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Incorporation of Salivary Gland Ultrasonography Into the American College of Rheumatology/European League Against Rheumatism Criteria for Primary Sjögren's Syndrome

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Objective. To assess whether the addition of salivary gland ultrasonography (SGUS) or replacement of current criteria items by SGUS influences the performance of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for primary Sjögren's syndrome.

Methods. Included were consecutive patients with complete data on all ACR/EULAR items (n = 243) who underwent SGUS in our primary Sjögren's syndrome expertise center. Clinical diagnosis by the treating physician was used as the gold standard. Separate analyses were performed for patients who underwent labial or parotid gland biopsies. The average score for hypoechogenic areas in 1 parotid and 1 submandibular gland was determined (range 0–3). Next, performance of the ACR/EULAR criteria was evaluated after addition of SGUS or replacement of current items by SGUS.

Results. Receiver operating characteristic analysis showed an optimal cutoff value of ≥1.5 for SGUS. The optimal weight for SGUS positivity was 1. Cutoff for ACR/EULAR fulfilment remained ≥4. In patients who underwent a labial gland biopsy (n = 124), the original criteria showed an area under the curve (AUC) of 0.965, sensitivity of 95.9%, and specificity of 92.2%. After the addition of SGUS, the AUC was 0.966, with a sensitivity of 97.3% and specificity of 90.2%. In patients who underwent a parotid gland biopsy (n = 198), similar results were found. Sensitivity of the criteria decreased substantially when SGUS replaced salivary gland biopsy or anti-SSA antibodies, while performance remained equal when SGUS replaced the ocular staining score, Schirmer's test, or unstimulated whole saliva flow.

Conclusion. Validity of the ACR/EULAR criteria remains high after incorporation of SGUS. With SGUS, clinicians are offered a larger array of tests to evaluate fulfillment of the ACR/EULAR criteria.

INTRODUCTION

Primary Sjögren's syndrome (SS) is a common systemic autoimmune disease affecting the exocrine glands, manifesting as keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) (1,2). Patients also often experience fatigue and several extraglandular manifestations (2).

Several classification criteria sets for primary SS have been developed during recent years. Of these, the 2002 American European Consensus Group (AECG) criteria have most often

been used in daily clinical practice for many years (3–5). Cornerstones of this criteria set are a focus score ≥1 in a salivary gland biopsy and the presence of anti-SSA/anti-SSB antibodies (3). These criteria take both subjective sicca symptoms and objective measures for the ocular and oral symptoms into account so that equal weights are assigned to the oral and ocular components (3). However, the AECG criteria have not been endorsed by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) (4,5). In an effort to reach international consensus regarding classification criteria for primary

SIGNIFICANCE & INNOVATIONS

- Salivary gland ultrasonography (SGUS) can be added to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria or replace the ocular staining score, Schirmer's test, or unstimulated whole saliva flow.
- The optimal weight of SGUS in the ACR/EULAR criteria is 1. The optimal cutoff of the modified ACR/EULAR score remains ≥4.
- The validity of the ACR/EULAR criteria remains high after incorporation of SGUS.
- The modified criteria enable a stepwise approach for classification, starting with anti-SSA antibodies and SGUS.

SS, recently the 2016 ACR/EULAR criteria were developed, consisting of items from the 2002 AECG and the 2012 ACR criteria (3–6). Both EULAR and the ACR have endorsed the ACR/EULAR criteria, and the criteria have been validated in multiple external cohorts (7–9). The ACR/EULAR criteria show high sensitivity and specificity regardless of the type of biopsy (parotid or labial) taken to assess the salivary gland focus score (8).

Upon a closer look at the ACR/EULAR criteria, a few key points become evident. First, salivary gland histopathology and the presence of anti-SSA antibodies deservedly remain cornerstones in the classification of primary SS. Second, tear gland involvement is measured using a functional test (Schirmer's test) and by imaging of structural damage of the ocular surface (ocular staining score [OSS]), while salivary gland involvement is only evaluated using a functional test (unstimulated whole saliva flow [UWS]). Removal of sialography and scintigraphy from the criteria is an advantage of the ACR/EULAR criteria, considering the invasiveness and limited validity of these procedures (4,10–12). However, the ACR/EULAR criteria now lack a test that measures structural salivary gland damage.

Currently, B-mode salivary gland ultrasonography (SGUS) is increasingly applied to assess structural changes of the salivary glands in primary SS. SGUS is noninvasive, nonirradiating, inexpensive, relatively easy to perform in an outpatient setting, and can be repeated for follow-up. Previous studies have demonstrated that SGUS has good accuracy to differentiate primary SS from nonprimary SS (9,13–17). Many scoring systems are applied for SGUS, but recent analyses have shown that limiting scoring to hypoechogenic areas in both the submandibular and parotid gland on 1 side suffices for accurate differentiation between primary SS and nonprimary SS (18). Scoring of hypoechogenic areas showed good intra- and interobserver reliability (19,20). This reduction of the scoring system further increases the feasibility of the technique for common application in a diagnostic setting.

In clinical cohort studies, the addition of SGUS to the AECG and ACR criteria has been shown to increase the sen-

sitivity of these criteria, with a minor decrease in their specificity (10,21). Unfortunately, SGUS was not tested as a new diagnostic technique in the cohorts in which the ACR/EULAR criteria were developed and validated and not considered to be included in the criteria. Therefore, our primary objective was to assess whether the presence of hypoechogenic areas on SGUS as a criteria item influences the performance of the ACR/EULAR criteria. The second objective was to evaluate the performance of the ACR/EULAR criteria when replacing current items with SGUS. Both objectives were evaluated in a large cohort of patients clinically suspected of primary SS.

PATIENTS AND METHODS

Study population. The study population for this cohort study consisted of all eligible consecutive patients who underwent an SGUS examination in the University Medical Center Groningen between October 2014 and July 2017. SGUS was performed as a routine diagnostic imaging technique in new patients clinically suspected of primary SS as well as during baseline visits of primary SS patients included in the Efficacy and Safety of Abatacept in Patients With Primary Sjögren's Syndrome phase III trial (NCT02067910) or the Registry of Sjögren's Syndrome in the University Medical Center Groningen: Longitudinal observational cohort study.

Exclusion criteria were age <18 years, the presence of an associated systemic autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus), or current use of biologic disease-modifying antirheumatic drugs. Patients lacking a clinical diagnosis and patients with an incomplete diagnostic evaluation according to the ACR/EULAR criteria were also excluded. The clinical diagnosis by experienced treating physicians was used as the gold standard in all analyses. If a diagnosis was not clearcut, consensus was achieved by consulting at least 1 other experienced physician. This study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Medical Ethics Committee of the University Medical Center Groningen (METc 2018/309), which waived the requirement of written informed consent.

SGUS. SGUS was performed using the MyLabSeven scanner (Esaote), equipped with a high-resolution linear probe (4–13 MHz). All SGUS images were scored by JFvN, KD, or AJS, who previously showed good interobserver agreement when scoring hypoechogenic areas (19). Median intraclass correlation coefficients were 0.74 for parotid glands and 0.71 for submandibular glands. The presence of hypoechogenic areas was scored as: 0 = no hypoechogenic areas, 1 = a few scattered areas, 2 = several areas, and 3 = numerous hypoechogenic areas (17). The average score for the presence of hypoechogenic areas (range 0–3) in the submandibular and parotid gland on the right side was deter-

mined, which was previously shown to accurately differentiate between primary SS and nonprimary SS (18). If the right parotid or submandibular gland could not be scored (e.g., because of previous removal of that gland), scores of the left side were used. Receiver operating characteristic analysis was used to determine the optimal cutoff value for SGUS to identify patients who were clinically diagnosed with primary SS by the treating physicians by choosing the cutoff for which the sum of sensitivity and specificity was the highest.

Classification according to the original ACR/EULAR criteria. All included patients had been subjected to a complete multidisciplinary evaluation according to the ACR/EULAR criteria (4,5), including a labial gland biopsy, a parotid gland biopsy, or both. Separate analyses were performed, in which classification according to the ACR/EULAR criteria was determined using the outcomes of either labial or parotid gland biopsy results. Patients who underwent both a labial and parotid gland biopsy were included in both analyses, with the results of either their labial or parotid gland biopsy being used to determine the ACR/EULAR classification.

Incorporation of SGUS into the ACR/EULAR criteria. SGUS positivity was added as an item to the ACR/EULAR criteria. To keep the original criteria applicable, the weight of the original criteria items was kept as they were, i.e., 3 points for the presence of anti-SSA antibodies and a focus score ≥1; and 1 point for an abnormal UWS, Schirmer's test, and OSS score (4,5). To select the optimal weight of SGUS, separate analyses of the performance of the modified ACR/EULAR criteria were performed, assigning a weight of either 1, 2, or 3 points for a positive SGUS.

Replacement of current ACR/EULAR criteria items by ultrasound. Next, 5 additional criteria sets were developed, in which SGUS replaced 1 of the current items. The weight of the original items was again kept equal to the original criteria, and the optimal weight of the SGUS item was determined by doing separate analyses using a weight of 1, 2, or 3 points for a positive SGUS.

Statistical analysis. Statistical analyses were executed using SPSS software, version 23. Receiver operating characteristic analysis was performed to determine the accuracy of the original ACR/EULAR score, the ACR/EULAR score with the addition of SGUS, and the ACR/EULAR score with SGUS as replacement of original items to predict the clinical diagnosis. The area under the curve (AUC) was interpreted as no discrimination (0 to 0.5), or with the accuracy judged as poor (>0.5 to 0.7), fair (>0.7 to 0.8), good (>0.8 to 0.9), or excellent (>0.9 to 1.0) (22). Optimal cutoff values of the different ACR/EULAR scores were determined by choosing the cutoff for which the sum of sensitivity and specificity was the highest. Patients were then classified according to this cutoff for the original and modified criteria sets. Finally, absolute agreement, sensitivity, and specificity of the original and modified ACR/EULAR criteria sets, with clinical diagnosis as the gold standard, were determined and compared.

RESULTS

SGUS was performed in 363 patients. Of these, 243 patients were eligible for inclusion (Figure 1). Of the 243 included patients, 45 underwent only a labial biopsy, 119 underwent only a parotid gland biopsy, and 79 underwent both a labial and parotid gland
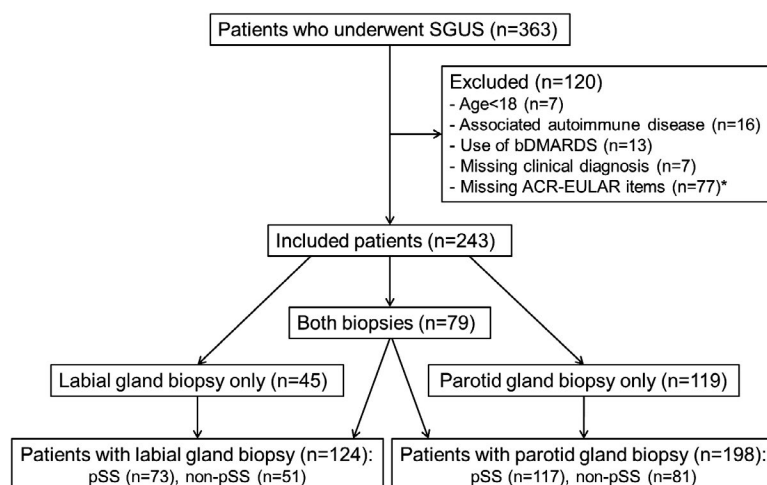
Figure 1. Flow chart of patient inclusion. * = missing items were salivary gland biopsy (n = 72), Schirmer's test (n = 4), ocular staining score (n = 2), and unstimulated whole saliva flow (n = 2). In the majority of these patients, either the patients could be classified as primary Sjögren's syndrome (pSS) without the need of a positive salivary gland biopsy result, or a positive biopsy result would not have resulted in a clinical diagnosis of primary SS. SGUS = salivary gland ultrasound; bDMARDs = biologic disease-modifying antirheumatic drugs; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.

Table 1. Characteristics of study population*

Characteristics	Primary SS (n = 147)	Nonprimary SS (n = 96)
Age, mean ± SD years	53 ± 14	52 ± 14
Female sex	131 (89)	81 (84)
SGUS score, median (IQR)	2.0 (1.0–2.5)	0.5 (0.5–1.0)
SGUS score ≥1.5	106 (72)	10 (10)
FS ≥1 in labial gland biopsy†	64 (88)	5 (10)
FS ≥1 in parotid gland biopsy‡	89 (76)	2 (2)
Anti-SSA positive	125 (85)	9 (9)
Ocular staining score ≥5	70 (48)	11 (12)
Schirmer ≤5 mm/5 minute	113 (77)	56 (58)
Unstimulated whole saliva ≤0.1 ml/minute	105 (71)	42 (44)

* Values are the number (%) unless indicated otherwise. SS = Sjögren's syndrome; SGUS = salivary gland ultrasonography; IQR = interquartile range; FS = focus score (foci/4 mm^2).
† N = 124 (73 primary SS, 51 nonprimary SS).
‡ N = 198 (117 primary SS, 81 nonprimary SS).

biopsy. Including the patients who underwent both biopsies, 124 underwent a labial biopsy, and 198 underwent a parotid gland biopsy.

Characteristics of patients with primary SS and nonprimary SS are shown in Table 1. All included patients fulfilled the entry criteria of the ACR/EULAR criteria. The characteristics of the patients who underwent a labial gland biopsy were similar to those of the patients who underwent a parotid gland biopsy (data not shown). The median time between SGUS and salivary biopsies was 7 months for labial gland biopsies and 6 months for parotid gland biopsies.

Performance of SGUS. The accuracy of SGUS to predict clinical diagnosis was good, with an AUC of 0.860 (95% confidence interval [95% CI] 0.821–0.900), and an optimal cutoff value of ≥1.5. SGUS was therefore considered positive when the average score for the presence of hypoechogenic areas in 1 parotid and 1 submandibular gland was ≥1.5. Based on this cutoff point, SGUS was positive in 106 patients with primary SS and 6 patients with nonprimary SS and negative in 41 patients with primary SS and 90 patients with nonprimary SS. Absolute agreement with clinical diagnosis was 80.7%, sensitivity was 72.1%, and specificity was 93.8%.

Performance of ACR-EULAR criteria with addition of SGUS. Supplementary Table 1, parts A and B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24017/abstract, shows the performance of the ACR/EULAR criteria when SGUS was added to the criteria, using a weight of 1, 2, or 3 for a positive SGUS. The performance of the ACR/EULAR criteria including SGUS was highest when a positive SGUS was assigned a weight of 1 point. The optimal cutoff point of the original ACR/EULAR score to discriminate between primary SS and nonprimary SS was

confirmed to be ≥4. After the addition of SGUS to the ACR/EULAR criteria with a weight of 1 point, the optimal cutoff point of the modified ACR/EULAR score to discriminate between primary SS and nonprimary SS remained ≥4 (see Supplementary Table 1, parts A and B, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24017/abstract). Based on these results, in the following analyses a cutoff of ≥4 was used for the original and modified ACR/EULAR score. A positive SGUS results in an increase of 1 point in the modified ACR/EULAR score (Table 2, parts A and B).

In patients who underwent a labial gland biopsy (n = 124), the original ACR/EULAR criteria showed an AUC of 0.965 (95% CI 0.932–0.997) to predict clinical diagnosis (Figure 2). Absolute agreement with clinical diagnosis was 94.4%, sensitivity was 95.9%, and specificity was 92.2%. After the addition of SGUS, the modified ACR/EULAR criteria showed an AUC of 0.966 (95% CI 0.934–0.998), absolute agreement remained the same, sensitivity slightly increased to 97.3%, and specificity slightly decreased to 88.2%.

The same analyses were performed in patients who underwent a parotid gland biopsy (n = 198), and similar results were found (Figure 2). In this group, the original criteria showed an AUC of 0.954 (95% CI 0.925–0.984) to predict clinical diagnosis. Absolute agreement with clinical diagnosis was 92.9%, sensitivity was 91.4%, and specificity was 95.1%. After the addition of SGUS, the modified ACR/EULAR criteria showed an AUC of 0.964 (95% CI 0.939–0.989), absolute agreement remained the same, sensitivity slightly increased to 92.3%, and specificity slightly decreased to 93.8%. To summarize, the addition of SGUS to the ACR/EULAR criteria resulted in negligible changes in the performance of the criteria and did not change its optimal cutoff point.

Table 2. Original and modified ACR/EULAR criteria incorporating salivary gland ultrasound*

Item	Weight, points
Original ACR/EULAR criteria	
Focal lymphocytic sialadenitis and FS ≥1	3
Anti-SSA positive	3
OSS ≥5 in at least 1 eye	1
Schirmer's test ≤5 mm/5 minutes in at least 1 eye	1
UWS flow rate ≤0.1 ml/minute	1
Modified ACR/EULAR criteria: addition of ultrasound	
Focal lymphocytic sialadenitis and FS ≥1	3
Anti-SSA positive	3
OSS ≥5 in at least 1 eye	1
Schirmer's test ≤5 mm/5 minute in at least 1 eye	1
UWS flow rate ≤0.1ml/minute	1
Average SGUS score for hypoechogenic areas ≥1.5	1

* For both sets, patients with a score of ≥4 are classified as primary Sjögren's syndrome. ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; FS = focus score (foci/4 mm^2); OSS = ocular staining score; UWS = unstimulated whole saliva flow; SGUS = salivary gland ultrasonography.
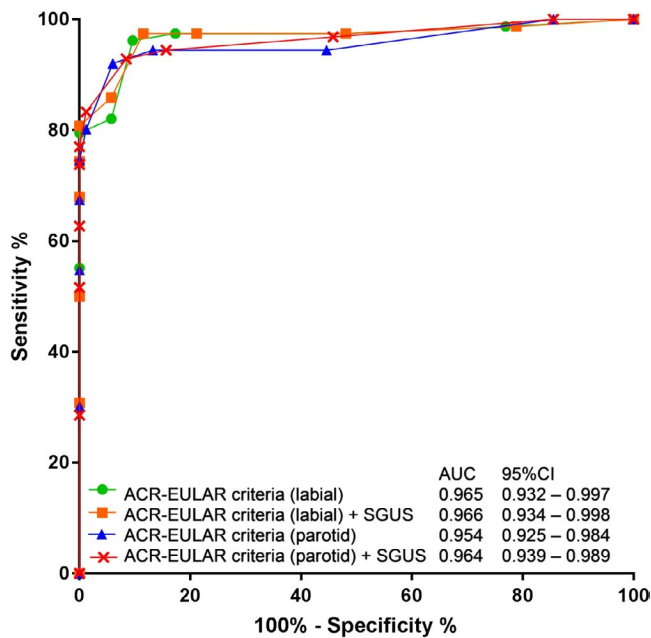
Figure 2. Receiver operating characteristic curves of the original American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria and adjusted criteria with the addition of salivary gland ultrasonography (SGUS). AUC = area under the curve; 95% CI = 95% confidence interval.

Performance of ACR-EULAR criteria with replacement of items by SGUS. For the following analysis, 5 modified sets of criteria were used, in which one of the original items was replaced with SGUS. When SGUS replaced current criteria items in patients who underwent a labial gland biopsy (n = 124), the optimal weight for SGUS was again 1 point, regardless of which original criteria item was replaced by SGUS (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley. com/doi/10.1002/acr.24017/abstract). The optimal cutoff point to discriminate between primary SS and nonprimary SS remained ≥4.

When SGUS replaced the labial gland biopsy or anti-SSA antibodies, there was a considerable decrease in accuracy and sensitivity, while there was only a slight decrease in specificity compared to the original criteria (Table 3A and Figure 3A). On the other hand, when SGUS replaced the OSS, Schirmer's test, or UWS, no major changes in accuracy, sensitivity, and specificity occurred.

The same analyses were performed in patients who underwent a parotid gland biopsy (n = 198). When SGUS replaced the OSS, Schirmer's test, or UWS, the optimal weight for SGUS was again 1 point (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley. com/doi/10.1002/acr.24017/abstract), with only minor changes in sensitivity and specificity and even an increase in accuracy (Table 3B and Figure 3B). When SGUS replaced the parotid gland biopsy or anti-SSA antibodies, the optimal weight for SGUS was 3 points. However, regardless of whether SGUS was assigned 1, 2, or 3 points in these analyses, accuracy of the ACR/EULAR criteria dropped substantially (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/ acr.24017/abstract).

To summarize, SGUS can replace the OSS, Schirmer's test, or UWS in the classification of primary SS without major changes in the performance of the criteria. The salivary gland biopsy or the measurement of anti-SSA antibodies, on the other hand, cannot be completely replaced by SGUS since this replacement led to a considerable decrease in the performance of the criteria.

DISCUSSION

In this large clinical cohort study, we aimed to investigate the performance of the ACR/EULAR criteria when a positive SGUS was added to the criteria. The performance of the ACR/EULAR criteria was best when SGUS was assigned a weight of 1 point.

Table 3. Performance of the original and modified ACR/EULAR criteria sets with salivary gland ultrasonography (SGUS) replacing current items*

	AUC	95% CI	Agreement	Sensitivity	Specificity
Patients with labial gland biopsy (n = 124)					
Original ACR/EULAR criteria	0.965	0.932–0.997	94.4	95.9	92.2
SGUS replacing labial gland biopsy	0.903	0.849–0.957	87.9	82.2	94.1
SGUS replacing anti-SSA antibodies	0.943	0.902–0.985	89.5	86.3	94.1
SGUS replacing OSS	0.964	0.931–0.996	93.5	95.9	88.2
SGUS replacing Schirmer's test	0.969	0.938–1.000	93.5	94.5	92.2
SGUS replacing UWS	0.967	0.937–0.998	93.5	97.3	88.2
Patients with parotid gland biopsy (n = 198)					
Original ACR/EULAR criteria	0.954	0.925–0.984	92.9	91.4	95.1
SGUS replacing parotid gland biopsy	0.925	0.887–0.962	88.4	83.8	95.1
SGUS replacing anti-SSA antibodies	0.918	0.879–0.956	86.9	79.5	97.5
SGUS replacing OSS	0.964	0.938–0.990	93.4	92.3	95.1
SGUS replacing Schirmer's test	0.964	0.939–0.989	89.9	84.6	97.5
SGUS replacing UWS	0.969	0.946–0.992	92.9	90.6	96.3

* Values are the percentage unless indicated otherwise. In all criteria sets, a weight of 1 point for SGUS and cutoff value of ≥4 for fulfilment of the criteria was used. ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; AUC = area under the curve; 95% CI = 95% confidence interval; OSS = ocular staining score; UWS = unstimulated whole saliva flow.
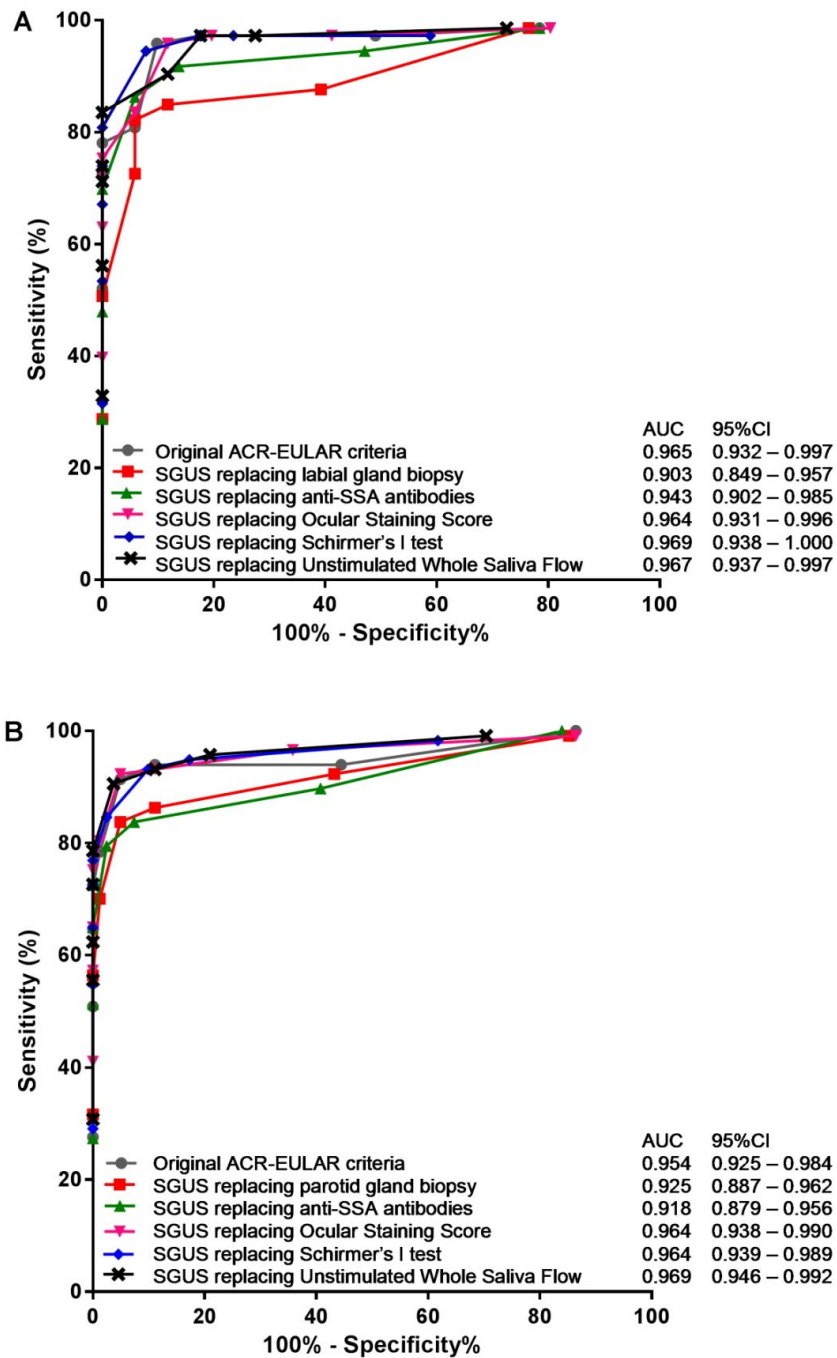
Figure 3. Receiver operating characteristic curves of the original American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria and adjusted criteria with replacement of original items by salivary gland ultrasonography (SGUS). **A**, ACR/EULAR criteria including labial gland biopsy outcome. **B**, ACR/EULAR criteria including parotid gland biopsy outcome. AUC = area under the curve; 95% CI = 95% confidence interval.

In the first part of this study, we showed that addition of SGUS to the ACR/EULAR criteria only marginally increased sensitivity and marginally decreased specificity, while overall accuracy remained the same. Although the addition of SGUS did not improve the accuracy of the ACR/EULAR criteria in our cohort, it improves their feasibility in clinical practice, by allowing rheumatologists to choose from a larger array of tests.

Previously, 2 other studies incorporated SGUS in the ACR/EULAR classification criteria (23,24). In the study by Le Goff et al (23), in which the AECG and ACR/EULAR classification criteria were compared, the addition of SGUS to the ACR/EULAR criteria was also investigated. However, the authors arbitrarily assigned a weight of 1 point to a positive SGUS and used the same cutoff value as the original ACR/EULAR criteria (i.e., ≥4).

In our study, we confirmed statistically that the optimal weight to assign to SGUS was indeed 1 point and that the optimal cutoff value to classify a patient as having primary SS remained ≥4. In the study by Le Goff et al (23), similar results were found regarding the performance of the ACR/EULAR criteria after addition of SGUS, i.e., sensitivity was slightly increased and specificity slightly decreased.

In the study by Takagi et al (24), the weight of the original criteria items was also kept. In contrast to our study, 3 points were assigned to SGUS positivity, and the optimal cutoff point to discriminate between SS and non-SS increased to ≥5. The combined ACR/EULAR and SGUS scoring system showed an improved accuracy compared to the original criteria. Unfortunately, a fair comparison between the study of Takagi et al (24) and ours cannot be made since the methodology of their study differed greatly from ours. Importantly, complete data regarding the ACR/EULAR items were only available in a small subset of the included patients (62 of 213 patients); Saxon's test, which measures stimulated whole saliva, was used instead of UWS, and patients with secondary SS were not excluded. Furthermore, a different, more complicated SGUS score was used.

In the second part of this study, the performance of the ACR/EULAR criteria was evaluated when SGUS replaced current classification items. We found that SGUS could replace the OSS, Schirmer's test, or UWS in the classification of primary SS without decreasing the accuracy of the ACR/EULAR criteria. However, when SGUS replaced the salivary gland biopsy in the classification of primary SS or the measurement of anti-SSA antibodies, the performance of the criteria significantly decreased.

In a previous study, we showed that the combination of a positive SGUS and the presence of anti-SSA antibodies had a positive predictive value of 97% for classification as primary SS, according to the ACR/EULAR criteria (14). Based on these results, Mossel et al suggested that for classification purposes, the first step of a classification evaluation could be SGUS and determination of anti-SSA positivity. When both are positive, patients can already be classified as primary SS. The current study confirms these results because the combination of anti-SSA positivity and SGUS positivity is indeed enough for fulfillment of the adjusted ACR/EULAR criteria. As the next step in the evaluation for classification, we recommend a salivary gland biopsy since the sensitivity of the ACR/EULAR criteria decreased substantially when the salivary gland biopsy was completely replaced by SGUS. When it comes to clinically diagnosing a patient with primary SS, on the other hand, we prefer a full evaluation, including SGUS and as many items of the ACR/EULAR criteria as possible, to allow a clinician to decide on the best possible treatment for that particular patient.

When SGUS is added to the ACR/EULAR criteria, the cutoff of 4 points can be fulfilled solely based on Schirmer's test, OSS, UWS, and SGUS. In our database, this combination only occurred in 1 patient, who was clinically diagnosed as non-SS. Therefore, we cannot draw a definite conclusion about the validity of the ACR/EULAR criteria in this specific subgroup. Based on our expert opinion, we would recommend only classifying such a patient as primary SS if a positive biopsy result or anti-SSA antibodies are also present until there are more data available regarding this subgroup.

In this study, we used a simplified SGUS scoring system, similar to the ones used by other groups (15,21,23). However, the lack of a consensus scoring system complicates the incorporation of SGUS into the ACR/EULAR criteria. Jousse-Joulin et al (20) recently published an atlas with consensual definitions of SGUS abnormalities. The next step will be to agree on a consensus scoring system with a validated cutoff. As soon as a validated cutoff is set, SGUS hopefully will be incorporated into the ACR/EULAR criteria. The addition of SGUS, as a measure for structural damage of the salivary glands, would balance the ACR/EULAR criteria by including 2 items to measure tear as well as salivary gland involvement.

A strong point of our study is the use of a large cohort of patients from daily clinical practice, including patients with primary SS as well as nonprimary SS sicca, with complete data for all ACR/EULAR items. Furthermore, analyses were performed separately for patients who underwent a labial and/or a parotid gland biopsy, which makes our data relevant to all diagnostic centers regardless of the type of biopsy performed. A potential limitation of the study is the use of clinical diagnosis performed by expert clinicians working in a tertiary referral center for primary SS, instead of expert consensus, as the gold standard. However, using expert consensus as the gold standard would also have introduced bias depending on the familiarity of the experts with SGUS in primary SS.

In conclusion, the validity of the ACR/EULAR criteria remains high after incorporation of SGUS. SGUS is noninvasive, nonirradiating, inexpensive, and relatively easy to perform in an outpatient setting and could replace OSS, Schirmer's test, or UWS in centers with less access to these tests. Incorporation of SGUS into the ACR/EULAR criteria improves their feasibility in clinical practice by allowing rheumatologists to choose from a larger array of tests. The modified criteria enable a step-wise approach for classification, starting with determination of anti-SSA antibodies and SGUS, which decreases the number of invasive salivary gland biopsies needed for classification.

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