Ultrasonographic Scoring Systems – A Systematic Review

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In 1988, Bradus et al. reported the finding of multiple cystic changes in parotid glands in four out of six patients with Sjögren's syndrome on ultrasound. Based on the histopathologic examination of the excised major salivary glands, these cystic changes could be correlated with dilated salivary ducts surrounded by dense lymphocytic infiltrate [1]. Since this report, sonographically depicted morphological changes of salivary glands have been extensively studied in Sjögren's syndrome. Heterogeneity or inhomogeneity of the glandular parenchyma along with the presence of hypoechogenic areas has been consistently recognized as the hallmark pathological features [2]. Other characteristics and abnormalities reported with various frequency are an altered echogenicity of salivary glands (compared to surrounding tissues/muscles or thyroid gland), hyperechoic bands, calcifications and hyperechoic aggregates, changes in the size of salivary glands (increased or decreased), delineation of salivary glands from surrounding tissues with non-visibility of (posterior) glandular border, and the presence and number of abnormal lymph nodes. In patients with Sjögren's syndrome, different sonographic lesions can coexist and be found in varying proportions. An association with different disease stages has been suggested; e.g., hypoechoic areas have been correlated with inflammatory foci, and hyperechoic bands with the damage and fibrosis [3, 4]. Morphological lesions of salivary glands observed in Sjögren's syndrome have been lately defined and validated by a EULAR ultrasound primary Sjögren's syndrome study group [5]. As the most reliable sonographic characteristics emerged salivary gland homogeneity and echogenicity [5]. However, due to lack of access to tissue for a direct histopathological analysis, the substrate of morphological lesions such as hypoechoic areas or hyperechoic bands currently remains elusive.

In an effort to quantify morphological features depicted with ultrasound, several scoring systems have been developed in the last three decades [6–15], Table 12.1). Scoring systems have always been a subject of modifications and/or simplifications, which was reflected in a high heterogeneity between studies included in the meta-analysis by Delli et al. (identifying 37 studies with overall 33 different sonographic scoring systems) [16]. De Vita et al. have to be credited to provide the first comprehensive semi-quantitative scoring system in patients with Sjögren's syndrome [6]. From the initially five morphological features evaluated (parenchymal inhomogeneity, echogenicity, glandular volume, posterior glandular border, and presence of peri- and/or intra-glandular lymph nodes), a stepwise discriminant analysis revealed a significant discriminative power only for parenchymal inhomogeneity. The latter encompassed hypoechogenic areas, cysts, hyperechoic bands, and/or calcifications and was graded from mild, evident to gross. Characteristic of Sjögren's syndrome was any degree of inhomogeneity of parotid glands, and/or gross inhomogeneity of submandibular glands. Later, with the improved performance of ultrasound machines, Grade 1 (mild inhomogeneity) of the original De Vita's scoring was better specified and redefined. Using De Vita scoring, Baldini et al. found inhomogeneity Grade 2 or 3 characteristic of Sjögren's syndrome [17]. In addition, Luciano et al. demonstrated that a cut-off ≥ 2 of the De Vita scoring enabled the optimal discrimination between Sjögren's syndrome and undifferentiated connective tissue disease patients with sicca symptoms [18].

Salaffi et al. developed a 5-grade ultrasound score based on four parameters: the presence and the size of hypoechoic areas, the presence of echogenic bands, the size/volume of the salivary glands, and the visibility of posterior glandular border [8]. The final score was a sum of the individual scores (0–4) of each parotid and submandibular gland, and ranked from score 0 (minimum) to 16 (maximum). The score was originally evaluated in 30 patients with primary Sjögren's syndrome, and the same number of asymptomatic controls.

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The sonographic pattern was considered abnormal when both parotids or both submandibular glands exhibited a minimum score of 1. In a follow-up study on 77 Sjögren's syndrome patients and 79 symptomatic sicca controls, Salaffi et al. demonstrated that salivary gland ultrasound performed better compared to salivary gland scintigraphy or sialography in diagnosing Sjögren's syndrome [19]. The optimal sensitivity-to-specificity ratio was reached with a cut-off of 6, resulting in a diagnostic sensitivity of 75.3% and diagnostic specificity of 83.5%. Interobserver reliability of ultrasound was investigated in 12 patients and found to be good to excellent, with kappa values of 0.83, 0.79, and 0.72 for parenchymal homogeneity, echogeneity, or evaluation of glandular volume, respectively. Through the modification of scoring from Salaffi et al., Cornec et al. developed a five-grade (Grades 0–4) scoring system and showed that simply counting the highest grade of the four glands while setting the cut-off at 2 points provided the best diagnostic value for Sjögren's syndrome [13].

Hocevar et al. described an extensive composite semi-quantitative scoring system, evaluating five morphological features in parotid and submandibular glands: parenchymal echogenicity, homogeneity, the presence of hypoechoic areas, the presence of hyperechoic reflections, and clearness/delineation of salivary gland borders [11]. The scoring was evaluated in a cohort of 218 patients with sicca symptoms, 68 of whom were finally diagnosed with primary Sjögren's syndrome. Considering the best sensitivity-to-specificity ratio, the cut-off result characteristic of Sjögren's syndrome was set at 17, resulting in 58.8% diagnostic sensitivity and 98.3% diagnostic specificity. The reliability of designed semi-quantitative scoring system was later verified on 28 Sjögren's syndrome patients and 29 healthy controls [20]. The study showed a high interobserver agreement between

Table 12.1 Scoring systems for ultrasonographic evaluation of salivary glands in Sjögren's syndrome

Publication (year)	Glands evaluated	Sjögren's syndrome classification criteria	Control group	Definition of scoring	Final score/ cut-off	Diagnostic performance (sensitivity/ specificity, %)
De Vita et al. (1992)	PG SMG	Copenhagen AECG	SC HC UCTD	A score differentiated between different degrees of inhomogeneity: Mild inhomogeneity (1 point): diffuse or localized micro-areolar structure Evident inhomogeneity (2 points): multiple scattered hypoechogenic areas, usually of variable size and not uniformly distributed, and/or multiple punctate or linear nonshadowing densities Gross inhomogeneity (3 points): large circumscribed or confluent hypoechogenic areas, and/or gross linear densities, and/or multiple cysts or multiple calcifications resulting in severe damage of glandular architecture Final score was a sum of grades for paired parotid and paired submandibular glands Score was later redefined: Grade 0: complete homogeneity Grade 1: mild inhomogeneity – isolated hypoechoic areas, without hyperechoic bands Grade 2: evident inhomogeneity: multiple scattered hypoechoic areas of variable size, not uniformly distributed, and/or few hyperechoic bands Grade 3: gross inhomogeneity – large or confluent hypoechoic areas, and/or diffuse hyperechoic bands	0–6/≥1 0–6/≥2	88.8/84.6 65/96
Makula et al. (1996)	PG	ESCG	SC HC	Three grades of glandular inhomogeneity are distinguished: Mild inhomogeneity with diffuse hypoechoic areas less than 2 mm, with blurred borders. Evident inhomogeneity with 2–6 mm diameter hypoechoic areas with sharp borders predominate Gross inhomogneity with large (> 6 mm) circumscribed hypoechoic areas	Evident or gross inhomogeneity	71.7/100

Table 12.1 (continued)

Publication (year)	Glands evaluated	Sjögren's syndrome classification criteria	Control group	Definition of scoring	Final score/ cut-off	Diagnostic performance (sensitivity/ specificity, %)
Salaffi et al. (2000 and 2008)	PG SMG	ESCG (2000) AECG (2008)	SC	A 5-grade ultrasonographic score based on four parameters (the presence and the size of hypoechoic areas, presence of echogenic bands, the size of the salivary glands, and the visibility of posterior glandular border): Grade 0: Normal salivary glands Grade 1: Regular contour, small hypoechoic areas, without echogenic bands, regular or increased glandular volume and ill-defined posterior glandular border Grade 2: Regular contour, evident multiple scattered hypoechogenic areas usually of variable size (<2 mm) and not uniformly distributed, without echogenic bands, regular or increased glandular volume and ill-defined posterior glandular border Grade 3: Irregular contour, multiple large circumscribed or confluent hypoechogenic areas (2–6 mm) and/or multiple cysts, with echogenic bands, regular or decreased glandular volume and no visible posterior glandular border Grade 4: Irregular contour, multiple large circumscribed or confluent hypoechogenic areas (>6 mm), and/or multiple cysts or multiple calcifications, with echogenic bands, resulting in severe damage to the glandular architecture, decreased glandular volume and posterior glandular border not visible A final score was a sum of the scores (0–4) for all four glands	0–16/≥7	75.3/83.5
El Miedany et al. (2004)	PG	AECG	SC HC	Based on a study by Makula et al., a 4-grade score of glandular inhomogeneity was created: Grade 0: Normal homogenous parenchyma Grade 1: Mild inhomogeneity seen as diffuse hypoechoic areolae <2 mm with blurred borders Grade 2: moderate inhomogeneity with 2–6 mm diameter large hypoechoic areas, with sharp borders Grade 3: Severe inhomogeneity with >6 mm large circumscribed hypoechoic areas	0–3/≥1	93.6/95.0 (according to minor salivary gland biopsy 98.8%/93.6)
Niemelä et al. (2004)	PG SMG SLG	AECG	SC HC	Parenchymal structure was categorized into five grades: Grade 0: normal Grade 1: mild inhomogeneity (hypoechoic areas <2 mm) Grade 2: evident inhomogeneity (hypoechoic areas of 2–6 mm) Grade 3: gross inhomogeneity (hypoechoic areas >6 mm) Grade 4: adipose degeneration of the gland (adipose tissue echogenicity and parenchymal atrophy) Grades 1–4 in any of glands were considered pathologic	0–4/≥1	78/94

(continued)

Table 12.1 (continued)

Publication (year)	Glands evaluated	Sjögren's syndrome classification criteria	Control group	Definition of scoring	Final score/ cut-off	Diagnostic performance (sensitivity/ specificity, %)
Hocevar et al. (2005)	PG SMG	AECG	SC	A scoring that evaluates five parameters: *Echogenicity* Grade 0: normal Ggrade 1: decreased *Homogeneity:* *G*grade 0: homogeneous gland Ggrade 1: mild inhomogeneity, Grade 2: evident inhomogeneity Grade 3: gross inhomogeneity *Hypoechoic areas*: Grade 0: absent Grade 1: few Grade 2: several Grade 3: numerous *Hyperechoic bands/reflections* in submandibular glands: Grade 0 absent Grade 1 present *Hyperechoic bands/reflections* in parotid glands: Grade 0 absent Grade 1 few Grade 2 several Grade 3 numerous *Delineation of glandular borders*: Grade 0 regular defined borders Grade 1 partly defined borders Grade 2 ill-defined borders Grade 3: borders not visible The final US score was a sum of the five grades for all four glands	0–48/≥17	58.8/98.7
Milic et al. (2010)	PG SMG	AECG	SC HC	Parenchymal inhomogeneity was graded from 0 to 3: Grade 0: no inhomogeneity Grade 1: mild inhomogeneity Grade 2: evident inhomogeneity Grade 3: gross inhomogeneity Grade 1 was interpreted as a normal finding. Final score was a sum of the grades for each of the glands.	0–12/≥6	95.1/90.0
Cornec et al. (2013)	PG SMG	Clinical diagnosis	SC	A 5-grade score assesses glandular inhomogeneity as follows: Grade 0: normal homogeneous glands Grade 1: small hypoechogenic areas without echogenic bands Grade 2: multiple hypoechogenic areas <2 mm with echogenic bands Grade 3: multiple hypoechogenic areas measuring 2–6 mm with hyperechogenic bands Grade 4: multiple hypoechogenic areas measuring >6 mm or multiple calcifications with echogenic bands The highest grade of the 4 glands was considered for the analysis	0–4/≥2	62.8/95.0

Table 12.1 (continued)

Publication (year)	Glands evaluated	Sjögren's syndrome classification criteria	Control group	Definition of scoring	Final score/ cut-off	Diagnostic performance (sensitivity/ specificity, %)
Theander et al. (2014)	PG SMG	AECG	SC	Simplified a score from Hocevar et al., scoring only different degrees of glandular inhomogeneity: Grade 0: completely homogeneous Grade 1: mildly inhomogeneous Grade 2: several rounded hypoechoic lesions Grade 3: numerous or confluent rounded hypoechoic lesions The final score was the highest score in any of the four salivary glands	0–3/≥2	51.4/98.2
Jousse-Joulin, et al. (2019)	PG SMG	–	–	Consensual scoring system evaluating different degrees of inhomogeneity: Grade 0: normal glandular parenchyma Grade 1: mildly inhomogeneous glands without anechoic/hypoechoic areas Grade 2: moderately inhomogeneous glands with focal anechoic/hypoechoic areas Grade 3: severely inhomogeneous glands with anechoic/hypoechoic areas occupying the entire gland Descriptive recording of fatty glands and fibrotic glands	0–3/≥2 in at least 2 glands	–

Legend: *PG* parotid gland, *SMG* submandibular gland, *SLG* sublingual gland, *ESCG* European Community Study Group criteria, *AECG* American European Consensus Group classification criteria, *ACR-EULAR* American College of Rheumatology and European League Against Rheumatism classification criteria, *SS* Sjögren's syndrome, *SC* symptomatic controls, *HC* healthy controls, *UCTD* undifferentiated connective tissue disease

the two ultrasonographers for the assessment of glandular homogeneity (Cohen's kappa 0.90), hypoechoic areas (kappa 0.88), and final ultrasound score (kappa 0.90), though moderate for the evaluation of salivary gland borders and hyperechoic reflections (κ, 0.50 and κ, 0.52, respectively). Stemming from the sonographic evaluation described by de Vita et al. and Hocevar et al., Milic et al. developed a new score, grading (from 0 to 3) different degrees of inhomogeneity in each parotid and submandibular gland [12]. The final score ranked from 0 to 12. The score was evaluated in 115 patients with primary Sjögren's syndrome, 44 with secondary Sjögren's syndrome, 50 asymptomatic controls, and 36 healthy individuals. The optimal cut-off of 6 resulted in 95.1% diagnostic sensitivity and 90.0% diagnostic specificity for primary Sjögren's syndrome. Theander et al. similarly modified Hocevar's score, with the evaluation of a single parameter, that is, glandular homogeneity in accordance with the original publication [14]. The final score was the highest score in any of the examined parotid and submandibular glands. A score of 2 or 3 was interpreted as abnormal and typical for Sjögren's syndrome. More recently, Mossel et al. showed in a multivariate analysis that the evaluation of hypoechogenic areas with or without grading of the parenchymal echogenicity according to Hocevar score was sufficient to predict the classification of patients according to the ACR-EULAR 2019 classification criteria [21].

Few studies directly compared the diagnostic performance of different ultrasound scores [22–25]. In a comparative study from Lin et al., the scoring system by Hocevar et al. demonstrated superior likelihood ratio and accuracy, yet the Milic's scoring system was preferred for its balance between the diagnostic value and inter−/intra-observer agreement [22]. Zhang et al. compared a 0–16 points versus a 0–48 points scoring system and found a higher sensitivity using the 0–48 scoring system versus a superior specificity of the 0–16 system [23]. Qi et al. reported no significant difference between the four different scoring systems tested (Salaffi et al., Theander et al., and partial parotid and submandibular scoring system) [24]. Finally, a multicentre cross-sectional study compared the performance of 4 different scoring systems (Hocevar et al., Milic et al., Cornec et al., and Salaffi et al.) in a population of 97 patients with sicca symptoms, 39 of whom were had primary and 22 secondary Sjögren's syndrome [25]. The receiver-operating characteristic (ROC) curves and the positive likelihood ratio (LR+) of the four scores showed similar diagnostic perfor-

mance for primary Sjögren's syndrome (AUC 0.891 (95%CI, 0.812–0.970), LR 7.4; AUC 0.897 (95%CI 0.821–0.973), LR 11.8; AUC 0.885 (95%CI, 0.804–0.965), LR 11.8; and 0.915 (95%CI, 0.848–0.982), LR 11.3; for Hocevar et al., Milic et al., Cornec et al., and Salaffi et al. scores, respectively). The study also reported a good interobserver reproducibility (kappa, 0.71 ± 0.13) with 85.7% agreement between ultrasonographers to determine the pathological character of the salivary glands [25].

With the aim to standardize ultrasound assessment and to reach the widespread international consensus, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) salivary gland ultrasound task force group recently developed and proposed a novel scoring system based on the consensual ultrasound definitions of elementary lesions seen in Sjögren's syndrome [15]. OMERACT consensus recognized glandular inhomogeneity with anechoic/hypoechoic areas/foci as the most important morphological feature of Sjögren's syndrome and proposed a 4-grade semi-quantitative score to grade the severity of these lesions as follows: Grade 0, representing normal glandular parenchyma; Grade 1, representing mildly inhomogeneous glands without anechoic/hypoechoic areas; Grade 2, representing moderately inhomogeneous glands with focal anechoic/hypoechoic areas; Grade 3, representing severely inhomogeneous glands with anechoic/hypoechoic areas occupying the entire gland. The consensual scoring system recommends the evaluation of parenchymal morphological lesions in paired parotid and submandibular glands and a cut-off of 2 in at least two examined glands for a positive result for Sjögren's syndrome. In a web-based video clip exercise, the OMERACT score showed excellent intra-observer reliability (Cohen's kappa 0.81 (95% CI, 0.77 to 0.84)) and good interobserver reliability (Light's kappa 0.66 (95% CI, 0.61 to 0.70)); the reliability performance was subsequently confirmed in a patient-based exercise [26].

Two morphological features which were not addressed in the initially proposed OMERACT scoring, were the presence of fatty lesions and of fibrotic lesions (reflected ultrasonographically in hyperechoic bands). According to the proposal, a descriptive finding of fatty lesions or fibrotic lesions should be considered when the proposed semi-quantitative scoring system cannot be applied. In a subsequent patient reliability exercise, fatty lesions and diffuse hyperechoic bands were scored as Grades 1 and 3, respectively [26]. Although reproducible and feasible, the construct and criterion validity of the OMERACT scoring system has yet to be shown on a large patient cohort, including classification criteria, histopathological findings, immunoserological findings, or tests of salivary gland function of Sjögren's syndrome.

Which score to select? An inherent weakness of all current scoring systems is an observer's bias in the assessment of morphological changes of salivary glands. Nevertheless, quantitative analyses of ultrasound findings in salivary glands were infrequent in the past [27, 28]. To overcome the subjective nature of sonographic evaluation, the multicentre project HarmonicSS recently proposed an artificial intelligence algorithm for the automated segmentation of salivary gland ultrasound images, of which the preliminary results have been reported recently [29, 30].

Where, when, and how to apply salivary gland ultrasound?

Salivary gland ultrasound could have several potential roles in Sjögren's syndrome.

Firstly, salivary gland ultrasound may support the diagnosis of Sjögren's syndrome, particularly in facilitating early disease recognition. Salivary gland sonographic findings are strongly associated with salivary gland function (assessed with salivary flow tests and/or salivary gland scintigraphy), histological, and serologic features of Sjögren's syndrome [19, 31–33]. Investigating the validity of major salivary gland ultrasound in comparison to biopsies of parotid and labial glands and anti-SSA antibody status in a group of patients with clinically suspected primary Sjögren's syndrome [32], Mossel et al. showed a good agreement between ultrasonography and parotid (83%) or labial (79%) gland biopsy. Negative ultrasound predicted negative parotid gland biopsy, while positive ultrasound predicted positive labial gland biopsy. Furthermore, the combination of positive ultrasound and anti-SSA antibodies was highly predictive for Sjögren's syndrome, whereas the combination of negative ultrasound and absent anti-SSA antibodies made a classification of Sjögren's syndrome unlikely [32].

In addition, a pathological salivary gland ultrasound correlated with the immunoserological profile of Sjögren's syndrome [33–36]. Moreover, the presence of a higher number of autoantibodies was associated with a higher probability of a pathological ultrasound result in one study [37].

An Italian group recently demonstrated that Sjögren's syndrome patients with normal salivary gland ultrasound on either the De Vita et al. score or the OMERACT score had a milder disease phenotype featured by a less impaired salivary gland function, a lower ESSDAI, and more often a negative labial gland biopsy [38].

The comparison between classification criteria and major salivary gland ultrasound showed that pathological ultrasound predicted the classification of Sjögren's syndrome, though negative ultrasonographic result did not exclude it. Comparing the performance of salivary gland ultrasound with three different classification criteria, that is, the American European Consensus Group (AECG) classification criteria, American College of Rheumatology (ACR) classification criteria, and ACR-European League Against Rheumatism (EULAR) classification criteria, an agreement, a sensitivity, and a specificity of 82%/71%/92%,

86%/77%/92%, and 80%/67%/94%, respectively, were demonstrated [32].

The diagnostic value of salivary gland ultrasound in Sjögren's syndrome was further evaluated in a recent meta-analysis [39]. Based on data from 54 different studies, the authors reported an 80% (95% CI, 77%–83%) pooled diagnostic sensitivity and a 90% (95% CI, 87%–92%) pooled diagnostic specificity for Sjögren's syndrome. The pooled positive and negative likelihood ratios were 8 (95% CI: 6.4–10) and 0.22 (95% CI: 0.19–0.25), respectively [39]. The meta-analysis also revealed that the diagnostic performance of ultrasound was not significantly affected by different classification criteria used for Sjögren's syndrome, nor patient age, or disease duration time.

Recently, Jousse-Joulin et al. proposed salivary gland ultrasonography as an initial screening tool in the diagnostic algorithm of clinically suspected Sjögren's syndrome, followed by confirmational investigations such as immunoserology and/or histology (minor salivary gland biopsy) [40].

With the aim to further address the diagnostic utility of salivary gland ultrasound, investigators studied the inclusion of salivary gland ultrasound into the current ACR/EULAR 2016 classification criteria [41–44]. Le Goff et al. used a 5-grade scoring system (grades 0–4) to assess four major salivary glands (paired parotid and submandibular glands), with the highest grade recorded and considered abnormal when the score was ≥2 [41]. When using a physician diagnosis of Sjogren's syndrome as a gold standard and adding ultrasound into the ACR/EULAR 2016 criteria with the assigned weight of 1 point, the sensitivity of modified criteria improved (from 87.4% to 91.1%), while the specificity slightly decreased (from 95.4% to 93.8%). Notably, none of the patients who fulfilled modified criteria, i.e., criteria that included ultrasound criterion, did qualify as a Sjögren's patient without positive minor salivary gland histology or presence of anti-SSA antibody [41]. The improved performance of modified ACR/EULAR 2016 criteria after adding ultrasound to classification items was confirmed by other authors (Takagi et al. and Geng et al. [42, 43]. In a study of similar design and using a 4-grade scoring system to quantify the presence hypoechoic areas (Grade 0, no hypoechoic areas; Grade 1, few scattered hypoechoic areas; Grade 2, several hypoechoic areas; and Grade 3, numerous hypoechogenic areas; as a pathologic ultrasound result, an average score for one parotid and one submandibular gland was determined at 1.5). Van Nimwegen et al. recently confirmed that the optimal weight of salivary gland ultrasound in the modified ACR/EULAR 2016 criteria was 1 point and that ultrasound could replace Schirmer's test, ocular staining score, or unstimulated whole saliva flow test without decreasing the accuracy of ACR/EULAR 2016 criteria. In contrast, the substitution of a histological or serological item for ultrasound resulted in a significantly decreased performance of the ACR/EULAR 2016 criteria [44] Their conclusions are in line with those from the multicentre study UTOPIA, which showed an improved sensitivity (change from 90.2% to 95.6%), with quite similar specificity (change from 84.1% to 82.6%) following the inclusion of salivary gland ultrasound to ACR/EULAR 2016 criteria. In the latter study, a 5-grade ultrasonographic scoring focused on the extensiveness of anechoic/hypoechoic foci in paired parotid and submandibular glands (Grade 0, anechoic/hypoechoic foci; Grade 1, hypo/anechoic areas occupying less than 25% of the gland surface area; Grade 2, hypo/anechoic areas occupying 25%–50% of the gland surface area; Grade 3, hypo/anechoic areas occupying more than 50% of the gland surface area; and Grade 4, hypo/anechoic areas occupying the entire gland surface area). A score ≥ 2 was defined as characteristic for Sjögren's syndrome [45].

Although these studies largely prove the diagnostic value of ultrasound in Sjögren's syndrome, further data on the discriminatory value of ultrasound versus diseases mimicking Sjögren's syndrome are needed before the technique can be implemented in the classification criteria [46]. Several disorders like sarcoidosis, IgG4 disease, amyloidosis, or HIV infection may affect the salivary glands and are currently considered exclusion criteria in the ACR-EULAR classification [47]. A recent study that compared cohorts of patients with Sjögren's syndrome, sarcoidosis, AL amyloidosis, and healthy controls, while applying the Hocevar ultrasound score, showed that 27% of amyloidosis and 19% of sarcoidosis patients scored positive for Sjögren's syndrome [48]. Furthermore, ultrasound differentiation between Sjögren's syndrome and IgG4-related disease is particularly challenging as hypoechoic areas and a reticular pattern (a mixture of hypoechoic areas and hyperechoic bands) are common for both diseases, although IgG4-related disease tends to target submandibular glands more than parotid glands, and the nodal lesions of submandibular glands were much more frequent in IgG4-related disease compared to Sjögren's syndrome [49, 50].

Secondly, major salivary gland ultrasound could represent an additional index to evaluate disease activity and prognosis. The association between ultrasound scores and extraglandular manifestations of Sjögren's syndrome and more severe disease activity (assessed by EULAR Sjögren's syndrome disease activity index – ESSDAI and/or EULAR Sjogren's Syndrome Patient Reported Index- ESSPRI) have been found in many [14, 51–55], but not all, [31, 37] cross-sectional studies. In one recent study, patients with the most pronounced ultrasound findings had a 3.5 times higher risk of moderate or high disease activity assessed by ESSDAI [52]. Strong association between sonographic findings and clinical (salivary gland enlargement, purpura, or cryoglobulinaemic vasculitis), histological (germinal centre-like structures in salivary gland biopsy), or immunological markers

(such as immunoglobulin mono/oligoclonality, CD4-T cell lymphopenia, reduced number of memory B cells in circulation) of lymphoma risk are of clinical significance. Nevertheless, before including salivary gland ultrasound as a prognostic marker, additional prospective and longitudinal studies are required.

Finally, salivary gland ultrasound could have a role of precursor, i.e., predicting and/or monitoring response to treatment [56–59]. In a randomized double-blind trial on treatment with rituximab versus placebo, Fisher et al. assessed morphological changes of parotid and submandibular glands, and semi-quantitatively scored 5 domains: the number of involved glands, glandular echogenicity, glandular heterogeneity based on the presence of hypoechoic areas, the size of hypoechoic areas, and posterior glandular border. The total ultrasound score ranged from 0 (minimum) to 11 (maximum). In the rituximab group, the investigators found more improvement in the total ultrasound score compared to the placebo group. Analysis of individual components of the total ultrasound score, however, revealed glandular delineation as the only domain with statistically significant improvement following rituximab treatment [56].

Similarly, a sub-study of the TEARS trial evaluated morphological changes of paired parotid and submandibular glands after treatment with rituximab [57]. Based on the presence and size of hypoechoic areas and the presence of hyperechoic bands, glandular echostructure was graded on a scale from 0 to 4 (Grade 0, indicated a normal homogeneous gland; Grade 1, small hypoechoic areas without echogenic bands; Grade 2, multiple < 2 mm large hypoechoic areas with hyperechoic bands; Grade 3, multiple 2–6 mm large hypoechoic areas with hyperechoic bands; and Grade 4, multiple > 6 mm large hypoechoic areas or multiple calcifications with hyperechoic bands). In each patient, both the highest score of the four glands and the sum of individual scores (range 0–16) were considered for the analysis.

The study showed an association between the severity of morphological changes in major salivary glands seen on ultrasound and the lack of response to a single rituximab course. Next, this study also showed a significant improvement of echostructure of parotid glands in rituximab compared to placebo-treated patients (50% vs. 7%, respectively) [57].

In addition, Diekhoff et al. performed a single-centre, double-blind study investigating ianalumab, that is, a monoclonal antibody against B cell activating factor receptor, versus placebo [58]. Parotid and submandibular glands were evaluated using B mode (scoring from de Vita et al), power Doppler, contrast-enhanced ultrasound and parotid glands. After a 24-week period, numerical improvement in salivary gland morphology (defined as attaining ≥1-point reduction from baseline De Vita score) and declining glandular inflammation were observed in the treated versus placebo group compared to baseline [58].

Grading morphological changes seen on salivary gland ultrasonography at baseline helped to predict treatment outcomes. Takagi et al. evaluated the response to the treatment of xerostomia [59]. These authors graded the presence and the extent of three different morphological features (hypoechoic areas, echogenic bands, and glandular contours) in each parotid and submandibular gland from 0 to 4 (Grade 0, representing normal glands and Grade 4, representing the most severe changes with generalized hypoechoic areas, echogenic bands in the parenchyma, and irregular glandular contour). The final score was the sum of the two gland types (parotid and submandibular glands) on either side. They found the baseline ultrasound score as the most significant predictor of net salivary flow rate increase [59].

In conclusion, the promising role of salivary gland ultrasound as an important outcome domain for clinical trials should be further investigated.

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