

Weight of salivary-gland ultrasonography compared to other items of the 2016 ACR/EULAR classification criteria for Primary Sjögren's Syndrome

Jousse-Joulin, Sandrine; Gatineau, Florence; Baldini, Chiara; Baer, Alan; Barone, Francesca; Bootsma, Hendrika ; Bowman, Simon; Brito-Zeron, Pilar; Cornec, Divi; Dorner, Thomas; de Vita, Salvatore; Fisher, Benjamin; Hammenfors, Daniel; Jonsson, Malin; Mariette, Xavier; Milic, Vera; Nakamura, Hideki; Ng, Wan-Fai; Nowak, Emmanuel; Ramos-Casals, Manuel

DOI:

[10.1111/joim.12992](https://doi.org/10.1111/joim.12992)

License:

Other (please specify with Rights Statement)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Jousse-Joulin, S, Gatineau, F, Baldini, C, Baer, A, Barone, F, Bootsma, H, Bowman, S, Brito-Zeron, P, Cornec, D, Dorner, T, de Vita, S, Fisher, B, Hammenfors, D, Jonsson, M, Mariette, X, Milic, V, Nakamura, H, Ng, W-F, Nowak, E, Ramos-Casals, M, Rasmussen, A, Seror, R, Shiboski, C, Nakamura, T, Vissink, A, Saraux, A & Devauchelle-Pensec, V 2019, 'Weight of salivary-gland ultrasonography compared to other items of the 2016 ACR/EULAR classification criteria for Primary Sjögren's Syndrome', *Journal of Internal Medicine*.
<https://doi.org/10.1111/joim.12992>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

This is the peer reviewed version of the following article: Jousse-Joulin, S, Gatineau et al, on behalf of the EULAR US-pSS Task Force. Weight of salivary gland ultrasonography compared to other items of the 2016 ACR/EULAR classification criteria for Primary Sjögren's syndrome. *J Intern Med* 2019; <https://doi.org/10.1111/joim.12992>., which has been published in final form at <https://onlinelibrary.wiley.com/doi/full/10.1111/joim.12992> This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 19. Apr. 2024

Weight of Salivary-Gland Ultrasonography compared to Other items of the 2016

ACR/EULAR Classification Criteria for Primary Sjögren's Syndrome

Sandrine Jousse-Joulin¹, Florence Gatineau², Chiara Baldini³, Alan Baer⁴, Francesca Barone⁵, Hendrika Bootsma⁶, Simon Bowman⁷, Pilar Brito-Zerón⁸, Divi Cornec¹, Thomas Dorner⁹, Salvatore de Vita¹⁰, Benjamin Fisher⁵, Daniel Hammenfors¹¹, Malin Jonsson¹², Xavier Mariette¹³, Vera Milic¹⁴, Hideki Nakamura¹⁵, Wan-Fai Ng¹⁶, Emmanuel Nowak², Manuel Ramos-Casals⁸, Astrid Rasmussen¹⁷, Raphaelae Seror¹³, Caroline H Shiboski¹⁸, Takashi Nakamura¹⁹, Arjan Vissink²⁰, Alain Saraux¹, and Valerie Devauchelle-Pensec¹, on behalf of the EULAR US-pSS Task Force

1 Rheumatology department, Cavale Blanche Hospital and Brest Occidentale University, INSERM UMR 1227, Brest, FRANCE

2 INSERM CIC 1412, Brest Medical University Hospital, Brest, FRANCE

3 Rheumatology unit, University of Pisa, Pisa, ITALY

4 Department of Medicine (Rheumatology), Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA

5 Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

6 Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Centre Groningen, Groningen, THE NETHERLANDS

7 Department of Rheumatology, University Hospitals, Birmingham NHS Trust, Birmingham, UK

8 Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona, SPAIN

- 9 Department of Medicine, Rheumatology and Clinical Immunology, Charite
Universitätsmedizin Berlin and DRFZ Berlin, GERMANY
- 10 Clinic of Rheumatology, Department of Medical and Biological Sciences, University
Hospital “Santa Maria della Misericordia”, Udine, ITALY
- 11 Department of Rheumatology, Haukeland University Hospital, Norway,
and Department of Clinical Science – Section for Rheumatology, University of Bergen,
NORWAY
- 12 Department of Clinical Dentistry – Section for Oral and Maxillofacial Radiology,
University of Bergen, Bergen, NORWAY
- 13 Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance
Publique, Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre,
Université Paris Sud, INSERM, Paris, FRANCE
- 14 Institute of Rheumatology, School of Medicine, University of Belgrade, Belgrade,
SERBIA
- 15 Department of Immunology and Rheumatology, Unit of Advanced Medical Sciences,
Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School
of Biomedical Sciences, Nagasaki City, Nagasaki 852-8501, JAPAN
- 16 Institute of Cellular Medicine, Newcastle University & NIHR Newcastle Biomedical
Research Centre, Newcastle upon Tyne, NE2 4HH, UK
- 17 Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research
Foundation, Oklahoma City, Oklahoma, USA
- 18 Department of Orofacial Sciences, School of Dentistry, University of California, San
Francisco, California, USA
- 19 Department of Radiology and Cancer Biology, Nagasaki University Graduate School of
Biomedical Sciences, Nagasaki 852-8588, JAPAN

20 Department of Oral and Maxillofacial Surgery, University of Groningen, University
Medical Centre Groningen, Groningen, THE NETHERLANDS

Corresponding author: Valérie Devauchelle-Pensec, Rheumatology department, Cavale
Blanche Hospital and Brest Occidentale University, EA 2216, ERI 29, Brest, FRANCE

Phone: +33 298 347 264

E-mail: valerie.devauchelle-pensec@chu-brest.fr

Keywords: Ultrasonography. Salivary glands. Primary Sjögren's syndrome. Diagnosis.
Classification criteria.

Financial support: None of the authors had financial interest which could create a potential
conflict of interest with this work

Short title:

Contribution of Adding Salivary-Gland Ultrasonography to 2016 ACR/EULAR

Classification Criteria for Primary Sjögren's Syndrome

Five key words:

Ultrasonography. Salivary glands. Primary Sjögren's syndrome. Diagnosis. Classification
criteria

ABSTRACT

OBJECTIVE: Major Salivary gland ultrasonography (SGUS) is widely used for the diagnosis of primary Sjögren's syndrome (pSS). Our objective was to assess the contribution of SGUS compared to other items of the 2016 ACR/EULAR pSS classification criteria, based on expert opinion.

METHODS: A secure web-based relational database was used by 24 experts from 14 countries to assess 512 realistic vignettes developed from data of patients with suspected pSS. Each vignette provided classification criteria items and information on history, clinical symptoms, and SGUS findings. Each expert assessed 64 vignettes and each vignette was assessed by 3 experts. A diagnosis of pSS was defined according to at least 2 of 3 experts. Validation was performed in the independent French DiapSS cohort of patients with suspected pSS.

RESULTS: A criteria-based pSS diagnosis and SGUS findings were independently associated with an expert diagnosis of pSS ($p < 0.001$). The derived diagnostic weights of individual items in the 2016 ACR/EULAR criteria including SGUS were : anti-SSA, 3; focus score ≥ 1 , 3; SGUS score ≥ 2 , 1; positive Schirmer's test, 1; dry mouth, 1; and salivary flow rate < 0.1 mL/min, 1. The corrected C statistic area under the curve for the new weighted score was 0.96. Adding SGUS improve the sensitivity from 90.2 % to 95.6% with a quite similar specificity 84.1% versus 82.6%. Results were similar in the DiapSS cohort: adding SGUS improve the sensitivity from 87% to 93%.

CONCLUSION: SGUS had similar weight compared to minor items and its addition improves the performance of the 2016 ACR/EULAR classification criteria.

INTRODUCTION

Lymphocytic infiltration of the salivary glands (SGs) is a key pathologic feature of primary Sjögren's syndrome (pSS) (1, 2). Currently available tools for assessing the SGs include salivary flow measurement, minor labial salivary gland (LSG) biopsy (3, 4), sialography, and scintigraphy (5). In addition, salivary gland ultrasonography (SGUS) holds considerable appeal (6), as it is non-invasive, non-irradiating, and can be repeated as an outpatient investigation (7-9). Many researchers and clinicians have identified SGUS as a valuable diagnostic tool and potential criteria item for disease classification of pSS (10-14).

The 2016 ACR/EULAR classification criteria set for pSS was developed and validated using three international patient cohorts (15, 16). The set includes five weighted items: focal lymphocytic sialadenitis with a focus score (FS) ≥ 1 by LSG and presence of anti-SSA(Ro) antibodies are each weighted 3 and considered to be major items; whereas a positive ocular staining score (OSS ≥ 5), positive Schirmer's test (≤ 5 mm/5 min), and unstimulated whole salivary (UWS) flow rate ≤ 0.1 mL/min each have a weight of 1. These criteria are designed to be applied only to patients who have subjective ocular and/or oral dryness and/or a positive item on the EULAR Disease Activity Index for pSS (ESSDAI) (17). A score ≥ 4 indicates pSS.

However, the diagnosis and classification of pSS continue to be challenging, as many other conditions can produce similar presentations. Continued efforts to improve current criteria sets are therefore warranted to increase diagnostic accuracy and decrease time to diagnosis.

Adding SGUS as a criterion has been reported to improve the performance of classification criteria (18). In a cohort of patients with suspected SS, adding SGUS to the American-European Consensus Group (AECG) criteria set increased sensitivity from 77.9%

to 87%, and similar results were obtained with the 2016 ACR/EULAR classification criteria (10, 19). Many of the patient cohorts used to develop and validate the 2016 ACR/EULAR criteria were initiated in the early 2000s, and none was assessed using SGUS, whose metrological properties were unknown at the time. Consequently, inclusion of SGUS in the criteria set was not possible (15, 16). However, the ACR and EULAR used a well-defined and established method with which they had already acquired experience when developing criteria for rheumatoid arthritis and scleroderma. This method assigns weights to each criterion in the set, thereby allowing the subsequent addition of criteria provided they are assigned the appropriate weights.

The international EULAR US-pSS Task Force was created in 2012 with the objectives of standardizing SGUS (13, 20, 21), maximizing its usefulness in pSS, developing a reliable SGUS scoring system, and assessing the addition of an SGUS score to pSS classification criteria sets according to OMERACT and EULAR recommendations. Experts were considered for this task force if they worked with SS centers for excellence and were involved in active published research on pSS. Meetings and projects were designed each year at ACR and EULAR meetings to evaluate the metrological properties of SGUS (20-22), create an atlas, and develop a consensual score (21). The score assesses greyscale (B-mode) homogeneity lesions (21) for each of the four major SGs (two parotid and two submandibular glands), focusing on anechoic/hypoechoic foci as follows: 0, no lesions; 1, hypo/anechoic areas occupying less than 25% of the gland surface area; 2, hypo/anechoic areas occupying 25% to 50% of the gland surface area; 3, hypo/anechoic areas occupying more than 50% of the gland surface area; and 4, hypo/anechoic areas occupying the entire gland surface area. **A score ≥ 2 is associated with Sjogren.**

The objective of the UTOPIA (Ultrasound TO diagnose and classify PrImAry Sjögren's syndrome) study reported here was to evaluate the weight that should be assigned

to SGUS if added to the 2016 ACR/EULAR pSS classification criteria set. To this end, an international panel of pSS experts examined clinical vignettes. Our working hypothesis was that SGUS could be used in a standardized manner to evaluate patients with pSS in both daily practice and clinical trials.

METHOD

We used data from patients with suspected pSS to develop realistic clinical vignettes. Experts assessed the vignettes and determined whether they indicated probable or definitive pSS. Potential effects on this expert pSS diagnosis of adding SGUS findings to the available information were evaluated (17).

Design of the vignettes

A rheumatologist (CB) collected the main demographic data and signs of pSS from the Sjögren's Clinic database at the University of Pisa, Italy (23, 24). This step considered only patients for whom all relevant data were available, including the 2016 ACR/EULAR classification criteria, systemic manifestations, and SGUS findings. Controls were patients referred for suspected pSS in whom a comprehensive workup did not support a diagnosis of pSS.

Concerning the vignette: Each feature was assigned a weight based on its frequency in the patient cohort (e.g., sex, age, parotid gland enlargement, and systemic manifestations including inflammatory arthritis, cytopenia, interstitial lung disease, peripheral neuropathy, and Raynaud's phenomenon).

A computer algorithm designed by one of us (FG) determined all possible combinations of the 2016 ACR/EULAR classification criteria (ocular and oral dryness, anti-

SSA antibodies positive vs. negative, Schirmer's test $>$ vs. ≤ 5 mm/5 min, LSG with FS <1 vs. ≥ 1 , UWS flow rate $>$ vs. ≤ 0.1 mL/min, and OSS <5 vs. ≥ 5), disease duration <3 years or ≥ 3 years, and standardized SGUS score <2 vs. ≥ 2 . These variables were handled in the vignette as a binary variable. The number of combinations was 512, and 512 vignettes were therefore created.

Each vignette (supplementary file) provided information on the medical history (symptom duration, sex, age), clinical symptoms (ocular and oral dryness), and systemic manifestations (see above). In each vignette, the patient had subjective ocular and/or oral dryness or a systemic manifestation. Disease duration was given in each vignette to assess whether this information was significantly associated with the diagnosis made by experts.

All the vignettes were reviewed independently by three experts (VDP, AS, DC) and found to be clinically plausible.

Panel of experts

Of 25 invited pSS experts, 24 participated in the study. Among them, 19 were from 12 European countries, 3 from North America, and 2 from Japan. Only 10 were EULAR US-pSS Task Force members, to minimize potential bias due to a strong favorable opinion of the contribution of SGUS to the diagnosis of pSS within the task force. Of the 24 experts, 20 were rheumatologists, 3 were dentists, and 1 was a radiologist. Each expert evaluated 64 vignettes using a secure web-based relational database. Thus, each vignette was evaluated by 3 experts. The experts used four diagnostic categories to assess the vignettes: pSS definitely absent, pSS unlikely, pSS probable, and pSS definitely present. The vignette was considered to indicate pSS when 2 of the 3 experts gave a diagnosis of probable or definite pSS.

Validation in the independent DiapSS cohort

For validation of the vignette assessment findings, we used the French DiapSS cohort of patients with suspected pSS (18, 25). As previously described, the diagnoses in these patients were established by consensus among three of us (AS, SJJ, and VDP). A diagnosis of pSS did not require fulfillment of the 2002 AECG or 2016 ACR/EULAR classification criteria. For this study, we assessed the performance of the 2016 ACR/EULAR classification criteria with and without the SGUS score.

Statistical analysis

The statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). The vignettes were divided into two groups based on whether 2 of the 3 experts gave a diagnosis of probable or definite pSS (defined here as an expert pSS diagnosis). We then sought to determine which features other than the classification criteria were significantly associated with an expert pSS diagnosis. For each vignette, the 2016 ACR/EULAR score was computed, and Student's *t* test was then applied to compare mean score values between the two groups of vignettes. The chi-square test was used to compare the two groups of vignettes regarding the proportion of pSS diagnoses defined as a 2016 ACR/EULAR score ≥ 4 and as an SGUS score ≥ 2 . Univariate and multivariate logistic regression models were built to identify features (including the SGUS score value and established classification criteria) associated with an expert pSS diagnosis. Significance was assessed using Wald tests.

To assess the weight of the SGUS score and of the 2016 ACR/EULAR criteria, we relied on estimated coefficients from the fitted logistic regression models. The results were then used to derive a modified score (ACR/EULAR + SGUS score). Cutoffs were

determined by plotting receiver operating characteristics (ROC) curves and computing the areas under the curve (AUC). Sensitivity and specificity of the 2016 ACR/EULAR score and modified 2016 ACR/EULAR+ SGUS score for diagnosing pSS were assessed on the vignette data (learning sample) and DiapSS data (validation sample). The characteristics of patients in the DiapSS cohort were described as mean and standard deviation for continuous variables and number and percentage for categorical variables.

RESULTS

Assessment of the vignettes

Of the 512 vignettes, 366 were classified by at least 2 of the 3 experts as indicating probable or definite pSS, i.e., were given an expert pSS diagnosis as defined for this study. Of these 366 vignettes, 330 (90.2%) had a 2016 ACR/EULAR score ≥ 4 and 205 (56%) had an SGUS score ≥ 2 . Of the 146 vignettes for which pSS was deemed absent or unlikely, 22 (15.0%) had a 2016 ACR/EULAR score ≥ 4 .

Items associated with an expert pSS diagnosis (Table 1)

By univariate analysis, the 2016 ACR/EULAR score and SGUS score were significantly associated with an expert pSS diagnosis. Multivariate analysis showed that each of these associations was independent ($p < 0.001$ for all associations). Logistic regression analysis identified six vignette features that were significantly and independently associated with an expert pSS diagnosis, namely, positive anti-SSA (weight, 4), FS ≥ 1 (weight, 4), SGUS score ≥ 2 (weight, 2), positive Schirmer's test (weight, 1), xerostomia (weight, 1), and UWS flow rate < 0.1 mL/min (weight, 1).

2016 ACR/EULAR + SGUS score: vignette evaluation

The results of the logistic regression analysis were then used to derive a modified score (ACR/EULAR + SGUS score) and discussed by the experts.

Adding the SGUS score to the 2016 ACR/EULAR classification criteria set produced the following weights: positive anti-SSA, 3; FS \geq 1, 3; SGUS score \geq 2, 1; positive Schirmer's test, 1; OSS \geq 5, 1; and UWS flow rate \leq 0.1 mL/min, 1 (Table 2). OSS was not significantly associated with an expert pSS diagnosis but was kept in this study because it is a 2016 ACR/EULAR classification item.

Figure 1 and table 3 show the ROC curve and the different cutoff. A cutoff of 4 provided the best sensitivity 95.6 (93.0-97.5) with a specificity of 82.6 (76.0-88.0). Adding SGUS improve the sensitivity from 90.2 % to 95.6% with a quite similar specificity 84.1% versus 82.6%.

Specificity was highest with a cutoff of 5 (95.9 [91.3-98.5], whose sensitivity was 81.4 (77.1-85.3). So, adding SGUS improve the sensitivity from 68.9 % to 81.4% with a quite similar specificity 97.3% versus 95.9%

The AUC was better when using the 2016 ACR/EULAR set with addition of the SGUS (figure 1).

The panel of experts considered that classification should not be recommended only with the sum of the minor criteria. So the classification with US should be considered with SGUS item that could substitute one of the other minor criteria with a cutoff of 4 or in addition to the other items with a cutoff of 5 (table 2)..

Validation of the weight of SGUS versus other items of the 2016 ACR/EULAR criteria in an independent patient cohort

The validation cohort was composed of 164 patients from the DiaPSS cohort. Mean age was 55 ± 14 years, and 68 (41%) patients had an SGUS score ≥ 2 (18, 25). Of the 164 patients, 80 were given an expert diagnosis of pSS and 84 were not (Table 4). The SGUS score was ≥ 2 in 52 (65%) patients with pSS and 16 (5%) without pSS ($p < 0.001$). Adding SGUS increased sensitivity to a similar degree as in the vignette study, i.e., for the 2016 ACR/EULAR criteria set, from 87% to 93%; specificity decreased slightly, from 84% to 82%.

We determined how many patients in the validation cohort had a modified 2016 ACR/EULAR + SGUS score=4 due only to the presence of minor criteria (positive Schirmer's test, 1 point; OSS ≥ 4 , 1 point; UWS flow rate < 0.1 mL/min, 1 point; and SGUS score ≥ 2 , 1 point). No patient had an ACR/EULAR with SGUS score ≥ 4 without having an FS ≥ 1 or positive anti-SSA antibodies.

DISCUSSION

SGUS has been shown to contribute to the classification and the diagnosis of pSS (26, 27) and is used routinely by experts to assess patients with suspected pSS. SGUS findings were not included in recent classification criteria because the cohorts used to develop them were initiated at a time when SGUS was not yet fully developed. However, the method used to create these new criteria sets allows the addition of items proven to be useful. We evaluated whether adding SGUS findings improved the performance of the 2016 ACR-EULAR criteria set, to determine whether further work using the ACR-EULAR methodology is warranted to develop and validate a new criteria set including the SGUS (28).

In our clinical-vignette study, an abnormal SGUS score (21) was significantly associated with an expert pSS diagnosis, by both univariate and multivariate analyses. Adding SGUS improved the sensitivity of the classification criteria for detecting pSS, with little or no loss of specificity. To our knowledge, no other item has been shown to improve the performance of pSS classification criteria sets in groups of patients (29).

We assessed the contribution of SGUS to classify pSS patients by adding the SGUS score to the other criteria in the 2016 ACR/EULAR set. The results showed that an $OSS \geq 5$ was not significantly associated with an expert pSS diagnosis. However, an $OSS \geq 5$ contributed to classify pSS in the 2016 ACR/EULAR criteria. A majority of experts on our panel felt that an $OSS \geq 5$ deserved to be kept among the classification criteria. We therefore kept it in the criteria set, with the same weight as the Schirmer and UWS criteria. However, there is a need for a new objective tool that detects ocular dryness effectively, requires only widely available material, and can be performed by non-ophthalmologists.

Surprisingly, disease duration (<3 years vs. ≥ 3 years) was not associated with an expert pSS diagnosis. In previous studies, the only feature that reflected disease progression was the nature of the cells in the LSG biopsy (30). SGUS abnormalities have been reported to occur early, at the clinical onset of pSS (10). However, SGUS evidence of parenchymal abnormalities in patients with pSS exhibited little or no change over a 2-year period (25). These data support the potential usefulness of SGUS as a classification criterion for pSS. It would be interesting to investigate whether adding SGUS improves diagnostic performance in patients who have only systemic manifestations or very early pSS.

In our vignette study, adding SGUS improved the sensitivity of ACR/EULAR classification criteria sets, by 5% to 10%. Specificity improved only slightly, suggesting that some of the experts may have lacked confidence in the SGUS score. As an expert pSS diagnosis was defined as at least two of the three experts considering that the vignette

indicated probable or definite pSS, and only half the experts had experience with SGUS, an SGUS score ≥ 2 may not have markedly increased the probability of an expert pSS diagnosis. In the DiaPSS cohort of patients with suspected pSS, the sensitivity gain obtained by adding SGUS was greater, while specificity non significantly decreased. A recent score derived from ours was also recently defined by the OMERACT (31), and confirmed good inter and intrareliabilities of greyscale lesions and anechoic/hypoechoic foci using a semi quantitative evaluation.

The 2016 ACR/EULAR classification criteria were built as weighted items and can be modified. Adding SGUS increases the performance of the set although 2016 ACR/EULAR classification criteria already had an excellent diagnostic performance (criteria AUC is 0.95 and criteria plus SGUS AUC is 0.96). Depending on the cutoff, SGUS increase the sensitivity with the same specificity than the 2016 ACR/EULAR classification criteria with a cutoff of 4, or keep a good specificity while increasing sensitivity with a cutoff of 5. Using a cutoff of 4, is more easily for practitioners and SGUS item could substitute other minor items of the criteria, rather than being added to the others minor criteria

One of the limitations of our study is that the various specialties involved with diagnosing pSS were not equally represented in the panel of experts, as 20 of the 24 experts were rheumatologists and 3 were oral medicine or dentistry. All are experts in Sjogren and participate to elaborate large cohorts of Sjögren patients and to the development of the 2016ACR/EULAR criteria. We relied on fictitious vignettes, in a departure from the method used for the development and validation of the 2016 ACR-EULAR criteria set. The absence of a significant association between an OSS ≥ 5 and an expert pSS diagnosis suggests that the absence of ophthalmologists among the panel members may have resulted in insufficient importance being given to the OSS. Despite these limitations, our results strongly suggest

that the SGUS score assists in the classification of pSS and deserves inclusion in the next iteration of the ACR-EULAR classification criteria for pSS, which is currently being developed. Furthermore, our study confirms the diagnostic usefulness of SGUS in clinical practice, thus offering a new tool to clinicians involved in the diagnosis and management of pSS.

In conclusion, an abnormal SGUS score was associated with an expert pSS diagnosis. With our study methodology, the weight of the SGUS score was similar to that of minor criteria (UWS flow rate and Schirmer test). Adding an SGUS score ≥ 2 to the 2016 ACR/EULAR classification criteria improved sensitivity without substantially modifying specificity when an expert pSS diagnosis was used as the reference standard. The next step will be to formally re-evaluate the 2016 ACR/EULAR criteria set with the SGUS score in patient cohorts at both the development and the validation stages.

References

1. Mariette X, Criswell LA. Primary Sjogren's Syndrome. *The New England journal of medicine*. 2018;379(1):97.
2. Saraux A, Pers JO, Devauchelle-Pensec V. Treatment of primary Sjogren syndrome. *Nat Rev Rheumatol*. 2016;12(8):456-71.
3. Fisher BA, Jonsson R, Daniels T, Bombardieri M, Brown RM, Morgan P, et al. Standardisation of labial salivary gland histopathology in clinical trials in primary Sjogren's syndrome. *Ann Rheum Dis*. 2017;76(7):1161-8.
4. Guellec D, Cornec D, Jousse-Joulin S, Marhadour T, Marcorelles P, Pers JO, et al. Diagnostic value of labial minor salivary gland biopsy for Sjogren's syndrome: a systematic review. *Autoimmun Rev*. 2013;12(3):416-20.
5. Vitali C, Monti P, Giuggioli C, Tavoni A, Neri R, Genovesi-Ebert F, et al. Parotid sialography and lip biopsy in the evaluation of oral component in Sjogren's syndrome. *Clin Exp Rheumatol*. 1989;7(2):131-5.
6. Devauchelle-Pensec V, Zabotti A, Carvajal-Alegria G, Filipovic N, Jousse-Joulin S, De Vita S. Salivary gland ultrasonography in primary Sjogren's syndrome: opportunities and challenges. *Rheumatology (Oxford)*. 2019.
7. Carotti M, Salaffi F, Manganelli P, Argalia G. Ultrasonography and colour doppler sonography of salivary glands in primary Sjogren's syndrome. *Clin Rheumatol*. 2001;20(3):213-9.
8. De Vita S, Lorenzon G, Rossi G, Sabella M, Fossaluzza V. Salivary gland echography in primary and secondary Sjogren's syndrome. *Clin Exp Rheumatol*. 1992;10(4):351-6.
9. Yonetsu K, Takagi Y, Sumi M, Nakamura T, Eguchi K. Sonography as a replacement for sialography for the diagnosis of salivary glands affected by Sjogren's syndrome. *Ann Rheum Dis*. 2002;61(3):276-7.
10. Cornec D, Jousse-Joulin S, Marhadour T, Pers JO, Boisrame-Gastrin S, Renaudineau Y, et al. Salivary gland ultrasonography improves the diagnostic performance of the 2012 American College of Rheumatology classification criteria for Sjogren's syndrome. *Rheumatology (Oxford)*. 2014;53(9):1604-7.
11. Hammenfors DS, Brun JG, Jonsson R, Jonsson MV. Diagnostic utility of major salivary gland ultrasonography in primary Sjogren's syndrome. *Clin Exp Rheumatol*. 2015;33(1):56-62.
12. Milic VD, Petrovic RR, Boricic IV, Marinkovic-Eric J, Radunovic GL, Jeremic PD, et al. Diagnostic value of salivary gland ultrasonographic scoring system in primary Sjogren's syndrome: a comparison with scintigraphy and biopsy. *J Rheumatol*. 2009;36(7):1495-500.
13. Mossel E, Delli K, van Nimwegen JF, Stel AJ, Kroese FGM, Spijkervet FKL, et al. Ultrasonography of major salivary glands compared with parotid and labial gland biopsy and classification criteria in patients with clinically suspected primary Sjogren's syndrome. *Ann Rheum Dis*. 2017.
14. Wernicke D, Hess H, Gromnica-Ihle E, Krause A, Schmidt WA. Ultrasonography of salivary glands -- a highly specific imaging procedure for diagnosis of Sjogren's syndrome. *J Rheumatol*. 2008;35(2):285-93.
15. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis*. 2017;76(1):9-16.

16. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjogren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis & rheumatology*. 2017;69(1):35-45.
17. Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. *Ann Rheum Dis*. 2010;69(6):1103-9.
18. Cornec D, Jousse-Joulin S, Pers JO, Marhadour T, Cochener B, Boisrame-Gastrin S, et al. Contribution of salivary gland ultrasonography to the diagnosis of Sjogren's syndrome: toward new diagnostic criteria? *Arthritis Rheum*. 2013;65(1):216-25.
19. Le Goff M, Cornec D, Jousse-Joulin S, Guellec D, Costa S, Marhadour T, et al. Comparison of 2002 AECG and 2016 ACR/EULAR classification criteria and added value of salivary gland ultrasonography in a patient cohort with suspected primary Sjogren's syndrome. *Arthritis Res Ther*. 2017;19(1):269.
20. Jousse-Joulin S, Milic V, Jonsson MV, Plagou A, Theander E, Luciano N, et al. Is salivary gland ultrasonography a useful tool in Sjogren's syndrome? A systematic review. *Rheumatology (Oxford)*. 2016;55(5):789-800.
21. Jousse-Joulin S, Nowak E, Cornec D, Brown J, Carr A, Carotti M, et al. Salivary gland ultrasound abnormalities in primary Sjogren's syndrome: consensual US-SG core items definition and reliability. *RMD Open*. 2017;3(1):e000364.
22. Mossel E, Delli K, van Nimwegen JF, Stel AJ, Haacke EA, Kroese FGM, et al. The parotid gland connection: ultrasound and biopsies in primary Sjogren's syndrome. *Ann Rheum Dis*. 2017.
23. Baldini C, Pepe P, Quartuccio L, Priori R, Bartoloni E, Alunno A, et al. Primary Sjogren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. *Rheumatology (Oxford)*. 2014;53(5):839-44.
24. Vitali C, Palombi G, Baldini C, Benucci M, Bombardieri S, Covelli M, et al. Sjogren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjogren's syndrome, derived from an analysis of a cohort of Italian patients. *Arthritis Rheum*. 2007;56(7):2223-31.
25. Gazeau P, Cornec D, Jousse-Joulin S, Guellec D, Saraux A, Devauchelle-Pensec V. Time-course of ultrasound abnormalities of major salivary glands in suspected Sjogren's syndrome. *Joint Bone Spine*. 2018;85(2):227-32.
26. Jonsson MV, Baldini C. Major Salivary Gland Ultrasonography in the Diagnosis of Sjogren's Syndrome: A Place in the Diagnostic Criteria? *Rheum Dis Clin North Am*. 2016;42(3):501-17.
27. Bootsma H, Spijkervet FK, Kroese FG, Vissink A. Toward new classification criteria for Sjogren's syndrome? *Arthritis Rheum*. 2013;65(1):21-3.
28. Vitali C, Carotti M, Salaffi F. Is it the time to adopt salivary gland ultrasonography as an alternative diagnostic tool for the classification of patients with Sjogren's syndrome? *Arthritis Rheum*. 2013.
29. Cornec D, Saraux A, Pers JO, Jousse-Joulin S, Marhadour T, Roguedas-Contios AM, et al. Diagnostic accuracy of blood B-cell subset profiling and autoimmunity markers in Sjogren's syndrome. *Arthritis Res Ther*. 2014;16(1):R15.
30. Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. Characteristics of the minor salivary gland infiltrates in Sjogren's syndrome. *J Autoimmun*. 2010;34(4):400-7.

31. Jousse-Joulin S, D'Agostino MA, Nicolas C, Naredo E, Ohrndorf S, Backhaus M, et al. Video clip assessment of a salivary gland ultrasound scoring system in Sjogren's syndrome using consensual definitions: an OMERACT ultrasound working group reliability exercise. *Ann Rheum Dis.* 2019.