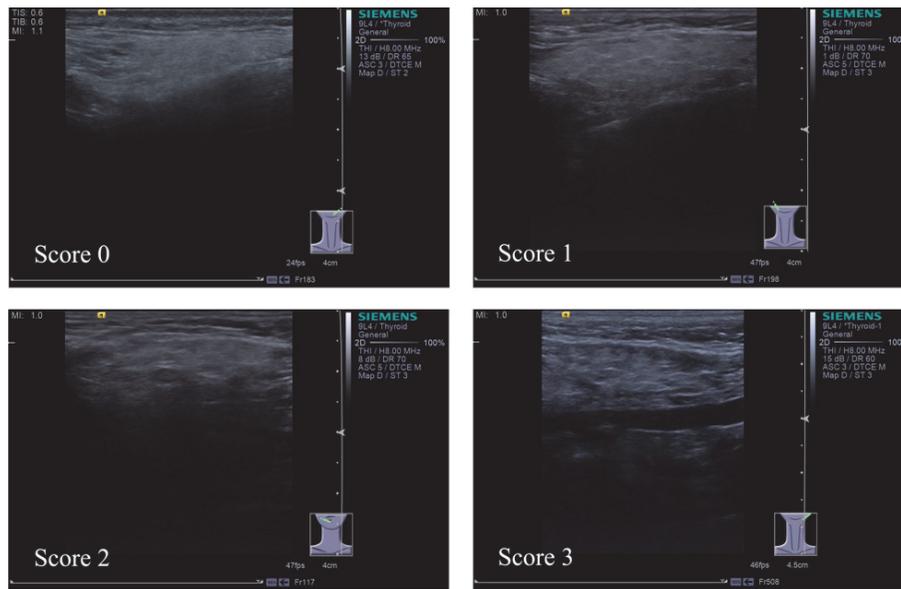


FIGURE 1: Representative B-mode ultrasound images for salivary glands: score 0 = complete homogeneity, score 1 = mild inhomogeneity, score 2 = evident inhomogeneity, and score 3 = gross inhomogeneity.

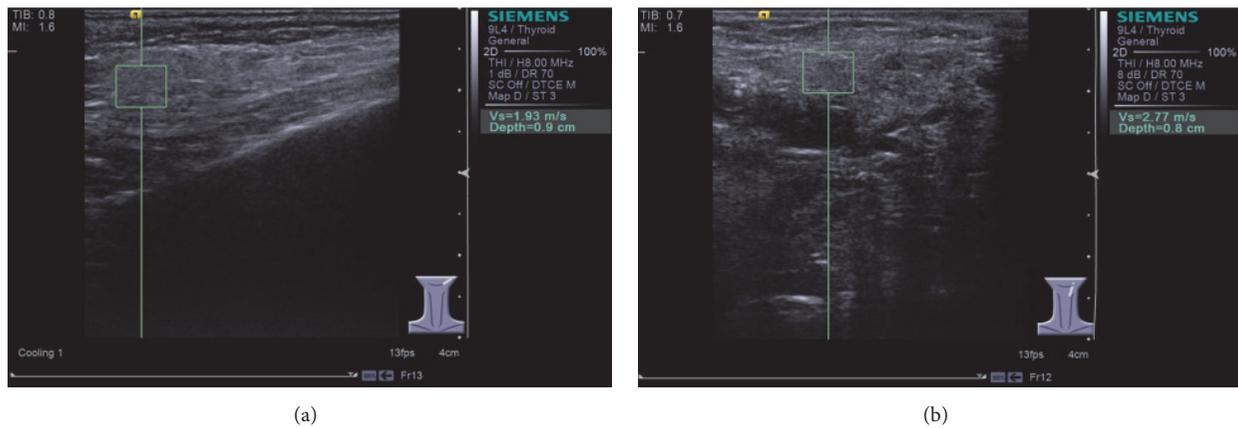


FIGURE 2: Representative images of parotid glands with shear wave velocity (SWV) measurements using Virtual Touch Quantification (VTQ). (a) SWV value was 1.93 m/s in a healthy volunteer and (b) 2.77 m/s in a SS patient.

of healthy controls is shown in Figure 3(a). The AUROC was 0.945, with a 95% confidence interval (CI) of 0.882–0.981. Using a cutoff value of 2.07 m/s, the sensitivity and specificity were 92.2% (95% CI: 81.1–97.8%) and 88.0% (95% CI: 75.7–95.5%), respectively. Similarly, the mean SWV value for submandibular glands of SS patients was significantly higher than that of controls ( $2.29 \pm 0.34$  m/s versus  $1.82 \pm 0.25$  m/s,  $P < 0.0001$ ). The ROC curve of SWV for separating submandibular glands of SS patients from those of healthy controls is shown in Figure 3(b). The AUROC was 0.854 (95% CI: 0.770–0.916). With a cutoff value of 2.06 m/s, the sensitivity and specificity were 76.5% (95% CI: 62.5–87.2%) and 92.0% (95% CI: 80.8–97.8%), respectively. In SS patients, the mean SWV value of parotid gland was significantly higher than that of the submandibular gland ( $2.81 \pm 0.66$  m/s versus  $2.29 \pm 0.34$  m/s,  $P < 0.001$ ).

After combining results of parotid and submandibular glands (by averaging), the mean SWV value of SS patients ( $2.55 \pm 0.41$  m/s) differed significantly from that of controls ( $1.83 \pm 0.20$  m/s) ( $P < 0.001$ ). The ROC curve for separating SS patients from healthy controls is shown in Figure 3(c). AUROC was 0.954 (95% CI: 0.893–0.986). With a cutoff value of 2.19 m/s, the sensitivity and specificity were 88.2% (95% CI: 76.1–95.6%) and 96.0% (95% CI: 86.3–99.5%), respectively.

**3.3. Diagnostic Performance of Combining SGUS Score and SWV Value for Separating SS Patients and Healthy Controls.** A classification tree analysis based on SGUS scores and SWV values was used for distinguishing SS patients from healthy controls. The classification tree included two classification nodes and three terminal nodes (Figure 4). The first node was separated by SGUS score, and the second node was split by

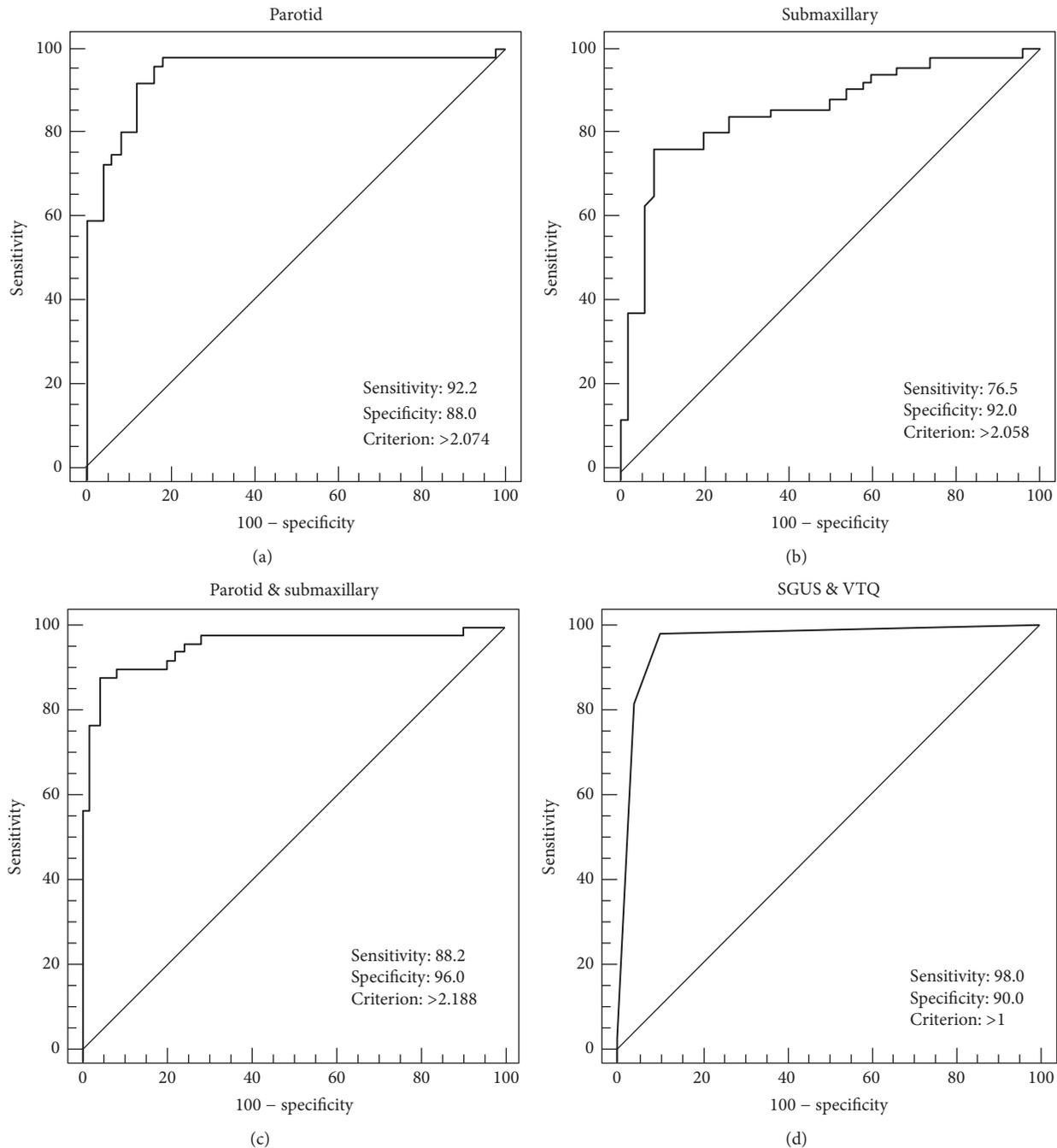


FIGURE 3: ROC curves with the optimal cutoff value, sensitivity, and specificity using (a) shear wave velocity (SWV) value of parotid glands; (b) SWV value of submandibular glands; (c) mean SWV value of parotid and submandibular glands; and (d) combination of SGUS score and mean SWV value.

VTQ value, with a threshold of 2.19 m/s. The mean accuracy and error of the classification tree estimated by performing 10-fold cross-validation were 92.1% and 0.03.

The ROC curve for separating SS patients from healthy controls using the classification tree is shown in Figure 3(d). AUROC was 0.962 (95% CI: 0.904–0.990). With a SWV cutoff value of 2.19 m/s, the sensitivity and specificity were 98.0% (95% CI: 89.6–100%) and 90.0% (95% CI: 78.2–96.7%), respectively.

**3.4. Diagnostic Performance of Separating SS Patients and Sicca Syndrome Patients.** The mean SWV values for parotid and submandibular glands of sicca syndrome patients (without SS) were  $1.93 \pm 0.28$  m/s and  $1.84 \pm 0.17$  m/s, respectively. After combining values of parotid and submandibular glands, the mean SWV value of sicca syndrome patients ( $1.88 \pm 0.15$  m/s) differed significantly from that of patients with SS ( $P < 0.001$ ). The ROC curve for separating sicca syndrome patients from SS patients had a sensitivity of 97.1% (95% CI:

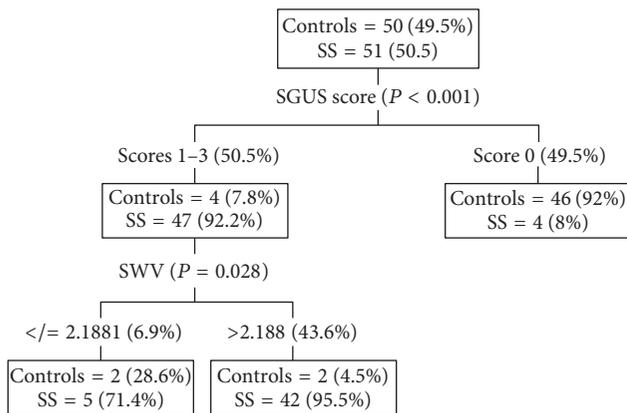


FIGURE 4: Classification tree for combination of SGUS score and mean SWV value. Each terminal node specifies numbers and percentages of SS and controls. The resulting correct classification rate was 92.1%.

85.1–99.9%), specificity of 88.2% (95% CI: 76.1–95.6%), and AUROC of 0.952 (95% CI: 0.884–0.987) with a cutoff value of 2.18 m/s.

Combining the SGUS scores and SWV values, the ROC curve yielded an AUROC of 0.954 (95% CI: 0.885–0.987), sensitivity of 97.1% (95% CI: 85.1–99.9%), and specificity of 92.2% (95% CI: 81.1–97.8%). The mean accuracy and error of the classification tree were 91.9% and 0.03, respectively.

#### 4. Discussion

The evaluation of salivary gland involvement contributes significantly to the diagnosis of SS. Therefore, development of noninvasive and accurate diagnostic strategies for salivary glands would significantly benefit SS patients. Our preliminary study demonstrates that VTQ may provide important information for diagnosis of SS.

In the study of Knopf et al. [20], the mean SWV values for the parotid and submandibular glands were 2.86 m/s and 2.17 m/s, respectively, in primary SS patients, and 1.87 m/s and 1.81 m/s, respectively, in healthy subjects. These values are very similar to results of our current study: 2.81 m/s and 2.29 m/s for parotid and submandibular glands, respectively, in SS patients, and 1.85 m/s and 1.82 m/s, respectively, for healthy volunteers. However, the optimal cutoff value for parotid glands in our study (2.074 m/s) was lower than that in the study of Knopf et al. (2.395 m/s) [20]. This difference may be due to selection of different controls in these two studies: controls in the Knopf study were non-SS patients with sicca symptoms and/or salivary gland swelling, whereas controls in our study were healthy volunteers without any sicca or salivary gland symptoms.

Shear wave velocity measurements provide an objective and quantitative evaluation of tissue stiffness, which may add important information complementary to B-mode ultrasound homogeneity for diagnosis of SS. The combination of B-mode ultrasonography and SWV has been investigated in a study of radiation submaxillitis [22]. However, there are

no prior reports on combination of SGUS score and SWV value in SS diagnosis. To the best of our knowledge, our study is the first research that investigates the diagnostic accuracy of combining simplified SGUS score and SWV value in classification of SS. Using a classification tree to combine SGUS score and SWV value, a mean accuracy of 92.1% could be achieved for separating SS patients from healthy volunteers in our study. A similar accuracy of 91.9 was achieved for separating sicca syndrome patients (without SS) from SS patients. SWV measurements are relatively easy to obtain during routine ultrasound imaging of the salivary glands. Cornec et al. [23] proposed that, in the diagnosis of primary SS, salivary gland biopsy should be performed only when the results of ultrasound imaging are negative. Therefore, the integration of SWV and SGUS score for improving the accuracy of ultrasound diagnosis may reduce the need of salivary gland biopsy in a substantial number of patients.

This study has several limitations. First, this is a single-center study with a relatively limited sample size, in which primary and secondary SS were not analyzed separately. Further studies with larger sample size are needed to confirm findings of this study. A large sample size would also allow the study of any potential correlations between SWV/SGUS and severity of SS. Second, sicca syndrome patients (without SS) had many different coexisting conditions, such as diabetes and chronic hepatitis. Future studies including non-SS patients without coexisting conditions may provide more insights into the diagnostic performance in a typical clinical setting.

In conclusion, the combination of SGUS and SWV value provides a promising tool in diagnosis of SS.

#### Competing Interests

The authors have no conflict of interests to disclose for this study.

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