Ultrasonographic evaluation of lacrimal glands in patients with primary Sjögren's syndrome

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Abstract

Objective

This study focused on distinguishing the characteristic ultrasonographic findings of lacrimal glands in primary Sjögren's syndrome (pSS) from those in idiopathic sicca syndrome. We aimed to set up a semi-quantitative scoring system of lacrimal gland ultrasonography (LGUS) for patients with pSS.

Methods

Fifty-six patients with pSS and 40 patients with idiopathic sicca syndrome were evaluated. Lacrimal glands were examined with ultrasonography using area, major/minor axis length, and five components (presence of intraglandular branch of lacrimal artery, inhomogeneity, hyperechoic bands, hypoechoic areas, and delineation). Except for the area and maximal/minimal length of lacrimal glands, other components were classified as dichotomous variables (present or absent). Using the receiver operating characteristics curve, we inferred the most appropriate combination of LGUS scoring for pSS diagnosis.

Results

Patients with pSS had a higher proportion of intraglandular branch of lacrimal artery (70.5% vs. 42.5%, p<0.001), inhomogeneity (72.3% vs. 46.3%, p<0.001), and hyperechoic bands (56.2% vs. 37.5%, p=0.016) than patients with idiopathic sicca syndrome. LGUS A, which represents the summation of one point assigned for the presence of intraglandular branch of lacrimal artery and one for inhomogeneity, was the most suitable diagnostic criterion (area under curve = 0.724, 95% confidence interval 0.620–0.828). If both sides have a score of 2, it results in a total of 4 points. With a cut-off value of 3 out of 4 points, LGUS A had 60.7% sensitivity, 71.1% specificity, 60.7% positive predictive value, and 72.5% negative predictive value.

Conclusion

Semi-quantitative scoring of LGUS was useful when distinguishing patients with pSS from those with idiopathic sicca syndrome. The combination of intraglandular branch of lacrimal artery and inhomogeneity on both sides was most suitable for classifying pSS using LGUS.

Key words

Sjögren's syndrome, xerophthalmia, dry eye syndromes, autoimmune diseases, scoring methods, diagnostic imaging

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease that affects the salivary and lacrimal glands and is mainly characterised by dry eyes and mouth (1, 2). Previous reports have presented classification criteria to reliably diagnose pSS (3-6). The 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criterion for pSS is based on biopsy, serology, and function of lacrimal and salivary glands. Although several diagnostic modalities have been proposed for this multisystemic autoimmune disease, there is no gold standard imaging test for its diagnosis. Several imaging tests have been attempted to distinguish pathologic findings from normal glands in pSS (7). In recent decades, salivary gland ultrasonography (SGUS) has been proven efficacious for the assessment of pSS and could be an alternative non-invasive diagnostic tool (8, 9). Few studies and trials have assessed lacrimal glands with imaging tools (10-14). Magnetic resonance imaging (MRI) of lacrimal glands in patients with pSS reveals a heterogeneous appearance and atrophy of the glands, which correlates with lower lacrimal flow rate, and increased fat infiltration (15, 16). Positron emission tomography/computed tomography (CT) with ^{11}C-Methionine, which is a protein synthesis marker, positively correlates with tear flow in pSS (17). However, due to the lack of feasibility of such diagnostic modalities, there is a need for non-invasive, cost-effective, and widely available diagnostic tools for assessing lacrimal glands.

In recent studies, lacrimal gland ultrasonography (LGUS) was performed to evaluate lacrimal glands to compare patients with pSS to patients with idiopathic sicca syndrome. De Lucia *et al*. performed a preliminary study for sonographic findings of lacrimal glands (18). Inhomogeneity of the gland on LGUS was associated with pSS diagnosis and the presence of anti-Ro/La antibodies with good intra- and inter-rater reliability. However, the study had limitations inherent to a small sample size, and there had been no attempt to establish a scoring system for LGUS.

The objectives of our study were to find distinctive LGUS findings of pSS and establish a semi-quantitative scoring system for practical use of LGUS by optimising the scoring method.

Materials and methods

Study population

This was a multi-centre cross-sectional study performed at Konkuk Medical Centre and Soonchunhyang University Hospital, Republic of Korea. We included 96 patients with idiopathic sicca syndrome who had been examined for pSS from December 2020 to September 2021. The diagnosis of pSS was established by the 2016 ACR/EULAR Classification Criteria. The patients with idiopathic sicca syndrome who did not fulfil the criteria were defined as the control group. The exclusion criteria were as follows: previous head and neck radiation treatment; infection with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus; sarcoidosis; lymphoma; graft versus host reaction; immunoglobulin (Ig) G4-related disease; and other autoimmune-mediated diseases (19). This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. It was approved by the Institutional Review Board of Konkuk University Medical Centre (KUMC 2020-11-043) and Soonchunhyang University Hospital (SCH 2021-01-009). All study participants gave their informed written consent before enrolment.

Clinical and serological tests

Clinical data and the data concerning the following serological tests were obtained from the medical charts: demographics, duration of sicca symptom, anti-nuclear antibody (ANA), anti-Ro/SSA, anti-La/SSB antibodies, rheumatoid factor (RF), IgG, complement 3 and 4, erythrocyte sediment rate (ESR), C-reactive protein (CRP), Schirmer's I test, unstimulated salivary flow rate (USFR), Visual Analogue Scale (VAS) for ocular and oral dryness (0–10 points), EULAR Sjögren's Syndrome Disease Activity Index, Sjögren's Syndrome Disease Damage Index, and EULAR Sjögren's Syndrome Patient Reported Index.

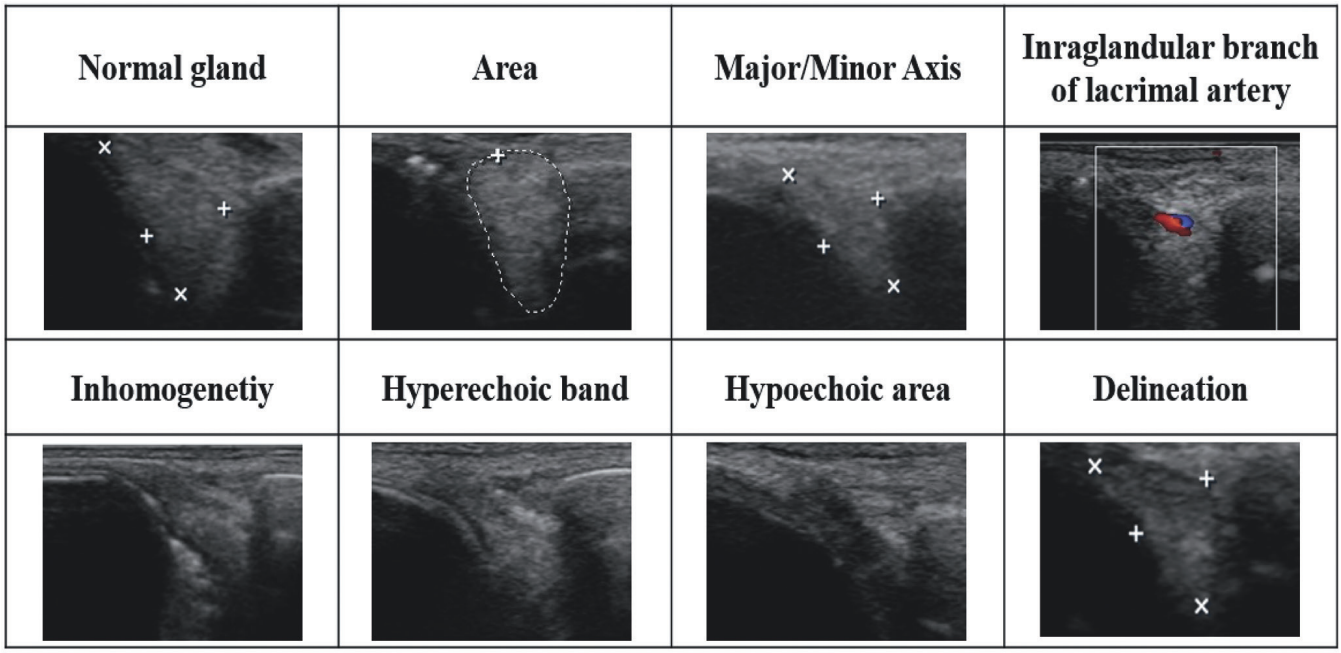

Fig. 1. Examples of sonographic findings of lacrimal glands in study patients.

Lacrimal gland ultrasonography (LGUS)

All ultrasound evaluations were performed by one experienced rheumatologist (KSH) who was blinded to the patients' information using HD15 US (Philips Ultrasound, Bothell, WA, USA). Patients in a supine position were asked to close their eyes so that the lacrimal gland could be located between the end of the eyelid and eyebrow. A linear probe at a frequency of 5–12 Hz was placed on the glands obliquely after identifying the eye globe and frontal process of the zygomatic bone (14, 18). Measurements were taken on the screen where the lacrimal gland appeared the largest. Bilateral lacrimal glands were assessed consecutively. We measured the area, major axis (the longest axis of the lacrimal gland), and minor axis (vertical to the longest one). Dichotomous variables of LGUS were selected from a previous study (14, 18), and some were derived from Hocevar's method of SGUS (20). Elementary features were defined as: Detection of intraglandular branch of lacrimal artery using colour Doppler ultrasound (0 points for absence and 1 point for the presence of a signal inside the lacrimal gland on colour Doppler); glandular parenchyma homogeneity (0 points for homogeneous and 1 point for inhomogeneous), hypoechoic areas (0 points for absence and 1 point for presence); hyperechoic band (0 points for absence and 1 point for presence); delineation (0 points for clear delineation and 1 point for unclear delineation) (Fig. 1).

LGUS scoring

The scoring of lacrimal glands was based on the summation of all the five features (presence of intraglandular branch of lacrimal artery, homogeneity, hyperechoic bands, hypoechoic areas, and delineation) in bilateral glands. Each feature on the left and right sides was given a score of 1 point. Subsequently, we composed combinations of features: LGUS A (total score 0–4) = presence of intraglandular branch of lacrimal artery + homogeneity; LGUS B (total score 0–6) = presence of intraglandular branch of lacrimal artery + homogeneity + hyperechoic bands; LGUS C (total score 0–8) = presence of intraglandular branch of lacrimal artery + homogeneity + hyperechoic bands + delineation; and LGUS D (total score 0–10) = presence of intraglandular branch of lacrimal artery + homogeneity + hyperechoic bands + delineation + hypoechoic area.

Salivary gland ultrasonography (SGUS)

Previous studies assessed salivary glands using the semi-quantitative scoring system proposed by Hocevar (8, 20); the cut-off value for classifying pSS was 14 points (8).

Statistical analysis

Data were analysed using descriptive statistics. Normality of the distribution was performed using the Kolmogorov-Smirnov test for numerical data. To compare the numerical data, student's t-test or Mann-Whitney U-test was applied according to the normality of distribution. Numerical variables were presented as mean ± standard deviation or median with interquartile range. For categorical data, χ^2 test and or Fisher's exact test was used. Pearson correlation analysis was performed to assess the correlation of LGUS score with SGUS and Schirmer's I test. Receiver operating characteristic (ROC) curves were calculated to distinguish the most appropriate LGUS scoring. We considered p-value <0.05 as statistically significant. Analyses were performed using the software SPSS statistical package (v. 25.0 for Windows, SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics and clinical symptoms

A total of 96 patients were enrolled in this study. Of these, 56 met the criteria

of the 2016 ACR/EULAR Classification Criteria for pSS, whereas 40 did not. Baseline characteristics and clinical symptoms are summarised in Table I. There was no difference in patients with pSS and idiopathic sicca syndrome in terms of age (56.2±16.0 *vs*. 60.4±17.1, p=0.226), percentage of female sex (82.1 *vs*. 82.5%, p=0.944), and symptom duration (3.0 *vs*. 3.0 years, p=0.886). Positivity for ANA, anti-Ro Ab, anti-La Ab, and RF was more frequent, and serum IgG levels and ESR were significantly higher in the pSS group than in the control group. With regards clinical aspects, patients with pSS had more positive Schirmer's I test (71.4 *vs*. 50.0%, p=0.042), USFR (71.4 *vs*. 47.5%, p=0.046), and SGUS (78.6 *vs*. 15.0%, p<0.001). However, no significant difference was found with regards to xeropthalmia, xerostomia, VAS ocular, and oral dryness.

Table I. Baseline characteristics of patients with primary Sjögren's syndrome and idiopathic sicca symptom.

Variable N (%) or median with IQR	Primary Sjogren's syndrome (N = 56)	Idiopathic Sicca Symptom (N = 40)	p-value
Age (year-old)	56.2 ± 16.0	60.4 ± 17.1	0.226
Female	46 (82.1%)	33 (82.5%)	0.944
Symptom Duration (year)	3.0 [1.0; 5.0]	3.0 [1.0;10.0]	0.886
Positive ANA	40 (71.4%)	14 (35.9%)	**0.001**
Positive Anti-Ro Ab	41 (75.9%)	9 (22.5%)	**< 0.001**
Positive Anti-La Ab	41 (75.9%)	3 (7.9%)	**< 0.001**
Positive RF	19 (33.9%)	5 (12.5%)	**0.031**
IgG	1378.5 [1155.0;1838.0]	1220.0 [924.0;1357.0]	**0.023**
C3	106.6 [83.9;124.0]	103.0 [86.5;110.8]	0.452
C4	23.5 ± 9.7	23.4 ± 7.9	0.972
ESR	25.0 [15.0;44.0]	10.0 [5.5;16.5]	**< 0.001**
CRP	0.1 [0.1; 0.3]	0.1 [0.1; 0.2]	0.890
Xeropthalmia	49 (87.5%)	33 (84.6%)	0.546
Xerostomia	51 (91.1%)	33 (84.6%)	0.310
Abnormal Schirmer's I test	40 (71.4%)	20 (50.0%)	**0.042**
Abnormal USFR	40 (71.4%)	19 (47.5%)	**0.046**
VAS of dry eye (total 10)	6.0 [4.0; 8.0]	5.0 [3.0; 6.5]	0.083
VAS of dry mouth (total 10)	6.0 [5.0; 7.8]	5.0 [3.0; 7.0]	0.235
ESSDAI	7.0 [3.0;11.5]	-	-
SSDDI	1.5 [1.0; 2.0]	-	-
ESSPRI	4.7 [1.5; 6.0]	-	-
SGUS	22.2 ± 11.2	8.3 ± 5.2	**< 0.001**
positive SGUS†	44 (78.6%)	6 (15.0%)	**< 0.001**

ANA: anti-nuclear antibody; anti-Ro Ab: anti-Ro 60 antibody; RF: rheumatoid factor; IgG: immunoglobulin G; C: complement; ESR: erythrocyte sediment rate; CRP: C-reactive protein; USFR: unstimulated salivary flow rate; VAS: visual analogue scale; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; SSDDI: Sjögren's Syndrome Disease Damage Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index

† Fourteen points of SGUS was considered positive finding for Primary Sjögren's syndrome.

LGUS findings

LGUS findings were obtained for the left and right sides, and the summation of the bilateral findings was analysed (Table II). The area was larger in the pSS group (p=0.037) than in the control group, whereas major and minor distance and the ratio of the minor axis to the major axis were not different between the two groups. All lacrimal glands were identified to an appreciable extent in both groups. Detection of intraglandular branch of lacrimal artery (70.5 *vs*. 42.5 %, p<0.001), inhomogeneity (72.3 *vs*. 46.3%, p<0.001), and hyperechoic bands (56.2 *vs*. 37.5%, p=0.022) were found more in the pSS group compared to in the idiopathic sicca syndrome group.

Table II. Lacrimal gland ultrasound findings of patients with idiopathic sicca symptom and primary Sjögren's syndrome.

Variable N (%) or median with IQR	Primary Sjögren's syndrome (N = 112)	Idiopathic sicca symptom (N = 80)	p-value
Area	0.324 ± 0.121	0.289 ± 0.089	**0.037**
Major axis	0.858 ± 0.188	0.853 ± 0.140	0.833
Minor axis	0.443 ± 0.169	0.431 ± 0.108	0.549
Ratio (minor axis / major axis)	0.524 ± 0.201	0.515 ± 0.142	0.705
Presence of intraglandular branch of lacrimal artery	79 (70.5%)	34 (42.5%)	**< 0.001**
Inhomogeneity	81 (72.3%)	37 (46.3%)	**< 0.001**
Hyperechoic bands	63 (56.2%)	30 (37.5%)	**0.016**
Hypoechoic areas	73 (65.2%)	41 (51.3%)	0.074
Delineation	84 (75.0%)	51 (63.8%)	0.128
Positive LGUS A†	34 (60.7%)	11 (27.5%)	**0.003**

†Positive LGUS A was classified with cut-off value 3 points.

LGUS scoring

Patients with positive LGUS A scores in the pSS group had lower CRP levels (0.075 *vs*. 0.165 mg/dL, p=0.014), higher VAS for dry eye (7.0 *vs*. 5.5, p=0.018), and more positive SGUS (88.2 *vs*. 63.6%, p=0.045) compared to patients with negative LGUS A score (Table III). They revealed less positive Schirmer's I test scores than patients with negative LGUS A scores, but the difference was not statistically significant (61.8% *vs*. 86.4%, p=0.101).

Of the 12 patients with negative SGUS scores in the pSS group, four (33.3%) had positive LGUS A scores and were younger than patients with negative LGUS A scores (44.5±19.8 *vs*. 67.0±10.3 years, p=0.024). However, other demographic characteristics and laboratory tests revealed no significant difference. Of the 44 patients with positive SGUS scores in the pSS group, 14 (31.8%) had negative LGUS A scores, and only their CRP level was higher than that of patients with positive LGUS scores (0.3 *vs*. 0.1 mg/dL, p=0.045).

ROC curves and calculated area under the curve of combinations with features were analysed (Fig. 2). All the combinations were lower than the area of the SGUS ROC curve (0.852,

Table III. Baseline characteristics of patients with positive and negative LGUS A score in primary Sjögren's syndrome.

Variable N (%) or median with IQR	Positive LGUS A† (n=34)	Negative LGUS A (n=22)	*p*-value
Age (year-old)	55.4 ± 16.7	57.6 ± 15.1	0.617
Female	29 (85.3%)	17 (77.3%)	0.491
Symptom Duration (year)	3.0 [2.0; 5.0]	3.0 [1.0; 5.0]	0.795
Positive ANA	24 (70.6%)	16 (72.7%)	1.000
Positive Anti-Ro Ab	30 (88.2%)	20 (90.9%)	1.000
Positive Anti-La Ab	9 (27.3%)	8 (36.4%)	0.677
Positive RF	11 (32.4%)	8 (36.4%)	0.984
IgG	1418.0 [1259.5;2091.5]	1201.0 [908.0;1640.0]	0.090
C3	104.2 [86.1;122.7]	106.6 [85.6;123.0]	0.971
C4	22.5 ± 8.9	25.0 ± 10.8	0.425
ESR	25.0 [15.0;43.5]	24.0 [18.0;47.0]	0.780
CRP	0.075 [0.035;0.115]	0.165 [0.070;0.625]	**0.014**
Xeropthalmia	30 (88.2%)	19/21 (86.4%)	0.802
Xerostomia	32 (94.12%)	19/21 (86.4%)	0.289
Abnormal Schirmer's I test	21/30 (61.8%)	19/21 (86.4%)	0.101
Abnormal USFR	21/32 (61.8%)	12/21 (57.1%)	0.533
VAS of dry eye (total 10)	7.0 [5.0; 8.0]	5.5 [2.0; 7.0]	**0.018**
VAS of dry mouth (total 10)	8.0 [3.0;11.5]	6.0 [4.0;11.0]	0.902
ESSDAI	2.0 [1.0; 3.0]	1.0 [1.0; 2.0]	0.347
SSDDI	15.8 ± 7.4	12.6 ± 3.8	0.095
ESSPRI	5.0 [0.3; 6.7]	4.3 [3.7; 5.0]	0.373
SGUS	24.0 ± 9.5	19.5 ± 13.1	0.136
positive SGUS	30 (88.2%)	14 (63.6%)	**0.045**

ANA: anti-nuclear antibody; anti-Ro Ab: anti-Ro 60 antibody; RF: rheumatoid factor; IgG: immunoglobulin G; C: complement; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; USFR: unstimulated salivary flow rate; VAS: visual analogue scale; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; SSDDI: Sjögren's Syndrome Disease Damage Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index.
† Positive LGUS A was classified with cut-off value 3 points.

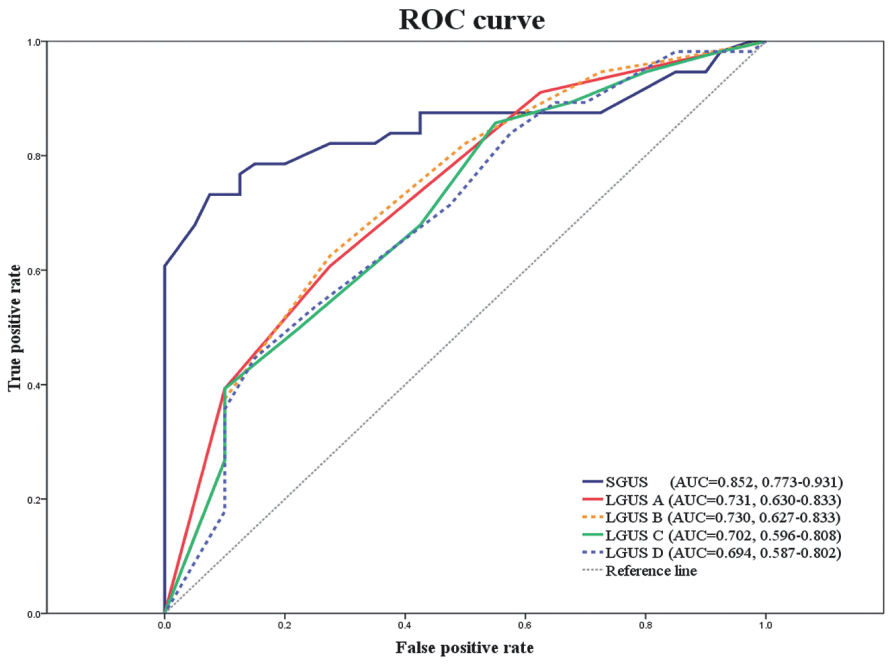

Fig. 2. ROC curve of lacrimal gland ultrasonography (LGUS) and salivary gland ultrasonography (SGUS).

95% CI: 0.773–0.931). Additionally, the areas under the ROC curve for each scoring combination were analysed. The area under the ROC curve for LGUS A was the largest of the LGUS scoring combinations (0.731, 95% CI: 0.627–0.833, $p<0.001$). LGUS A, with a cut-off value of 3 out of 4 points, had 60.7% sensitivity, 71.1% specificity, a positive predictive value of 60.7%, and a negative predictive value of 72.5%. SGUS scoring using Hocevar's scoring method (20) depicted a positive correlation with all LGUS scoring combinations (Table IV). The coefficient of correlation of LGUS A, which was the summation of intraglandular branch of lacrimal gland and homogeneity, was 0.328 ($p=0.014$).

Discussion

We observed different LGUS findings between patients with pSS and those with idiopathic sicca syndrome in the present study such as presence of intraglandular branch of lacrimal artery and inhomogeneity of glands. Second, we set up the semi-quantitative scoring system with those LGUS findings. Additionally, all LGUS scoring combinations had positive correlations with SGUS scoring. This study aimed to lay the foundation for the clinical application of LGUS.

The current classification criteria for autoimmune diseases include more objective findings than subjective symptom-based items. According to the 2012 and 2016 classification criteria for pSS, a labial biopsy can aid the diagnosis of pSS when patients with a suspicion of pSS do not present with specific autoantibodies, such as anti-Ro/SS-A Ab (3, 21). SGUS for pSS was proposed in the early 2000s (22). SGUS can detect structural abnormality of the salivary gland in pSS, and the latest findings illustrated the prognostic role of SGUS in pSS (23). Although SGUS is not selected as a diagnostic tool in the current classification criteria for pSS, it has a supplementary diagnostic role in practice.

Furthermore, the Outcome Measures in Rheumatology (OMERACT) group is working to set the standardised scoring system of SGUS (24). Unlike SGUS, the study on LGUS had been relatively seldomly performed, and there is a lack of data for reference (12-14). Not all patients with pSS complain of xerostomia and xerophthalmia simultaneously. Therefore, the detection of abnormalities and measurement of lacrimal

Table IV. Correlation between LGUS and SGUS in pSS patients.

Combination	Coefficient of correlation	*p*-value
LGUS A	0.328	0.014
LGUS B	0.361	0.006
LGUS C	0.436	0.001
LGUS D	0.423	0.001

LGUS: lacrimal gland ultrasonography; SGUS: salivary gland ultrasonography; pSS: primary Sjögren's syndrome; LGUS A: presence of intraglandular branch of lacrimal artery + homogeneity; LGUS B: presence of intraglandular branch of lacrimal artery + homogeneity + hyperechoic band; LGUS C: presence of intraglandular branch of lacrimal artery + homogeneity + hyperechoic band + delineation; LGUS D: presence of intraglandular branch of lacrimal artery + homogeneity + hyperechoic band + delineation + hypoechoic area.

glands using LGUS in patients with pSS are needed, especially in patients who only present with xerophthalmia. In this study, we developed a semi-quantitative scoring system of LGUS for the first time. The several proposed components (presence of intraglandular branch of lacrimal artery, inhomogeneity, and hyperechoic band) were significantly more presented in the pSS group than in the control group. This is similar to the previous study that reported inhomogeneity as a discriminant component of patients with pSS (18).

In this study, the area of lacrimal glands of patients with pSS with LGUS was larger than that of the control group. In the early disease stage, there is an enlargement of the lacrimal glands, followed by fatty deposition and atrophy (16). We included newly diagnosed patients with relatively short symptom duration to ensure recruitment of early-stage patients. Our study findings revealed discrepancies with regards to values of areas and major and minor axes, which were similar in both groups. Furthermore, lacrimal glands had varied shapes, such as oval, circular, diamond with blunt angles, and irregular, and since the size of lacrimal glands was small, a minute difference in size could have a significant impact. A possible explanation for these findings could be that oedema of lacrimal glands caused by inflammation led to an altered shape of the gland, which perhaps explains the inconsistency in the results pertaining to axes and areas. In addition, we observed that lacrimal glands in patients with pSS illustrated the presence of intraglandular branch of lacrimal artery, inhomogeneity, and hyperechoic bands while those in patients with idiopathic sicca syndrome did not. Studies on the lacrimal gland artery are extremely rare, and the few reported studies are not associated with pSS (12, 13, 25). Giovagnorio *et al*. identified intraglandular branch of lacrimal artery in 4 of 15 patients in patients with pSS while no data was found in normal glands (14). We verified the presence of intraglandular colour Doppler signal to be a distinctive feature of the disease. If intraglandular branch of lacrimal artery is not detectable, it should be carefully examined by tilting the probe of ultrasonography or switching from colour Doppler to Doppler. Another finding of our study was the inhomogeneity of lacrimal glands. The heterogeneous feature of lacrimal glands on MRI reflected fatty infiltration (15) similar to the inhomogeneity of the LGUS finding, which is a prominent feature in patients with pSS. Hyperechoic bands of major salivary glands indicate glandular damage and are associated with functional impairment of the gland (26). Although the study was unable to prove the association between the function of the lacrimal gland and hyperechoic bands, this feature of LGUS was more definite in patients with pSS and is expected to be an appropriate tool for diagnosis.

According to our study, the semi-quantitative evaluation of LGUS demonstrated good discriminative power in terms of classifying pSS patients. We evaluated ROC by combining components in various ways. LGUS A, which comprises the combination of intraglandular branch of lacrimal artery and inhomogeneity on each side, showed excellent power for diagnosing pSS (Fig. 2). One-third of patients with negative SGUS in pSS had positive LGUS A scores. Although the diagnostic power of LGUS was not superior to SGUS, it would be a useful method for patients with negative SGUS. In the future, comprehensive evaluation of SGUS and LGUS may increase the accuracy of ultrasonography with regards to pSS diagnosis.

Several studies have demonstrated a significant correlation between SGUS score and USFR in patients with pSS, which implies that severe structural change detected on SGUS can reflect dysfunction of salivary glands (26, 27). We evaluated the correlation between Schirmer's I test and LGUS score; however, none of the LGUS scores demonstrated a significant correlation with Schirmer's I test. Our study could not illustrate the role of LGUS in predicting dysfunction of lacrimal glands because of its small sample size and the varied symptom duration of the patients. Therefore, further studies on patients with pSS with short symptom duration or disease duration should be performed.

This study had several limitations. First and most important, the sample size was relatively small. According to us, abnormal findings related to inhomogeneity and intraglandular branch of lacrimal artery were the most reliable in differentiating pSS from idiopathic sicca syndrome. This should be validated with a study having a larger sample size. Second, the present study only showed results in a cross-sectional manner. Thus, the importance of LGUS on disease progression or change of LGUS was not evaluated. Third, it was unable to perform a reliability analysis of the observer. However, to minimise the error, three other experts supervised the ultrasound examination. Although ultrasonography completely depends on the observer's skill level, it is cost-effective and easier to perform than CT or MRI in clinical settings. Lastly, there was insufficient data to analyse the association between LGUS and ocular staining score. Ocular staining was not available in our medical centre. Future studies should focus on the association between lacrimal gland function and LGUS.

In summary, we demonstrated that LGUS findings, such as presence of intraglandular branch of lacrimal artery, inhomogeneity, and hyperechoic

bands, were more frequently detected in the pSS group than in the control group. Furthermore, the combination of two components, intraglandular branch of lacrimal artery and inhomogeneity, could be effectively used to diagnose pSS. LGUS is a feasible non-invasive method to evaluate abnormal findings of lacrimal glands. Therefore, the semi-quantitative evaluation of LGUS may become a component of the classification criteria for pSS in the future.

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