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Original article

Ultrasonography of major salivary glands: a highly specific tool for distinguishing primary Sjögren's syndrome from undifferentiated connective tissue diseases

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Abstract

Objectives. Recently, convincing data have been published on the value of salivary gland ultrasonography (SGUS) in differentiating primary SS from non-immune-mediated sicca syndrome. Limited data are available regarding the diagnostic accuracy of SGUS in distinguishing SS from other rheumatic diseases. The purpose of this study was to assess the usefulness of SGUS in distinguishing patients with SS from those with xerostomia and/or xerophthalmia and a diagnosis of stable UCTD.

Methods. This cross-sectional study consecutively enrolled 150 patients either diagnosed with SS (as established by the American–European Consensus Group criteria) or affected by UCTD but not SS. Parotid and submandibular glands on both sides were assessed for size, parenchymal echogenicity and inhomogeneity by means of SGUS, which was performed by a radiologist blinded to the diagnosis. Echostructural alterations of the salivary glands were graded from 0 to 3 (cut-off >2).

Results. This study included 109 patients: 55 with SS and 54 with UCTD. Patients with SS showed a higher SGUS score in comparison with those with UCTD [mean 2.2 (S.D. 1.8) *vs* 0.2 (S.D. 0.5), $P < 0.0001$]. The SGUS cut-off >2 showed a sensitivity of 65%, a specificity of 96%, a positive predictive value of 95% and a negative predictive value of 73% for SS diagnosis. A significant correlation was also found between the SGUS score and the minor salivary gland biopsy/focus score ($r = 0.484$, $P < 0.0001$).

Conclusion. This study confirmed the good sensitivity and the high specificity of SGUS in differentiating SS from other CTDs.

Key words: Sjögren's syndrome, salivary gland ultrasonography, classification criteria.

CLINICAL SCIENCE

Rheumatology key messages

- Our findings confirm salivary gland ultrasonography as a sensitive and highly specific tool for diagnosing SS.
- Among salivary gland ultrasonography parameters, parenchymal inhomogeneity was the most discriminant for diagnosing SS in our population.
- Salivary gland ultrasonography should be considered for inclusion in American–European Consensus Group criteria for SS.

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Introduction

In recent years salivary gland ultrasonography (SGUS) has been described as a practical, non-invasive technique, featuring high specificity that allows detection of the involvement of major salivary glands in both primary SS and secondary SS [1–6]. To date, many studies have

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demonstrated the accuracy and reliability of this procedure in diagnosing SS and, in particular, its value in differentiating SS from idiopathic sicca syndrome and drug-induced sicca syndrome [7–15]. Yet, there are few data supporting the diagnostic accuracy of this technique in distinguishing SS from other rheumatic diseases that may mimic SS [6, 16]. In fact, patients affected by rheumatic disorders often report symptoms such as dry eyes and dry mouth, but do not present characteristics fulfilling classification criteria for primary SS and secondary SS [17]; similarly, several autoantibodies, including anti-Ro/SSA and anti-La/SSB, might not contribute significantly to differentiating SS from other CTDs [18]. Thus, the inclusion of SGUS in the diagnostic algorithm of SS requires further confirmation through SGUS validation studies, including disease-control patients with sicca symptoms and other rheumatic disorders.

One clinical entity often considered in differential diagnosis with SS is represented by UCTDs [19]—a set of unclassifiable systemic autoimmune diseases that share clinical and serological manifestations with definite CTDs, but which do not, however, fulfil over time, any of the foreseen classification criteria [18]. In patients affected by stable UCTD, the prevalence of diseases such as xerostomia and xerophthalmia ranges from 8% to 40%; yet, none of such patients present a definite SS at long-term follow-up, despite 8–30% of such patients presenting anti-Ro/SSA antibodies [19]. Thus, in clinical practice, discriminating SS from UCTD still appears somewhat challenging.

In this study, we attempted to assess the diagnostic accuracy of SGUS in distinguishing SS from stable UCTD. We compared the performance of SGUS with traditional serological, histological and functional diagnostic tests included in the American–European Consensus Group (AECG) criteria [20], in order to verify whether SGUS might help in the recognition of SS in rheumatology settings, thus offering a valuable guide for setting up appropriate patient follow-up schedules and therapeutic protocols.

Patients and methods

Study population

This was a single-centre cross-sectional study performed at the Rheumatology Unit of the University of Pisa, a tertiary referral centre for rare systemic autoimmune diseases. The study enrolled 150 patients presenting at our centre between March 2011 and 2013 with a diagnosis of SS or UCTD.

Inclusion criteria were either: the diagnosis of SS including a confirmation by minor salivary gland biopsy, as established by the AECG criteria for the disease [20]; or a diagnosis of UCTD as established by the criteria set by Mosca *et al*. [21], along with the presence of sicca symptoms and a complete work-up ruling out a diagnosis of SS. The criterion for exclusion was the absence of a minor salivary gland biopsy for UCTD patients. Informed consent was obtained from all participants, and the study was performed in accordance with the ethical standards set by the Declaration of Helsinki 1975, revised 1983. The Ethics Committee of the University of Pisa (Italy) approved this study.

Clinical and laboratory examinations

At inclusion in the study, sicca symptoms were collected prospectively by means of the AECG questionnaire, which was administered to all patients by the same rheumatologist [20, 22]; additional data on the duration of sicca symptoms, glandular and extraglandular manifestations, patients' comorbidities and ongoing treatments were also recorded. Among laboratory abnormalities, information collected included: the presence of cytopenia [i.e. neutropenia (neutrophils $<1500/mm^3$); lymphopenia (lymphocytes $<1000/mm^3$); anaemia (haemoglobin <12 g/dl); thrombocytopenia ($<150\,000/mm^3$)], low levels of C3 (<90 mg/dl) and C4 (<20 mg/dl), and hypergammaglobulinaemia (IgG >16 g/l), thyroid function abnormalities and hepatitis C and B seropositivity. In addition to routine blood tests, we also assessed the presence of ANAs by indirect immunofluorescence assay on HEp-2 cells (a titre $\geqslant 1.160$ was considered positive), anti-Ro/SSA and anti-La/SSB (commercial ELISA kit) and RF (nephelometry). Schirmer's test and the Lissamine Green ocular test were performed by the same ophthalmologist, prospectively upon inclusion in the study. Unstimulated whole salivary flow was collected according to a sialometry protocol (AECG 2002) [20, 22]. Minor salivary gland biopsies (MSGBs) were re-read by the same pathologist who scored the degree of infiltration in terms of focus score (MSGB/FS) [23].

Ultrasonographic examination

Major salivary gland ultrasonography was performed by a radiologist, blinded to the diagnosis, by means of a Esaote Technos MPX machine equipped with a 7.5- to 12.5-MHz linear probe; patients were examined in supine position with their neck extended and the head slightly turned controlaterally. The parotid glands were scanned in both the longitudinal and transverse planes, while the submandibular glands were scanned in the longitudinal plane only. The ultrasonography parameters recorded were: size, parenchymal inhomogeneity, parenchymal echogenicity and posterior glandular border. Parenchymal echogenicity was defined as normal or decreased in comparison with the thyroid gland parenchyma and the surrounding soft tissue (muscular structures, subcutaneous fat, etc.). Parenchymal homogeneity was graded from 0 to 3 in accordance with the US scoring system described by De Vita *et al.* [7, 24], with grade 0 indicating complete homogeneity, and grade 3 indicating severe inhomogeneity. A mild level of inhomogeneity (score 1) was attributed to isolated hypoechoic areas, while an evident level of inhomogeneity (score 2) was assigned to evident scattered hypoechoic areas of variable size, not uniformly distributed, and/or to multiple punctate or linear non-shadowing densities. Finally, a gross level of inhomogeneity (score 3) was attributed to large circumbed or confluent

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hypoechoic areas, and/or to linear densities, and/or to multiple cysts or multiple calcifications. The SGUS score ranged from 0 to 6, and represented the sum of the single scores for each pair of parotid and submandibular glands. Consistent with previous studies [7, 24], a SGUS score $\geqslant 2$ was considered suggestive for SS. The SGUS scores were compared with patients' serology, sialometry and minor salivary gland FS.

Statistical analysis

Results were reported as means ± S.D. or as median (range) according to data distribution. Nominal variables were reported as absolute values and percentages. Data were compared using χ^2 tests, unpaired *t*-tests and Mann–Whitney U tests, as appropriate. Spearman's rank correlation was used to assess correlation between SGUS score, MSGB/FS and the EULAR primary Sjögren's syndrome disease activity index (ESSDAI). Sensitivity, specificity, positive predictive value and negative predictive value of the clinical diagnostic tests for SS were determined using 2×2 contingency tables. The optimal cut-off value for SGUS score was calculated as the area under the receiver operating characteristic curve

Results

Of the 150 patients recruited, 41 were excluded from the study because their diagnosis was not confirmed by biopsy findings. Of the remaining 109 patients included, 55 met the AECG criteria for SS, and 54 were diagnosed as having UCTD. Demographic and clinical characteristics of the patients are shown in Table 1. No differences between the two groups were observed with respect to gender, age at the time of SGUS examination, or frequency or duration of sicca symptoms. Laboratory tests, ocular tests and sialometry abnormalities were significantly more common in patients with SS.

Salivary gland ultrasonography findings: comparison between SS and UCTD

SGUS abnormalities were found in 36 of 55 (65%) SS *vs* 7 of 54 (13%) UCTD patients ($P < 0.0001$). The median SGUS score was significantly higher in patients with SS in comparison with UCTD controls [median (range) 2 (0–6) *vs* 0 (0–2), $P < 0.0001$]. In particular, salivary glands in SS patients more frequently showed evident parenchymal inhomogeneity, with more and larger hypoechoic and anechoic areas and hyperechoic bands (Fig. 1). In contrast, the vast majority of patients with stable UCTD showed normal glands or mild non-specific alterations (i.e. 87% for grade 0, 9% for grade 1 and 4% for grade 2). Fig. 2 shows the distribution of the De Vita SGUS score among SS and UCTD patients. No differences were detected between the two groups of patients for glandular size, enlarged intraglandular lymph nodes and/or posterior borders.

Table 1 Baseline demographic and clinical characteristics of patients with SS and UCTD

	SS (55)	UCTD (54)	*P*-value
Age, mean (S.D.), years	49 (14)	53 (14)	0.12
Female, *n* (%)	53 (96.4)	50 (92.6)	0.44
Duration of sicca symptoms, mean (S.D.), years	2.6 (2.2)	3.5 (4.1)	0.14
Xerostomia, *n* (%)	51 (93)	48 (89)	0.52
Xerophthalmia, *n* (%)	48 (87)	49 (91)	0.76
Ocular tests, *n* (%)	37 (67)	20 (37)	0.002
Unstimulated salivary flow, mean (S.D.)	2.3 (2.5)	3.5 (3.2)	0.04
Anti-Ro/SSA, *n* (%)	36 (65.5)	11 (20)	<0.0001
Anti-La/SSB, *n* (%)	13 (24)	None	<0.0001
RF, *n* (%)	27 (49)	8 (15)	<0.0001
Low C3 levels, *n* (%)	12 (22)	6 (11)	0.19
Low C4 levels, *n* (%)	9 (16)	3 (6)	0.12
Hypergammaglobulinaemia, *n* (%)	29 (51)	9 (17)	<0.0001
MSGB/FS, mean (S.D.)	2.9 (2.2)	0.1 (0.2)	<0.0001

MSGB/FS: minor salivary gland biopsy/focus score.

Diagnostic accuracy of SGUS for SS disease: a comparison with traditional serological, histological and functional tests

By setting a SGUS score cut-off value of 2 [area under the curve (AUC) 0.81; 95% CI 0.72, 0.89)] (Fig. 3), SGUS had 65% sensitivity and 96% specificity, with a positive predictive value of 95% and a negative predictive value of 73%. Anti-Ro/SSA had similar sensitivity, but lower specificity in differentiating SS from UCTD, as reported in Table 2. Ocular tests and sialometry were less specific than SGUS (Table 2).

Relationship between SGUS scores and SS disease features

We found that the mean (range) value of the SGUS score was significantly higher in patients with anti-Ro/SSA positivity [2 (0–5) *vs* 0 (0–6), $P = 0.001$] (Fig. 4A), anti-La/SSB positivity [3 (0–5) *vs* 0 (0–6), $P = 0.01$] (Fig. 4B), RF [2 (0–5) *vs* 0 (0–6), $P = 0.001$] (Fig. 4C) or hypergammaglobulinaemia [2 (0–5) *vs* 0 (0–6), $P < 0.0001$] (Fig. 4D). The overall SGUS score correlated directly with the MSGB/FS ($r = 0.484$, $P < 0.0001$), with patients with a MSGB/FS $\geqslant 3$ presenting a significantly higher mean (S.D.) SGUS score (Fig. 4E). Moreover, the SGUS score also correlated with the ESSDAI ($r = 0.420$, $P < 0.0001$) and, inversely, with the whole unstimulated salivary flow rate (USFR) ($r = -0{,}369$, $P < 0.0001$). More specifically, a greater SGUS score was detected in patients with an ESSDAI $\geqslant 5$ (Fig. 4F) and in patients with an USFR < 1.5 ml/15 min (Fig. 4G). We did not find any correlation between SGUS scores and duration of sicca symptoms.

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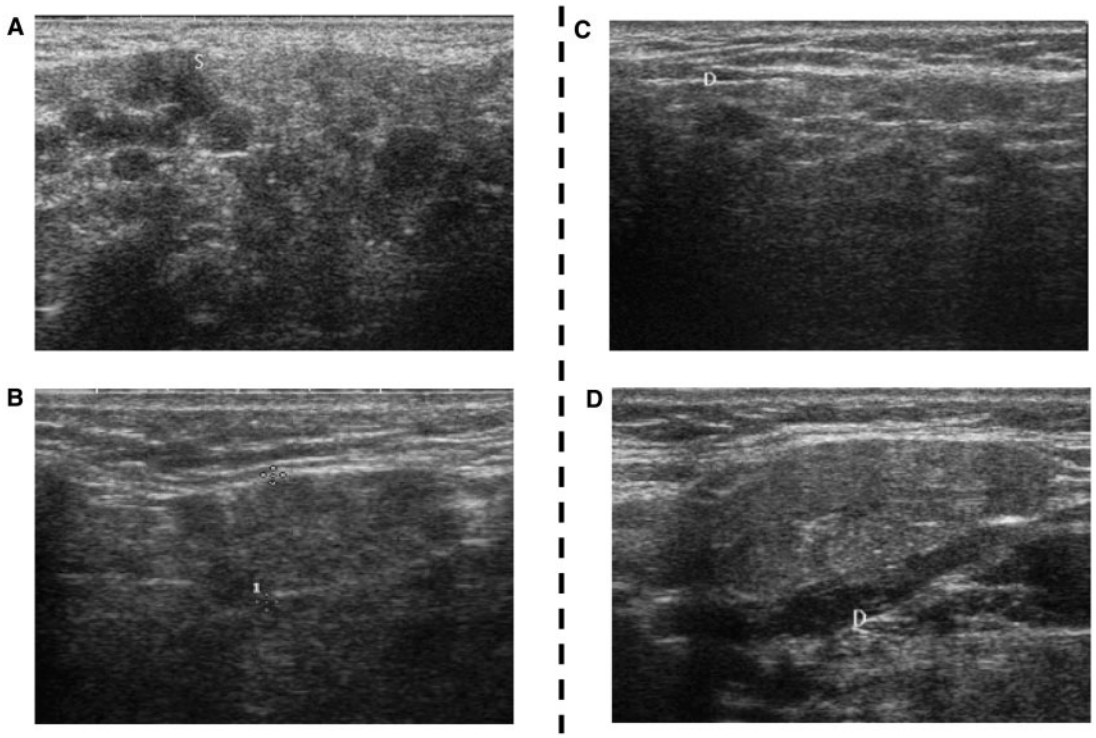
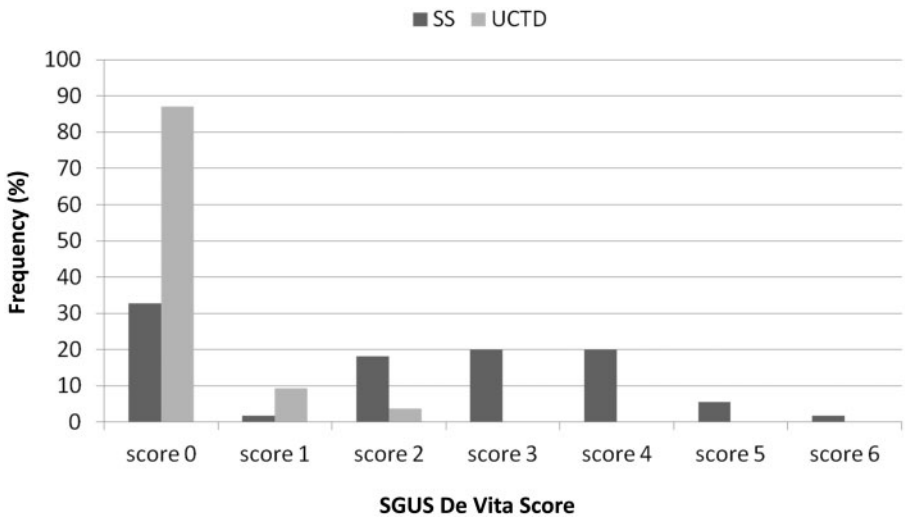
FIG. 1 Representative images illustrating salivary gland ultrasonography in patients with SS and UCTD



(**A**) SS parotid gland with confluent hypoechoic areas, multiple cysts and calcifications (grade 3) and (**B**) SS submandibular gland with hypoechoic area and hyperechoic bands (grade 2); (**C**) and (**D**) UCTD parotid and submandibular glands with non-specific mild changes (grade 1).

FIG. 2 Distribution of the SGUS findings in patients with SS and UCTD



Patients with SS presented SGUS score values evenly distributed across all the categories (i.e. 32.7% for score 0; 1.8% for score 1; 18.2% for score 2; 20% for score 3; 20% for score 4; 5.5% for score 5; 1.8% for score 6). On the other hand the prevalence of SGUS score values $\geqslant 1$ in patients with UCTD was significantly lower (i.e. 87% for score 0; 9.3% for score 1; 3.7% for score 2). SGUS: salivary gland ultrasonography.

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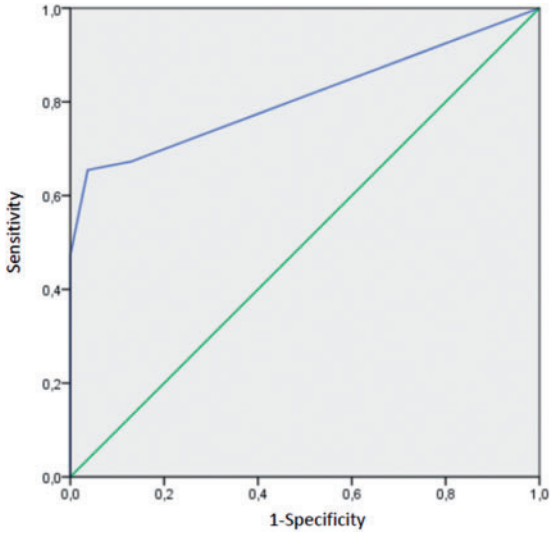
FIG. 3 Receiver operating characteristic curve showing the diagnostic accuracy of SGUS score for SS



Receiver operating characteristic (ROC) curve illustrating the performance of the SGUS score. The area under the curve of the ROC curve was 0.81 (95% CI 0.72, 0.89). The diagonal line represents the so-called line of no discrimination from the left bottom to the top right corners.
SGUS: salivary gland ultrasonography.

Discussion

Despite several studies in literature addressing the potential of SGUS, the present study is (to the best of our knowledge) the first specifically designed to verify the diagnostic accuracy of SGUS in distinguishing patients with SS from those with stable UCTD and those complaining of sicca symptoms. So far, a number of studies have confirmed SGUS to be a reliable tool for diagnosing SS in patients with sicca symptoms and suspected SS [1, 2] and always showed high specificity and sensitivity of >60%—independently of the grading system adopted [8]. More specifically, SGUS has been proved to be a valuable alternative to sialoscintigraphy in the diagnostic algorithm of SS, presenting a good correlation with the latter diagnostic technique [3, 5, 9, 10, 25]. Indeed, the accuracy of SGUS has become widely recognized as comparable to that of invasive methods such as scintigraphy and minor salivary gland biopsy [11, 12, 26, 27].

Regarding the diagnostic accuracy of SGUS in rheumatology settings, Wernicke *et al*. [6] extensively tested the performance of SGUS in 316 patients, including 21 patients with UCTD and other inflammatory rheumatic diseases and sicca symptoms as pathological controls; again, findings confirmed the accuracy of SGUS in differentiating SS from rheumatic disorders to be quite good. Similar conclusions were drawn in a work by Cornec *et al*. [16], in which the study population also included 11 patients affected by UCTDs.

TABLE 2 Diagnostic accuracy of SGUS score for SS diagnosis *vs* UCTD diagnosis: a comparison with standard tests

	Sensitivity	Specificity	PPV	NPV
SGUS score ⩾2	0.65	0.96	0.95	0.73
Anti-Ro/SSA antibodies	0.65	0.80	0.77	0.69
Schirmer's test ⩽5 mm/15 min	0.67	0.63	0.65	0.65
Unstimulated salivary flow ⩽1.5 ml/15 min	0.56	0.67	0.63	0.60
MSGB/FS	0.82	1.00	1.00	0.84

SGUS: salivary gland ultrasonography; MSGB/FS: minor salivary gland biopsy/focus score; PPV: positive predictive value; NPV: negative predictive value.

In line with the above-mentioned studies, the good sensitivity and high specificity of SGUS for the diagnosis of SS in rheumatology settings were confirmed by our findings as well, particularly in the differential diagnosis of SS from UCTD. In line with previous studies [7, 24], among all SGUS parameters, the most important variable in the diagnosis of SS in our population proved to be parenchymal inhomogeneity; in fact, evident multiple hypoechoic or anechoic areas were almost exclusively detected in the group of SS patients, whereas mild inhomogeneity (scores 0–1) was found mostly in the parotid and submandibular glands from the control group.

When compared with the other diagnostic tests for SS, SGUS presented a specificity that was only slightly lower than that of the MSGB, and a sensitivity that was comparable to those of Schirmer's test and the anti-Ro/SSA. Thus, even if MSGB presented the highest sensitivity and specificity, the diagnostic performance of SGUS was apparently even more reliable in distinguishing SS from UCTD compared with anti-Ro/SSA antibodies.

Finally, we found a good correlation between the SGUS score and both the whole USFR and the MSGB FS. In particular, a significantly higher SGUS De Vita score was found in those SS patients with FS ⩾ 3, a grade of salivary gland lymphocytic infiltration that is considered a negative prognostic index for subsequent lymphoproliferative complications in SS [28].

Despite the encouraging results, this study is not void of criticisms: being a single-centre study, the number of patients included was relatively limited and, most importantly, the control group was represented by patients diagnosed with UCTD, which is *per se* a heterogeneous entity. However, on the other hand, patients with UCTD had a stable disease, had been followed for a non-negligible amount of time and had all undergone minor salivary gland biopsy (which, to date, remains a cornerstone for SS diagnosis). Thus, even if further external validation studies appear undoubtedly necessary to corroborate any conclusions, our results seem to increase

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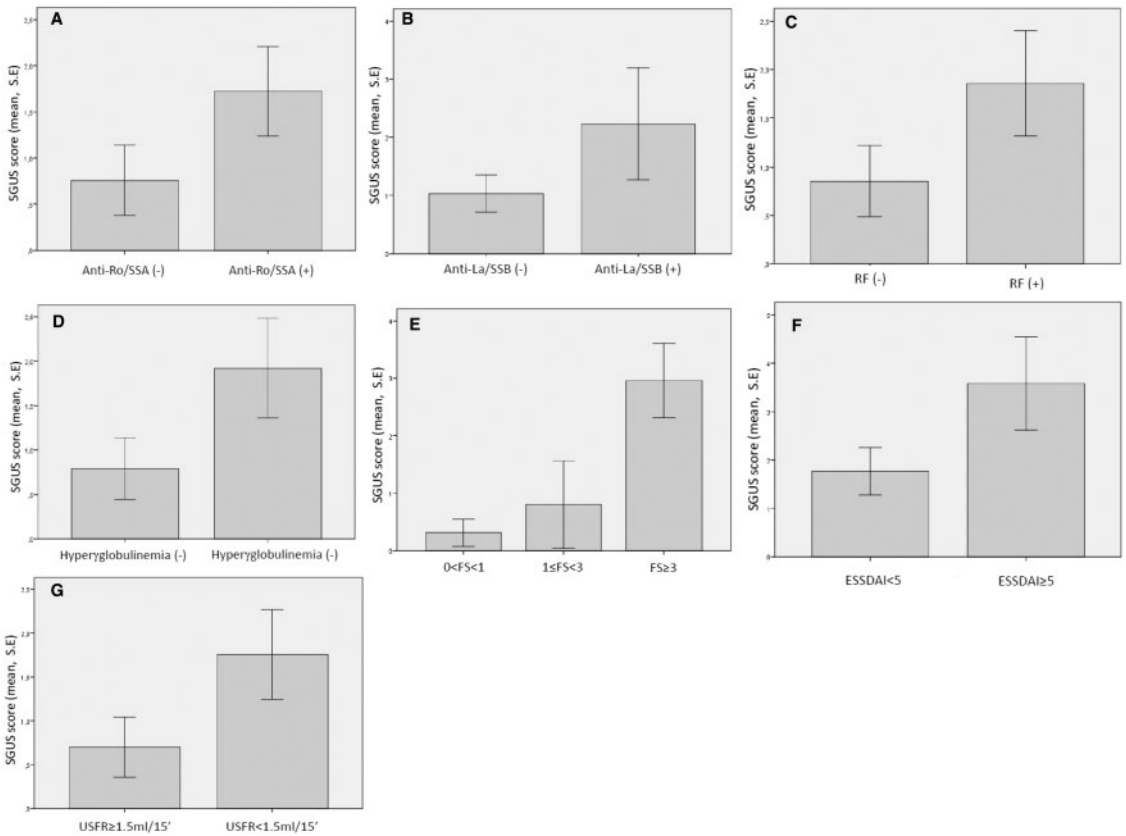
Fig. 4 Relationship between SGUS score and SS disease features



The graphs show the relationship between the median SGUS score and SS disease features, including: anti-Ro/SSA (**A**), anti-La/SSB (**B**), RF (**C**), hypergammaglobulinaemia (IgG) (**D**), minor salivary gland biopsy focus score (FS) (**E**), ESSDAI score (**F**) and the unstimulated salivary flow rate (**G**). SGUS: salivary gland ultrasonography.

the amount of evidence supporting the routine use of SGUS in the diagnostic algorithm of SS.

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