Clinical phenotyping of primary Sjögren's patients using salivary gland ultrasonography – data from the RESULT cohort

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Conflict of interest

The authors declare that they have no competing interests.

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ABSTRACT

Objective

To investigate salivary gland ultrasound (SGUS) abnormalities in relation to clinical phenotype and patient characteristics, disease activity and disease damage in patients with primary Sjögren's syndrome (pSS).

Methods

Consecutive outpatients included in our REgistry of Sjögren Syndrome LongiTudinal (RESULT) cohort were selected. Included pSS patients were classified according to the ACR-EULAR criteria and underwent full ultrasonographic examination (Hocevar score 0-48) at baseline. Total SGUS scores of ≥15 were considered positive. Patient characteristics, disease activity and disease damage were compared between the different SGUS groups.

Results

In total, 172/186 pSS patients were eligible, of whom 136 (79%) were SGUS positive. SGUS positive patients had significantly longer disease duration, higher ESSDAI, higher SSDDI, more often a positive parotid gland biopsy, anti-SSA/SSB antibodies, abnormal unstimulated whole saliva (UWS) and ocular staining score (OSS), and higher levels of IgG and rheumatoid factor compared with SGUS negative patients. Regarding patient-reported outcome measurements (PROMs), SGUS positive patients scored significantly lower on ESSPRI fatigue and pain, and more often found their disease state acceptable compared with SGUS negative patients.

SGUS total score showed significant associations with various clinical and serological parameters, and with PROMs. Highest associations were found for UWS (ρ=-0.551) and OSS (ρ=0.532).

Conclusion

SGUS positive patients show a distinct clinical phenotype compared with SGUS negative patients in all aspects of the disease: clinical, functional, serological and PROMs. SGUS could be a helpful tool in selecting patients for clinical trials and estimating treatment need.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a common systemic auto-immune disease[1]. Women are affected nine times more often than men[2]. pSS is a highly heterogeneous disease, which is reflected by the many different manifestations patients can have. Common symptoms, such as extreme fatigue and sicca symptoms have a major impact on the quality of life[1,3]. This heterogeneity already emerges during the diagnostic work-up of pSS, i.e., not every pSS patient has auto-antibodies or a focus score positive salivary gland biopsy, which suggests that there are different subgroups of patients. It would be of great value to be able to identify individual patients at high risk for a severe disease outcome. Prospective cohort studies are gaining more and more importance in this quest[4]. Since treatment options for pSS patients are eagerly awaited, but unfortunately still very limited, the search for patient stratification and proper selection methods for clinical trials is currently ongoing.

Regarding the care for (suspected) pSS patients, there is a unique collaboration between different departments at the University Medical Center Groningen (UMCG). The REgistry of Sjögren syndrome in Umcg – LongiTudinal (RESULT) cohort has been set up to identify biomarkers and clinical parameters that determine and predict the longitudinal course of pSS. Observational studies, like the RESULT cohort, are important as they provide information on long-term outcome of pSS, which reflects daily clinical practice.

Salivary gland ultrasonography (SGUS) is increasingly gaining acceptance as an imaging tool of the salivary glands in pSS. Nowadays, ultrasound is widely accessible in outpatient rheumatology clinics. SGUS is non-invasive and non-irradiating, which makes it patient-friendly and an ideal imaging modality for repeated use[5–7].

Previously, we have studied the validity of SGUS and found that a positive ultrasound, based on the total Hocevar score[6], predicts classification according to the American College of Rheumatology – European League Against Rheumatism (ACR-EULAR) criteria[8]. Subsequently we provided evidence that measuring only hypoechogenic areas in one parotid and one submandibular gland is sufficient to predict ACR-EULAR classification, which

increases the feasibility of SGUS[9]. Although a simpler scoring system suffices for classification purposes, it is not yet known whether SGUS abnormalities can also be used for patient stratification, long-term follow-up or even as selection method for clinical trials. Therefore, a full SGUS evaluation according to the Hocevar score is performed in each patient included in the RESULT cohort.

The aim of this study was to investigate SGUS abnormalities in relation to clinical phenotype and patient characteristics, disease activity and disease damage in patients with pSS.

MATERIALS & METHODS

REgistry of Sjögren syndrome in Umcg – LongiTudinal (RESULT) cohort

The observational RESULT cohort combines up-to-date quality of care with gathering long-term prospective follow-up data in a large cohort of patients. For participation in the RESULT cohort, we consider all consecutive patients with probable or confirmed pSS who visit the outpatient clinic of the Department of Rheumatology and Clinical Immunology in the UMCG, a tertiary referral expertise center. Inclusion in the RESULT cohort is ongoing and duration of follow-up will be 10 years.

The present cross-sectional analysis included the baseline visit of all patients who were included in the RESULT cohort between January 2016 and December 2018. Patients with missing ultrasonographic examination as well as patients who did not fulfill the ACR-EULAR criteria for pSS (i.e. probable pSS patients)[10,11] were excluded.

This study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Medical Ethics Committee of the UMCG; METC 2014/491. Al subjects provided informed consent.

Assessments

Imaging, clinical, functional, histopathological, serological parameters and patients-reported outcome measurements (PROMs) were obtained according to a fixed protocol.

Salivary gland ultrasound

B-mode SGUS was performed using the MyLabSeven scanner (Esaote, Genova, Italy), equipped with a high-resolution linear probe (4-13 MHz). All ultrasonographic images were scored real-time by trained readers (AJS, KD, JFN, EM, RW). Test-retest reliability in our center was demonstrated previously[12]. The scoring system by Hocevar et al.[6] was applied (range 0-48), including the components parenchymal echogenicity, homogeneity, presence of hypoechogenic areas, hyperechogenic reflections and clearness of the salivary gland border. Total SGUS score of ≥15 was considered positive[8].

Other assessments

Demographic characteristics, EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)[13], DAS28-ESR/CRP[14,15], number of tenderpoints, physician global disease activity (physician GDA), Sjögren's Syndrome Disease Damage Index (SSDDI)[16], unstimulated whole saliva flow (UWS)[17], Schirmer's test and ocular staining score (OSS)[18] were determined. Two methods were applied for Schirmer's test and OSS, i.e. when dividing in normal/abnormal the worst eye was selected and when applied as a continuous variable the mean of both eyes was used. A salivary gland biopsy was not mandatory for participation in the RESULT cohort and therefore, parotid and labial salivary gland focus score were recorded if available[19–21].

Serological parameters were determined, including presence of anti-SSA/SSB antibodies, immunoglobulin G (IgG) level, rheumatoid factor (RF) level, complement C3 and C4 levels and leukocyte count.

Patients completed a questionnaire, which included EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) dryness, fatigue and pain[22], patient acceptable symptom state (PASS), patient GDA and the 5-level EuroQol-5 dimensions health status questionnaire (EQ-5D-5L)[23].

Statistics

Statistical analyses were performed using IBM SPSS Statistics 23 (SPSS, Chicago, IL, USA). Descriptive parameters were expressed as number (%) of patients for categorical data and mean (SD) or median (IQR) for continuous data.

Patient characteristics, disease activity and damage were compared between SGUS negative (score <15) and positive (score ≥15) patients. Subsequently, based on the median score of the SGUS positive group, SGUS positive patients were arbitrarily divided into two equal groups; patients with scores ≥15, but <27 were defined as medium-positive and patients with scores ≥27 were defined as high-positive.

Fisher's exact test or Chi square were used as appropriate to evaluate differences in categorical variables between the ultrasound groups. Independent Samples T-test or Mann-Whitney U test were used as appropriate to evaluate differences in continuous variables between the ultrasound groups. ESSDAI subdomains were summarized descriptively.

The association between SGUS total score and continuous variables was analyzed using Spearman correlation coefficient (ρ), and interpreted as poor association (0.0-0.2), fair (0.2-0.4), moderate (0.4-0.6), good (0.6-0.8) or excellent (0.8-1.0)[24]. All parameters were also evaluated using univariate logistic regression analysis with SGUS outcome (positive vs. negative) as dependent variable. In case of residuals with non-Gaussian distribution, variables were transformed (log or square root), before being entered into the model. The explained variance was evaluated using Nagelkerke R^2. P-values ≤0.05 were considered statistically significant.

All analyses were repeated when only taking the average score for 'hypoechogenic areas' in the right parotid and submandibular gland into account[9], instead of the total SGUS score as described by Hocevar et al[6]. For this score, a cut-off value of ≥1.5 was considered positive[25].

RESULTS

Between January 2016 and December 2018, 186 patients were included in the RESULT cohort. Fourteen patients were excluded for the present analysis due to a missing (n=3) or incomplete (n=5) ultrasonographic examination, or because they did not fulfill the ACR-EULAR criteria (n=6). Of the eligible patients (n=172), mean age was 53 years (SD 13.9), 156 patients (91%) were female, 136 patients (79%) were SGUS positive (i.e. SGUS score ≥15)[8] and median time since diagnosis was 8 years (Table 1).

Comparison of SGUS negative and positive patients

Table 1 shows the characteristics of the total group of pSS patients, as well as of the patients with a positive or negative SGUS. There were no significant differences in general patient characteristics between the two groups, except for disease duration, which was longer in de SGUS positive patients.

SGUS positive patients had significantly higher ESSDAI scores, higher DAS28-ESR and higher physician GDA compared with SGUS negative patients, indicating higher disease activity (Table 1; Figure 1A,B; Suppl. Figure 1). Moreover, a parotid gland focus score ≥1, UWS ≤0.1ml/min and OSS ≥5 were more often seen in SGUS positive patients (Table 1). SSDDI , UWS , Schirmer's test and OSS also differed significantly between both groups, with more damage and worse salivary and lacrimal gland function in SGUS positive patients (Table 1; Figure 1C-E).

Regarding the serological parameters, anti-SSA and anti-SSB antibodies were more often present in SGUS positive patients. Furthermore, SGUS positive patients showed higher levels of IgG and RF, lower complement C3 and C4 levels and lower leucocyte counts compared with SGUS negative patients (Table 1; Figure 1F).

Regarding PROMs, SGUS positive patients scored significantly lower on ESSPRI fatigue and pain, and more often found their disease state acceptable, which indicates that SGUS positive patients experienced less symptoms (Table 1).

Results were confirmed with univariate logistic regression analyses (Table 2). The explained variance of individual parameters varied from 0.1% for body mass index (BMI) to 22.4% for parotid gland biopsy (focus score ≥1).

As an overview of the available data, a heatmap of the characteristics of the individual pSS patients is shown in Supplementary Figure 2. The patients order has been determined based upon the total SGUS score. Overall, our data show that SGUS positive patients have a distinct clinical phenotype compared with SGUS negative patients. These findings illustrate the results described above in another way.

Comparison of patients with medium-positive or high-positive SGUS scores

When subdividing the group of SGUS positive patients into medium- and high-positive patients, we observed that compared with patients with a medium-positive SGUS score, patients with a high-positive SGUS score significantly more often had an UWS ≤0.1ml/min, Schirmer's test ≤5mm/5min and OSS ≥5 (Table 3). Furthermore, SSDDI, UWS, Schirmer's test and OSS differed significantly between medium- and high-positive SGUS patients, showing more damage and a worse salivary and lacrimal gland function in the high-positive patients (Table 3).

Patients with high-positive SGUS scores experienced significantly more dryness, but less fatigue and pain compared with patients with a medium-positive SGUS score (Table 3).

Correlations of SGUS total score

Significant associations were found between SGUS total score and disease duration (ρ=0.279), symptom duration (ρ=0.234), ESSDAI (ρ=0.196), DAS28-ESR (ρ=0.159), physician GDA (ρ=0.217), SSDDI (ρ=0.398), UWS (ρ=-0.551), Schirmer's test (ρ=-0.349) and OSS (ρ=0.532) (Suppl. Table 1; Figure 2A-F and Figure 3A).

Furthermore, significant associations were found between SGUS total score and IgG level (ρ=0.264), RF level (ρ=0.343), complement C4 level (ρ=-0.200) and leucocyte count (ρ=-0.244) (Suppl. Table 1; Figure 3B,C).

Moreover, SGUS total scores showed significant association with PROMs; ESSPRI total score (ρ=-0.157), dryness (ρ=0.223), fatigue (ρ=-0.209) and pain (ρ=-0.314) (Suppl. Table 1; Figure 3D-F).

To summarize, an increase in SGUS abnormalities is associated with longer disease duration, more damage and worse gland function, and with more dryness symptoms.

SGUS – hypoechogenic areas only

When using only hypoechogenic areas to define SGUS positivity(9), multiple parameters showed similar results as when total Hocevar score was applied, except that no significant differences were found for: ESSDAI, DAS28-ESR, physician GDA, complement C3 and C4 levels, leucocyte counts and PASS (Suppl. Tables 2&3).

DISCUSSION

In our prospective observational RESULT cohort, we showed that SGUS positive patients have a distinct clinical phenotype compared with SGUS negative patients. This difference was found in all aspects of the disease; clinical, functional, serological and PROMs. SGUS could give an overall indication about the observable and experienced severity of pSS.

SGUS positive patients have higher systemic disease activity, measured by ESSDAI, DAS28-ESR and physician GDA, compared with SGUS negative patients. Of interest, SGUS positive patients score significantly worse on all individual items of the ACR-EULAR criteria, i.e. parotid gland biopsy, anti-SSA antibodies, Schirmer's test, OSS and UWS, compared with SGUS negative patients. Overall, total SGUS score showed the strongest association with OSS and UWS. In addition to these differences, SGUS positive patients score worse on SSDDI and serological parameters. These results show that SGUS enables us to identify patients with higher clinical and serological disease activity and more damage due to pSS.

Interestingly, SGUS positive patients experienced less fatigue and pain, both measured by ESSPRI, and more often found their disease state acceptable, which implies that these patients have a lower symptom burden. Perhaps patients who already have pSS (or symptoms) for several years are more used to it and developed their own coping strategy or they adjusted their expectations. Another possibility for the differences between SGUS negative and positive patients, is that there are indeed different phenotypic clusters of pSS patients. Very recently, Tarn et al.[26] defined four subgroups of pSS patients based upon the patient-reported outcomes dryness, fatigue, pain, anxiety and depression. Our data suggest that patients with high SGUS scores belong to a subgroup of patients with low symptom burden. Unfortunately, the Hospital Anxiety and Depression Scale (HADS) is not part of the questionnaires within our RESULT cohort. Therefore we were unable to verify whether SGUS scores also differ within these four subgroups of patients.

In the current study, we not only compared SGUS negative and positive patients based on a previously defined diagnostic cut-off point[8], but also zoomed in on the broad range of SGUS

positive patients. As expected, patients with a high-positive SGUS score showed more pSS-related damage (SSDDI) and lower salivary and lacrimal gland function and more glandular damage, compared with patients with a medium-positive SGUS score. Interestingly, there were no differences in the percentage of patients with a positive biopsy or presence of anti-SSA antibodies between both groups. This could be because most patients within our cohort score positive on these items, which makes it more difficult to see differences within subgroups of patients. Moreover, both, focus score and anti-SSA antibodies, were collected as absent/present rather than on a continuous scale. Furthermore, the differences in ESSPRI fatigue and pain remain, with less patient symptoms in the high-positive group. In contrast however, high-positive SGUS patients do indeed experience more dryness compared with the medium-positive patients, which is logical considering the relationship between SGUS and glandular function.

The association between SGUS and disease duration suggests that there is an increase in ultrasonographic abnormalities over time. In contrast, when looking solely at the SGUS positive patients, there is no difference in disease duration between patients with medium-positive or high-positive scores. This raises the question how long it takes for these SGUS abnormalities to develop and how long these abnormalities continue to worsen. Gazeau et al.[27] showed that a nearly two-year interval between consecutive SGUS examinations was not enough to see significant progression over time in a group of 49 suspected pSS patients. A possible explanation for the lack of difference in disease duration in medium-positive and high-positive SGUS patients might be inter-observer differences, as it was previously shown that SGUS scores between different observers show more variability when total score exceeds 20[12]. Alternatively, it could be postulated that after a certain disease duration SGUS lesions stabilize, as is the case with the production of saliva[28].

In our previous studies, we have shown that for diagnostic purposes it suffices to only measure hypoechogenic areas in one parotid and one submandibular gland[9] and that optimal cut-off for a positive SGUS is ≥1.5[25]. Since the use of SGUS to stratify pSS patients is essentially different from the use of SGUS for diagnostic purposes, we assessed whether

results would be similar when using total SGUS score compared with only measuring hypoechogenic areas. Regarding UWS, Schirmer's test, OSS and disease damage measured by SSDDI, results were the same when only the component hypoechogenic areas was taken into account. This suggests that evaluation of hypoechogenic areas can be used to identify patients with glandular dysfunction and overall pSS-related damage. However, no differences in ESSDAI, physician GDA and DAS28-ESR were found when SGUS positivity was solely based on hypoechogenic areas, although there were significant differences in serological activity. Therefore, the ultrasonographic component hypoechogenic areas should not be used to identify patients with high disease activity. For this purpose, a more comprehensive scoring system, like the Hocevar scoring system[6], may be preferred above a scoring system including only 1 component.

Previously, several groups studied associations between SGUS and clinical, serological, and patient-reported parameters[29–37]. However, there are considerable differences between some of these studies and our current study. The most important difference is that most studies focus on the possible diagnostic purposes of SGUS rather than its possible use for stratification of already classified pSS patients[30,33–35]. In our study, differences between the SGUS negative and positive patients cannot be attributed to the fact that there are non-SS sicca controls included, as we only included pSS patients in this study. In comparison with the previous studies, we included a considerable higher number of pSS patients. Nevertheless, previous studies found significant differences between SGUS negative and positive patients regarding ESSDAI[31], tear- and saliva production[29–32], presence of anti-SSA antibodies and/or anti-SSB antibodies[29–32], RF positivity[30,31], VAS dry mouth[32] and ESSPRI dryness[29], and, with the exception of the patient-reported dryness symptoms, we were able to confirm these results. In contrast, other studies did not find differences in ESSDAI[29,30] and SSDDI[30] between SGUS negative and positive patients. In a study including pSS as well as non-SS sicca controls, SGUS positive patients had higher labial gland focus score and more often had an OSS ≥3, UWS ≤0.1mL/min, were anti-SSA/SSB and RF positive and had hypergammaglobulinemia, compared with SGUS negative patients[33]. In a large mixed-

population of pSS patients and healthy controls, Milic et al.[36] found significant correlations between SGUS score and age, minor salivary gland biopsy, SSDDI, SSDAI (activity index) and ESSDAI. However, in contrast to our findings, the authors did not find a significant correlation between SGUS and disease duration and ESSPRI. Other studies also found associations between SGUS and ESSDAI[34] and several serological parameters[34,35,37], but again in a mixed population of pSS and non-SS sicca controls.

Other differences between previously performed studies and our current study relate to the applied SGUS scoring system and criteria set used for classification. Some studies, including this current study, applied the Hocevar scoring system[6], but different cut-off points were applied[29,30]. Furthermore, we applied the ACR-EULAR classification criteria, as did Kim et al.[33] and La Paglia et al.[37], whereas in all other studies, including the more recent ones, the AECG criteria were applied[29–32,34–36].

To confirm our results in different populations, a consensus scoring system with a validated cut-off is needed. Very recently, the first steps in reaching international expert consensus have indeed been taken by the OMERACT task force on Sjögren's syndrome[38]. Furthermore, the development of an SGUS endpoint for use in future clinical trials is part of the innovative medicines initiative (IMI) project 'NECESSITY'[39]. Two recent studies showed that the addition of SGUS improves the performance of the ACR-EULAR classification criteria[25,40]. In addition to the potential value of SGUS for diagnostic purposes, our results indicate that SGUS could also be used for patient stratification, e.g., for the selection of subgroups of patients for clinical trials. Although our results seem promising, the value of SGUS for patient stratification needs to be confirmed by other research groups. Currently, within the European Union, initiatives, i.e., the HarmonicSS research project, are already taken to improve stratification of pSS patients, also including the use of SGUS[41].

Our prospective observational cohort revealed that the majority of patients is SGUS positive. These patients have a longer disease duration, a higher disease activity and more pSS-related damage compared with SGUS negative patients, whereas SGUS negative patients

experience more fatigue and pain. In the future, SGUS hopefully can be used as a valid selection method for clinical trials, as it gives an overall indication of the disease.

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Contributorship

EM, designed the study, collected, analysed and interpreted the data, drafted the manuscript and approved the version to be published; JFvN, AJS, RFW, KD, GSvZ, LO, JV and LIL, collected data, critically revised the manuscript and approved the version to be published; AV, designed the study, collected data, critically revised the manuscript and approved the version to be published; FGMK, designed the study, critically revised the manuscript and approved the version to be published, SA designed the study, analysed and interpreted the data, critically revised the manuscript and approved the version to be published and HB, designed the study, collected data, critically revised the manuscript and approved the version to be published.

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FIGURES

Figure 1. Ultrasound total score (negative/positive) compared with A. total ESSDAI; B. Physician global disease activity; C. total SSDDI; D. Unstimulated whole saliva flow; E. Ocular staining score and F. total IgG level.

ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; SSDDI = Sjögren's Syndrome Disease Damage Index;

Figure 2. Scatterplots of ultrasound total score compared with A. Disease duration; B. total ESSDAI; C. SSDDI; D. Unstimulated whole saliva flow; E. Schirmer's test and F. Ocular staining score.

For Schirmer's test and OSS, the mean score of both eyes was calculated.

ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; SSDDI = Sjögren's Syndrome Disease Damage Index

Figure 3. Scatterplots of ultrasound total score compared with A. DAS28-ESR; B. IgG level; C. Rheumatoid Factor level; D. ESSPRI dryness; E. ESSPRI fatigue and F. ESSPRI pain.

DAS28 = 28 joint Disease Activity Score; ESR = erythrocyte sedimentation rate; ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index

Table 1. Patients characteristics and comparison of SGUS negative and positive patients.

Characteristic	Total group (n=172)	SGUS ≤14 (n=36)	SGUS ≥15 (n=136)	P value
General characteristics				
Age, years	52.9 (13.9)	56.0 (14.0)	52.0 (13.8)	0.13
Females	156 (90.7%)	31 (86.1%)	125 (91.9%)	0.29
Disease duration, years	8.0 (4.0-13.0)	5.0 (3.0-8.8)	8.5 (5.0-13.8)	**0.003**
Symptom duration, years***	15.0 (9.0-21.0)	11.0 (6.0-19.0)	15.0 (10.0-22.0)	0.06
BMI (kg/m^2)*	24.9 (4.2)	24.6 (3.6)	24.8 (4.3)	0.79
Clinical parameters				
ESSDAI total score*	4.0 (2.0-8.0)	2.0 (0.0-6.5)	4.0 (2.0-8.0)	**0.028**
ESSDAI categories*				**0.024**
ESSDAI = 0	25 (14.6%)	10 (27.8%)	15 (11.1%)	
ESSDAI = 1-4	75 (43.9%)	16 (44.4%)	59 (43.7%)	
ESSDAI ≥5	71 (41.5%)	10 (27.8%)	61 (45.2%)	
DAS28-ESR**	3.2 (1.0)	2.9 (0.8)	3.3 (1.0)	**0.027**
DAS28-CRP**	2.3 (1.9-2.6)	2.3 (1.9-2.5)	2.3 (1.8-2.7)	0.74
Tenderpoints**	1.5 (0.0-8.0)	2.0 (0.0-12.0	1.0 (0.0-8.0)	0.34
Physician GDA***	2.0 (1.0-3.0)	2.0 (1.0-3.0)	3.0 (1.0-4.0)	**0.026**
SSDDI total score***	2.0 (1.0-3.0)	1.5 (1.0-2.0)	2.0 (1.0-3.0)	**0.018**
UWS ≤0.1 mL/min**	111 (68.5%)	16 (45.7%)	95 (74.8%)	**0.001**
UWS flow, mL/min**	0.05 (0.01-0.13)	0.12 (0.03-0.27)	0.03 (0.00-0.11)	**<0.001**
Parotid gland biopsy, FS ≥1[1]	85 (81.0%)	12 (50.0%)	73 (90.1%)	**<0.001**
Labial gland biopsy, FS ≥1[2]	47 (81.0%)	11 (68.8%)	36 (85.7%)	0.14
Schirmer's test ≤5mm/5min**	121 (74.7%)	25 (69.4%)	96 (76.2%)	0.41
Schirmer's test ODS, mm/5min**	4.0 (0.9-10.0)	5.5 (2.6-11.1)	3.5 (0.0-9.6)	**0.020**
OSS ≥5*	58 (34.1%)	3 (8.3%)	55 (41.0%)	**<0.001**
OSS ODS total score*	2.5 (0.9-5.0)	0.5 (0.0-2.0)	3.5 (1.0-5.0)	**<0.001**
Serological parameters				
Anti-SSA antibodies*	154 (90.1%)	27 (75.0%)	127 (94.1%)	**0.001**

Anti-SSB antibodies*	92 (53.8%)	9 (25.0%)	83 (61.5%)	**<0.001**
IgG level >16.0 g/mL*	81 (47.4%)	5 (13.9%)	76 (56.3%)	**<0.001**
IgG level, g/mL*	15.5 (11.2-20.3)	11.2 (9.3-13.0)	16.9 (12.1-21.8)	**<0.001**
RF level >5.0 IU/mL*	115 (67.3%)	12 (33.3%)	103 (76.3%)	**<0.001**
RF level, IU/mL*	15.0 (2.6-42.0)	2.1 (0.6-10.6)	21.0 (5.2-51.0)	**<0.001**
Complement C3 level (g/L)*	1.12 (0.23)	1.20 (0.24)	1.10 (0.22)	**0.012**
Complement C4 level (g/L)*	0.19 (0.15-0.24)	0.20 (0.18-0.24)	0.18 (0.14-0.24)	**0.015**
Leucocyte count 10^9/L*	5.4 (1.9)	6.3 (2.0)	5.2 (1.8)	**0.002**
Patient-reported outcome measurements				
ESSPRI total score*	6.0 (4.3-7.0)	6.7 (5.0-7.7)	5.7 (4.3-7.0)	**0.016**
ESSPRI dryness*	6.0 (5.0-8.0)	6.0 (4.0-8.0)	7.0 (5.0-8.0)	0.26
ESSPRI fatigue*	7.0 (5.0-8.0)	8.0 (5.0-8.0)	7.0 (4.3-8.0)	**0.024**
ESSPRI pain*	5.0 (2.0-7.0)	7.0 (5.0-8.0)	4.5 (2.0-7.0)	**<0.001**
Patient GDA**	6.0 (4.0-8.0)	7.0 (4.3-8.0)	6.0 (4.0-8.0)	0.15
EQ-5D-5L****	0.77 (0.14)	0.73 (0.17)	0.80 (0.12)	0.23
PASS, acceptable**	117 (71.8%)	21 (58.3%)	96 (75.6%)	**0.042**

Data are expressed as number of patients (%), mean (SD) or median (IQR). *<5% missing data; **5-10% missing data; ***10-15% missing data; ****22% missing data. Data available for [1]61% and [2]34% of patients.

Schirmer's test ≤5mm/min and OSS ≥5 were considered positive if criteria were met in at least one eye. For Schirmer's test ODS and OSS ODS, the mean score of both eyes was calculated.

SGUS = salivary gland ultrasonography; BMI = body mass index; DAS28 = 28-joint Disease Activity Score; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; GDA = global disease activity; SSDDI = Sjögren's Syndrome Disease Damage Index; UWS = unstimulated whole saliva; FS = focus score; OSS = ocular staining score; RF = rheumatoid factor; ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index; EQ-5D-5L = 5-level EuroQol-5 dimensions health status questionnaire; PASS = patient acceptable symptom state.

Table 2. Logistic regression analyses of demographic, clinical, serological and patient reported outcome parameters to predict ultrasound outcome.

Characteristic	Univariate analysis OR (95% CI)	P value	R^2
General characteristics			
Age, years	0.979 (0.952-1.007)	0.13	0.021
Females	1.833 (0.593-5.662)	0.29	0.009
Disease duration, years	1.108 (1.028-1.195)	0.007	0.082
Symptom duration, years***	1.036 (0.991-1.083)	0.12	0.028
BMI (kg/m^2)*	0.988 (0.906-1.078)	0.79	0.001
Clinical parameters			
ESSDAI total score†*	1.438 (1.040-1.988)	0.028	0.046
DAS28-ESR**	1.607 (1.047-2.466)	0.030	0.048
DAS28-CRP**	1.276 (0.738-2.205	0.38	0.008
Tenderpoints**	0.976 (0.924-1.032)	0.40	0.007
Physician GDA***	1.473 (1.062-2.043)	0.020	0.064
SSDDI total score***	1.357 (1.053-1.748)	0.018	0.079
UWS ≤0.1 mL/min**	3.525 (1.622-7.663)	0.001	0.094
UWS flow, mL/min**	0.010 (0.001-0.138)	0.001	0.120
Parotid gland biopsy, FS ≥1[1]	9.125 (3.089-26.953)	<0.001	0.224
Labial gland biopsy, FS ≥1[2]	2.727 (0.696-10.684)	0.15	0.049
Schirmer's test ≤5mm/5min**	1.408 (0.621-3.194)	0.41	0.006
Schirmer's test ODS, mm/5min‡**	0.658 (0.459-0.942)	0.022	0.051
OSS ≥5*	7.658 (2.236-26.227)	0.001	0.141
OSS ODS total score*	1.598 (1.274-2.005)	<0.001	0.212
Serological parameters			
Anti-SSA antibodies*	5.292 (1.872-14.956)	0.002	0.084
Anti-SSB antibodies*	4.788 (2.088-10.984)	<0.001	0.136
IgG level >16.0 g/mL*	7.986 (2.927-21.795)	<0.001	0.192
IgG level g/mL*	1.129 (1.049-1.215)	0.001	0.121

RF level >5.0 IU/mL*	6.438 (2.897-14.305)	<0.001	0.192
RF level IU/mL*	1.020 (1.004-1.036)	0.012	0.094
Complement C3 level (g/L)*	0.132 (0.026-0.672)	0.015	0.055
Complement C4 level (g/L)*	0.026 (0.000-1.991)	0.10	0.024
Leucocyte count 10^9/L*	0.756 (0.622-0.919)	0.005	0.075
Patient-reported outcome measurements			
ESSPRI total score*	0.814 (0.662-1.001)	0.051	0.038
ESSPRI dryness‡*	1.680 (0.795-3.550)	0.17	0.016
ESSPRI fatigue*	0.837 (0.701-0.998)	0.047	0.040
ESSPRI pain‡*	0.380 (0.179-0.803)	0.011	0.075
Patient GDA†*	0.808 (0.427-1.529)	0.51	0.004
EQ-5D-5L***	10.489 (0.483-227.980)	0.14	0.026
PASS, acceptable**	2.212 (1.018-4.809)	0.045	0.036

† SQRT transformation; ‡LN transformation ; *<5% missing data; **5-10% missing data; ***10-15% missing data; ****22% missing data. Data available for [1]61% and [2]34% of patients.

BMI = body mass index; DAS28 = 28-joint Disease Activity Score; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; GDA = global disease activity; SSDDI = Sjögren's Syndrome Disease Damage Index; UWS = unstimulated whole saliva; FS = focus score; OSS = ocular staining score; RF = rheumatoid factor; ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index; EQ-5D-5L = 5-level EuroQol-5 dimensions health status questionnaire; PASS = patient acceptable symptom state.

Table 3. Comparison of SGUS positive patients with medium or high SGUS scores.

Characteristic	SGUS 15-26 (n=67)	SGUS 27-41 (n=69)	P value
General characteristics			
Age, years	53.1 (13.6)	51.0 (13.9)	0.39
Females	63 (94.0%)	62 (89.9%)	0.53
Disease duration, years	8.0 (4.0-14.0)	9.0 (6.0-13.5)	0.35
Symptom duration, years***	14.5 (8.0-21.8)	16.0 (11.0-22.0)	0.22
BMI (kg/m^2)*	24.8 (4.7)	24.8 (4.0)	0.99
Clinical parameters			
ESSDAI total score*	4.0 (2.0-8.0)	4.0 (2.0-8.0)	0.76
ESSDAI categories*			0.92
ESSDAI = 0	7 (10.6%)	8 (11.6%)	
ESSDAI = 1-4	30 (45.5%)	29 (42.0%)	
ESSDAI ≥5	29 (43.9%)	32 (46.4%)	
DAS28-ESR**	3.3 (1.0)	3.3 (1.0)	0.88
DAS28-CRP**	2.3 (1.7-2.7)	2.3 (2.0-2.7)	0.59
Tenderpoints**	2.0 (0.0-9.0)	0.0 (0.0-5.8)	0.19
Physician GDA***	2.0 (1.0-3.0)	3.0 (1.0-4.0)	0.28
SSDDI total score***	2.0 (1.0-3.0)	2.0 (2.0-5.8)	**0.001**
UWS ≤0.1 mL/min**	40 (60.6%)	55 (90.1%)	**<0.001**
UWS flow, mL/min**	0.08 (0.01-0.15)	0.01 (0.00-0.04)	**<0.001**
Parotid gland biopsy, FS ≥1[1]	36 (85.7%)	37 (94.9%)	0.27
Labial gland biopsy, FS ≥1[2]	18 (81.8%)	18 (90.0%)	0.67
Schirmer's test ≤5mm/5min**	41 (67.2%)	55 (84.6%)	**0.022**
Schirmer's test ODS, mm/5min**	5.0 (1.0-12.0)	2.0 (0.0-5.3)	**0.017**
OSS ≥5*	17 (25.8%)	38 (55.9%)	**<0.001**
OSS ODS total score*	2.0 (1.0-4.0)	4.0 (2.5-6.4)	**<0.001**
Serological parameters			
Anti-SSA antibodies*	60 (90.9%)	67 (97.1%)	0.16

Anti-SSB antibodies*	38 (57.6%)	45 (65.2%)	0.36
IgG level >16.0 g/mL*	37 (56.1%)	39 (56.5%)	0.96
IgG level, g/mL*	16.8 (12.0-19.9)	17.4 (12.1-22.6)	0.57
RF level >5.0 IU/mL*	47 (71.2%)	56 (81.2%)	0.17
RF level, IU/mL*	15.5 (3.0-36.3)	32.0 (8.5-57.5)	**0.037**
Complement C3 level (g/L)*	1.10 (0.23)	1.10 (0.22)	0.88
Complement C4 level (g/L)*	0.19 (0.15-0.24)	0.18 (0.13-0.22)	0.16
Leucocyte count 10^9/L*	5.3 (1.6)	5.1 (2.0)	0.64
Patient-reported outcome measurements			
ESSPRI total score*	6.0 (4.3-7.2)	5.7 (4.0-6.7)	0.30
ESSPRI dryness*	6.0 (4.0-8.0)	7.0 (5.0-8.0)	**0.050**
ESSPRI fatigue*	7.0 (5.0-8.0)	6.0 (4.0-7.0)	**0.042**
ESSPRI pain*	6.0 (3.0-7.0)	4.0 (2.0-6.0)	**0.019**
Patient GDA**	6.0 (4.0-7.5)	6.0 (4.0-8.0)	0.80
EQ-5D-5L***	0.78 (0.14)	0.78 (0.11)	0.94
PASS, acceptable**	45 (73.8%)	51 (77.3%)	0.65

Data are expressed as number of patients (%), mean (SD) or median (IQR). *<5% missing data; **5-10% missing data; ***10-15% missing data; ****22% missing data. Data available for [1]61% and [2]34% of patients.

Schirmer's test ≤5mm/min and OSS ≥5 were considered positive if criteria were met in at least one eye. For Schirmer's test ODS and OSS ODS, the mean score of both eyes was calculated.

SGUS = salivary gland ultrasonography; BMI = body mass index; DAS28 = 28-joint Disease Activity Score; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; GDA = global disease activity; SSDDI = Sjögren's Syndrome Disease Damage Index; UWS = unstimulated whole saliva; FS = focus score; OSS = ocular staining score; RF = rheumatoid factor; ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index; EQ-5D-5L = 5-level EuroQol-5 dimensions health status questionnaire; PASS = patient acceptable symptom state.

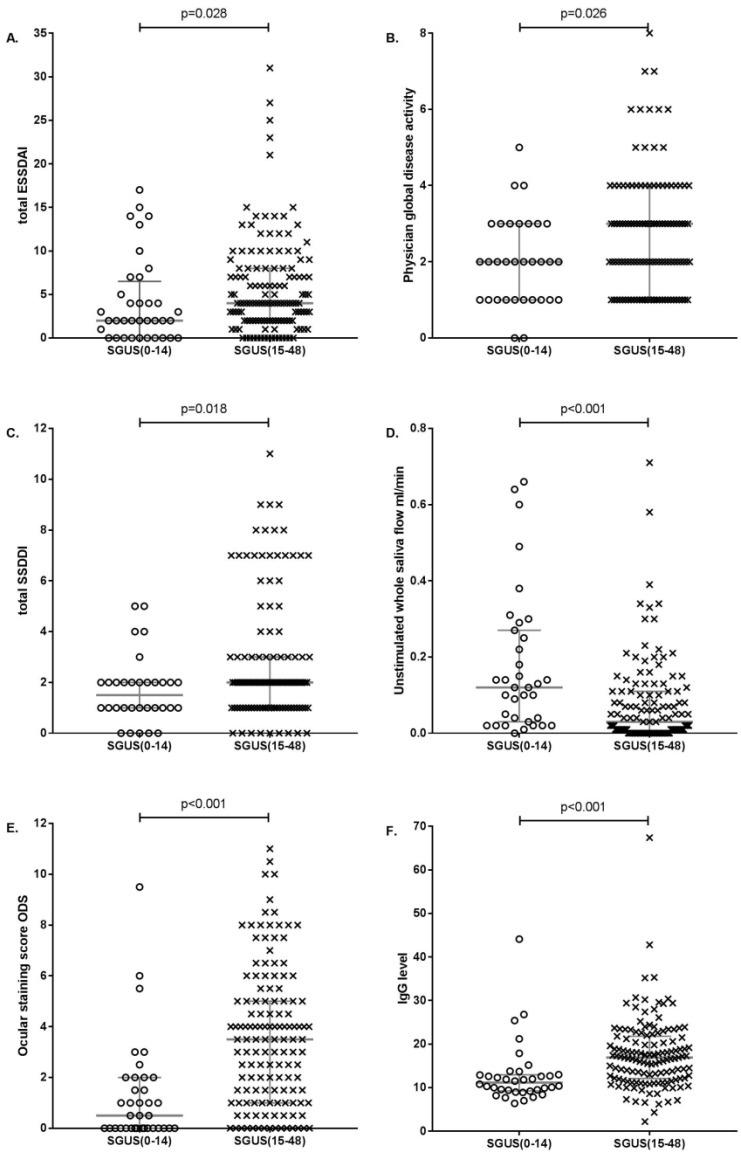

Figure 1. Ultrasound total score (negative/positive) compared with A. total ESSDAI; B. Physician global disease activity; C. total SSDDI; D. Unstimulated whole saliva flow; E. Ocular staining score and F. total IgG level.
ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; SSDDI = Sjögren's Syndrome Disease Damage Index

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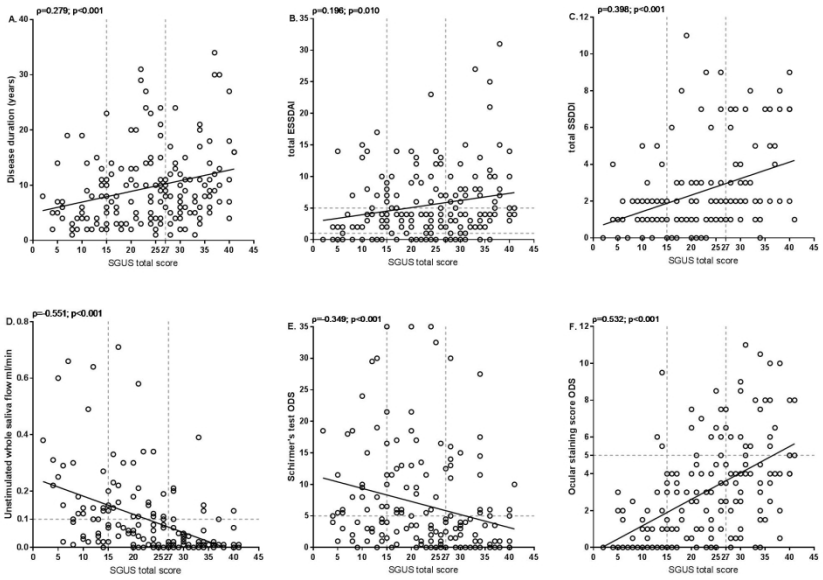

Figure 2. Scatterplots of ultrasound total score compared with A. Disease duration; B. total ESSDAI; C. SSDDI; D. Unstimulated whole saliva flow; E. Schirmer's test and F. Ocular staining score.
For Schirmer's test and OSS, the mean score of both eyes was calculated.
ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; SSDDI = Sjögren's Syndrome Disease Damage Index

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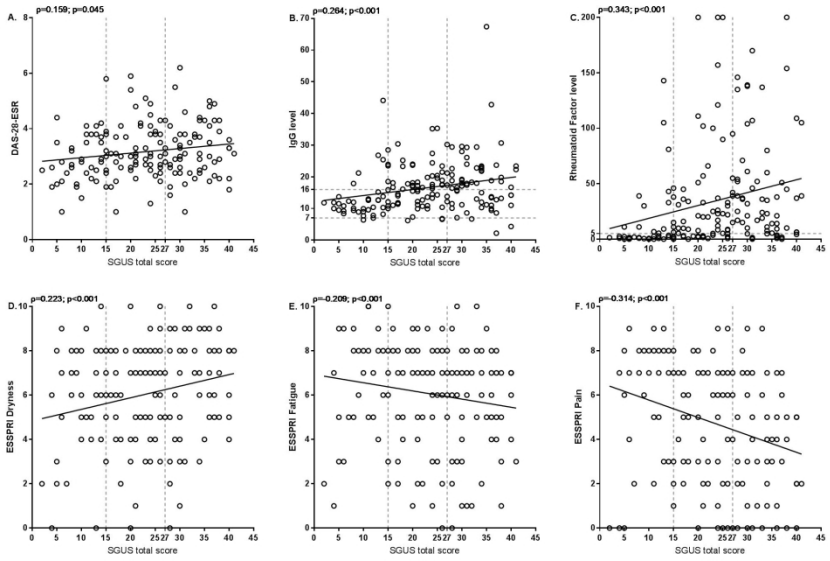

Figure 3. Scatterplots of ultrasound total score compared with A. DAS28-ESR; B. IgG level; C. Rheumatoid Factor level; D. ESSPRI dryness; E. ESSPRI fatigue and F. ESSPRI pain.
DAS28 = 28 joint Disease Activity Score; ESR = erythrocyte sedimentation rate; ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index

202x122mm (300 x 300 DPI)