Can ultrasound of the major salivary glands differentiate Sjögren's disease from its major mimics?

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Abstract

Objective

Ultrasound of the major salivary glands (SGUS) is widely used to assess the major salivary glands in Sjögren's disease (SjD). Little is known, however, regarding the diagnostic accuracy of SGUS to differentiate SjD from its mimics. This study aims to investigate the diagnostic accuracy of SGUS in differentiating SjD from other diseases with salivary gland involvement.

Methods

SGUS was performed in 20 consecutive patients with SjD and 20 consecutive patients with well-established systemic disease, i.e. with either sarcoidosis, amyloidosis, HIV infection or chronic HCV infection. Images were scored independently by two blinded observers using the Hocevar scoring system. Diagnostic accuracy to discriminate between the patient (sub-)groups was explored.

Results

The accuracy of SGUS to differentiate SjD from other systemic diseases was excellent (area under ROC curve of 0.91). The optimal cut-off value to define positive or negative ultrasound for SS was 15. Sensitivity, specificity, positive predictive value and negative predictive value were high, varying from 85-90%, and diagnostic odds ratio was 51. SGUS was positive in the vast majority of SjD patients (n=18), but also in 2 patients with HIV infection and one patient with sarcoidosis. SGUS score differed significantly between patients with SjD and other systemic diseases (median 27 vs. 10, $p<0.001$) as well as between SjD patients and patients with either sarcoidosis, amyloidosis, HIV or HCV infection (all $p<0.05$).

Conclusion

This study indicates that SGUS has a potentially high diagnostic accuracy to discriminate SjD from systemic diseases which can also cause salivary gland involvement.

Key words

Sjögren's syndrome, ultrasonography, diagnostic imaging, sarcoidosis, amyloidosis, HIV, Hepatitis C, sensitivity, specificity

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Introduction

The accuracy of B-mode ultrasound to evaluate the involvement of the major salivary glands in Sjögren's disease (SjD) and eventually to diagnose the disease continues to be a topic of interest (1, 2). It is generally agreed that salivary gland ultrasonography (SGUS) is a well-tolerated, non-invasive, inexpensive and non-irradiating imaging technique (3) exhibiting high reliability (4, 5). Studies have shown that SGUS may even replace in some cases more invasive diagnostic tests, like the salivary gland biopsy, as well as that it can be added in the array of tests used in the diagnostics of SjD (2, 6-11).

Studies have been published showing the added value of SGUS in the 2016 ACR-EULAR classification criteria (12, 13). However, none of those studies included a control group of patients with a disease mimicking SGUS, like sarcoidosis, amyloidosis, human immunodeficiency virus (HIV) and hepatitis C (HCV) infection. These diseases are known to affect the major salivary glands, cause dry mouth and they can have similar histopathological features with SjD (14-17). Until now, only sporadic data have been published to enlighten the diagnostic accuracy of SGUS to distinguish SjD from its mimics. The aim of this study was to assess the potential diagnostic accuracy of SGUS in differentiating patients with SjD and patients with sarcoidosis, amyloidosis, HIV or HCV infection.

Materials and methods

Patients

Twenty consecutive patients fulfilling the American College of Rheumatology – European League Against Rheumatism (ACR-EULAR) criteria for SjD (18) and 20 consecutive patients with well-established systemic diseases mimicking SjD, *i.e.* 5 patients with sarcoidosis, 5 patients with amyloidosis, 5 patients with HIV infection and 5 patients with HCV infection, were included in the department of Rheumatology and Clinical Immunology, Pulmonology and Internal Medicine in the period between April and August 2016. All patients with SjD underwent a SGUS as part of their diagnostic work-up. The diagnosis of sarcoidosis was made based on the clinical presentation, histologic proof of granulomatous inflammation, and exclusion of malignancy and infection as alternative cause of granulomas. Additionally, to ensure as much as possible a representative population of patients with sarcoidosis, we included patients with different organ involvement, *e.g.* parotid, lung and ocular involvement. Patients with amyloidosis were diagnosed based on a biopsy of bone marrow, subcutaneous fat tissue, minor salivary gland of the lip or musculus vastus lateralis. Patients with amyloidosis exhibited a wide range of system involvement, ranging from none to involvement of the kidneys, myocardium and Waldenström's macroglobulinemia. The diagnosis of HIV and HCV infection was based on the detection of circulating antibodies and a positive polymerase chain reaction (PCR). All patients visited the outpatient clinic of the department of Rheumatology and Clinical Immunology and the department of Internal Medicine, Infectious Diseases Service, of the University Medical Center Groningen. All patients with SjD were subjected to SGUS evaluation as part of the routine diagnostic work-up, patients with sarcoidosis, amyloidosis, HIV infection and chronic HCV infection provided written informed consent in accordance with the requirements of the ethics committee of the University Medical Center Groningen (METC waiver 016/120).

Ultrasonography

All patients were examined with the same ultrasonographic scanner (Esaote MyLabSeven, Genova, Italy), equipped with a high-resolution linear scanner (4-13MHz). Each patient was scanned in a supine position with the neck slightly extended and the head turned slightly to the opposite site. The parotid glands were examined in both axial and coronal planes, the submandibular glands only in the coronal plane.

The following images were stored from each patient and used: one showing the thyroid gland, one showing the right submandibular salivary gland, one showing the left submandibular salivary gland, two providing an over-

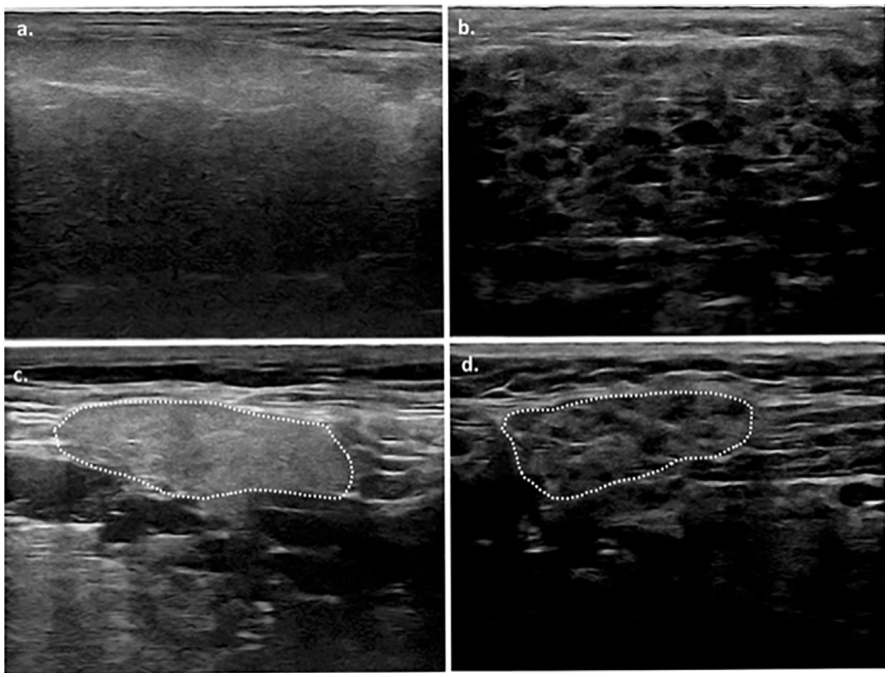

Fig. 1. Representative ultrasonographic images of the major salivary glands: **a**. parotid gland with normal echostructure; **b**. parotid gland with echostructure corresponding to SjD; **c**. submandibular gland with normal echostructure; **d**. submandibular gland with echostructure corresponding to SjD.

view of the right parotid gland and two providing an overview of the left parotid gland (Fig. 1). Images were anonymised and allocated to a random number.

All images were scored independently and in a random order by two observers (KD and JFN; for scoring system see below) on the same monitor (MultiSync E231, 23 inches, NEC, Illinois, USA). The observers were blinded for all other the diagnostic work up results, *i.e*., salivary gland biopsy, circulating auto-antibodies, salivary function tests, tear gland function tests and subjective oral and ocular symptoms.

Ultrasonographic assessments

The following ultrasonographic variables were assessed in the parotid and submandibular salivary glands according to the Hocevar scoring system: echogenicity, parenchymal homogeneity, the presence of hypoechogenic areas, and the clearness of posterior glandular border (3):

i. Parenchymal echogenicity was evaluated in comparison with the thyroid gland or when there was coincident thyroid gland disease by surrounding anatomical structures (muscular structures, sub- cutaneous fat). Echogenicity was graded 0 if echogenicity was comparable to the thyroid, and 1 if it was decreased.
ii. Homogeneity was graded 0 for a homogeneous gland, 1 for mild inhomogeneity, 2 for evident inhomogeneity, and 3 for a grossly inhomogeneous gland.
iii. Presence of hypoechogenic areas was graded 0 for no hypoechogenic areas, 1 for a few scattered areas, 2 for several areas, and 3 for numerous hypoechogenic areas.
iv. Hyperechogenic reflections in the parotid glands were graded 0 for no hyperechogenic reflections,1 for a few, scattered, 2 for several, and 3 for numerous hyperechogenic reflections, and in submandibular glands 0 for absent and 1 for present.
v. Clearness of salivary gland borders was graded 0 for clear, regular defined borders, 1 for partly defined borders, 2 for ill-defined borders, and 3 for borders not visible).

Finally, ultrasound total score (UTS) was calculated as the sum of the grades for the five variables described above for all four glands (range 0–48). According to the literature, the cut-off value to define positive or negative ultrasound for SjD was set at 15 (9, 19).

Data analysis

Statistical analyses were performed using IBM SPSS Statistics 23 (SPSS, Chicago, IL, USA).

Diagnostic accuracy of SGUS to discriminate between SjD and other systemic diseases was explored using area under the ROC curve (AUC), sensitivity, specificity, Youden's index, positive predictive value (PPV) , negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR). AUC was interpreted as no discrimination (0–0.5), poor accuracy (0.5–0.7), fair (0.7–0.8), good (0.8–0.9) or excellent (0.9–1.0) [Tape, https://darwin.unmc.edu/dxtests/]. Furthermore, differences in UTS between the patients (sub-)groups were analysed using the Mann-Whitney U-test. p-values <0.05 were considered statistically significant.

Results

Of the 20 included patients with SjD, the median age was 50 years (range: 20–71), 19 were female, and the median UTS was 27 (range: 11–40). Of the 20 included patients with systemic diseases or infectious diseases, the median age was 53 years (range: 25–80), 14 were male, and the median UTS was 10 (range: 6–29; Table I). Regarding the oral symptoms, 95% of the patients with SjD reported to have daily complaints of dry mouth longer than 3 months, 85% needed liquid, *e.g*. water, to swallow food and 70% reported recurrent or persistent swelling of the major salivary glands. Interestingly, in the group of patients with systemic diseases, 45% of the patients reported to have daily complaints of dry mouth longer than 3 months, 30% needed to drink sips of water to swallow food and 20% reported recurrent or persistent swelling of the major salivary glands. Fourteen individuals (70%) diagnosed with SjD tested positive for anti-Ro/La antibodies, while 6 patients (30%) did not. Among the 5 patients with sarcoidosis, only 3 underwent anti-Ro/La testing, with all cases returning negative results. Notably, the patient with sarcoidosis, whose SGUS findings were consistent with SjD, was part of this

Table I. Patients' characteristics.

Disease Group	Age median (range)	Gender male: female	Dry mouth >3 months n (%)	Recurrent/ swollen salivary glands n (%)	Need of liquid to swallow food n (%)	Ultrasound total score median (range)
SjD	50 (20-71)	1: 19	19 (95)	14 (70)	17 (85)	27 (11-40)
Other systemic diseases	53 (25-80)	14: 6	9 (45)	4 (20)	6 (30)	10 (6-29)
1. Sarcoidosis	44 (25-45)	3: 2	3 (60)	4 (80)	1 (20)	10 (9-29)
2. Amyloidosis	74 (53-80)	2: 3	3 (60)	0 (0)	2 (40)	11 (10-12)
3. HIV infection	58 (26-61)	5: 0	3 (60)	0 (0)	3 (60)	10 (9-27)
4. HCV infection	53 (29-69)	4: 1	0 (0)	0 (0)	0 (0)	10 (6-14)

Table II. Ultrasound of major salivary glands *versus* classification diagnosis (SjD or other systemic disease).

Cut-off point	**15**
Sensitivity	90
Specificity	85
Youden's index	0.75
PPV	86
NPV	89
LR+	6.0
LR-	0.1
DOR	51.0

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; DOR: diagnostic odds ratio.

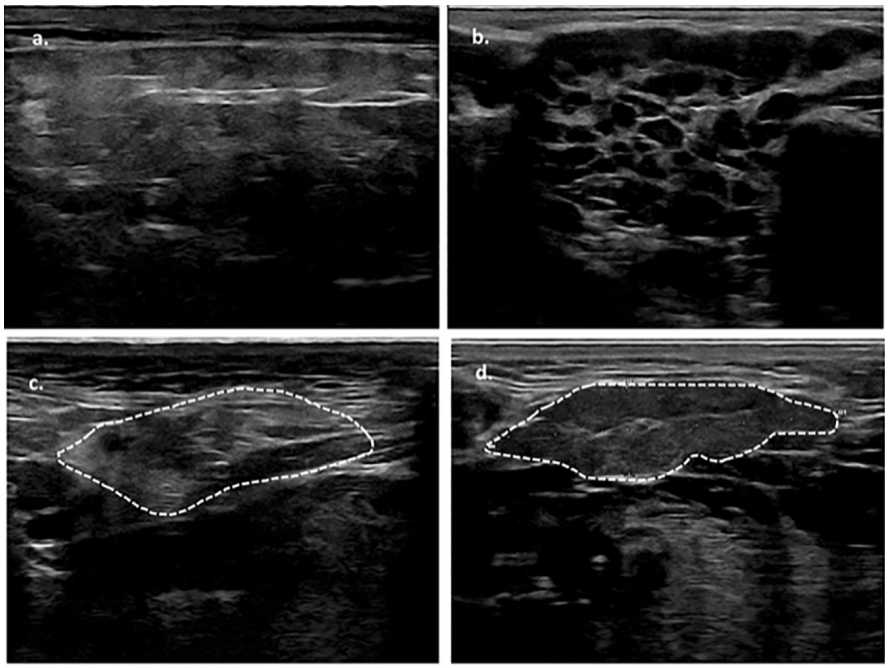

Fig. 2. Ultrasonographic images of the major salivary glands of patients with systemic diseases who had positive ultrasound for SjD: **a**. parotid gland of patient with HIV infection; **b**. parotid gland of patient with sarcoidosis; **c**. submandibular gland of patient with HIV infection; **d**. submandibular gland of patient with sarcoidosis.

subgroup and tested negative for anti-Ro/La antibodies. As for the remaining patients, no serological data pertaining to SjD were available, primarily due to a weakened suspicion of SjD during the diagnostic assessment, leading to the omission of further testing. Table I summarises the patient characteristics of all disease (sub)groups.

Inter-observer reliability in scoring the ultrasonographic images was excellent, with ICC of 0.88 for the UTS. Cohen's kappa was 0.80 and 0.85 and the percentage of absolute agreement was 90% and 93%, respectively, when cut-off value ≥17 and ≥15 was applied to define positive or negative ultrasound for SjD. The accuracy of SGUS to discriminate SjD from other systemic diseases was excellent, with area under ROC curve of 0.91 and the optimal cut-off value was 15. The agreement between SGUS positivity and positive diagnosis for SjD was good (κ=0.75 and percentage of absolute agreement was 87.5), with sensitivity of 90%, specificity of 85%, PPV of 86% and NPV of 89% (Table II). UTS was positive in 2 patients with HIV infection and one patient with sarcoidosis (Fig. 2). Regarding the patients with HIV, the first one (SGUS score=27) has reported having both dry mouth for longer than 3 months and recurrent/ swelling of the major salivary glands. The second patient (SGUS=18) did not report having any oral clinical symptoms that could point towards SjD, *i.e.* neither dry mouth, nor need of liquid to swallow food nor recurrent/ persistent swelling of the major salivary glands. The patient with sarcoidosis and SGUS compatible with SjD (SGUS-29) presented at the time of the SGUS examination with persistent swelling of the parotid glands. Interestingly, SGUS was negative in 2 patients with SjD.

SGUS differed significantly between patients with SjD and patients with systemic diseases mimicking SjD; (median 27 *vs*. 10, $p<0.001$) as well as between patients with SjD and the subgroup of patients with either sarcoidosis, amyloidosis, HIV or HCV infection ($p<0.05$; Fig. 3).

Discussion

The present study explored the use of SGUS in a representative population of consecutive patients diagnosed with SjD and its major mimics, *i.e.* sarcoidosis, amyloidosis, HIV infection and chronic HCV infection. The latter are systemic diseases that could also affect the major salivary glands, cause dry mouth or have similar histopathological features with SjD. These diseases are considered exclusion criteria for the classification of patients according to the 2016 ACR-EULAR classifi-

cation criteria (18), because patients with these diseases can mimic SjD and thus lead to a false positive diagnosis. This study indicates that SGUS has potential excellent diagnostic accuracy to discriminate SjD in a group level from associated systemic diseases with salivary gland involvement, viz. area under ROC curve of 0.91. The optimal cut-off value was 15 and showed DOR of 51. Furthermore, the median SGUS score was significantly higher in patients diagnosed with SjD compared to patients with these systemic diseases or infectious diseases.

The results of the present study are in agreement with the study of Law *et al*. (20), who also detected that the UTS was significantly higher in SjD patients compared to the rest of patients with a disease mimicking SjD. Additionally, Law *et al*. also identified that 19% of patients with sarcoidosis and 27% patients with amyloidosis had a SGUS compatible with SjD (20). Similarly with Law *et al*., we also identified that 1 of the five patients with sarcoidosis might present with a SGUS positive for SjD. In our study, however, none of the patients with amyloidosis had a SGUS compatible with SjD. The discrepancy between our study and the study of Law et al could be attributed to the different disease stage and/or disease duration of the patients with amyloidosis that were recruited.

To the best of our knowledge, no data have been published yet regarding the ultrasonographic characteristics in the major salivary glands of patients with HIV. Interestingly, in our study we detected that SGUS score was also positive in 2 patients with HIV infection. Benign lymphoepithelial cysts (BLEC) are a common manifestation in persons with HIV (16) and it is speculated that they might result in ultrasonographic characteristics resembling SS. SGUS score was also positive in and one patient with sarcoidosis (score=29). Possibly the presence of non-caseating granulomas in the parotid glands (17) might have led to this ultrasonographic appearance.

Luciano *et al*. showed that SGUS is a highly specific tool for distinguishing SjD from undifferentiated connective tissue diseases (21). Undifferentiated connective tissue diseases are a set of unclassifiable systemic autoimmune diseases that shares clinical and serological manifestations with definite connective tissue diseases, which, however, do not fulfil over time, any of the foreseen classification criteria (22). Similarly, Simizu *et al*. investigated SGUS in patients with IgG4-related sialadenitis and whether it can differentiate them from SjS (23). They concluded that changes in the submandibular glands affected by IgG4-related disease could be easily detected using SGUS and that SGUS could also differentiate IgG4-related disease from SjS (23). Recently, Liu *et al*. confirmed in a cohort of 150 patients with IgG4 related sialadenitis and 100 patients with SjD that indeed there are clear differences but also remarkable similarities in SGUS between both diseases (24).

It needs to be emphasised that when coming across a SGUS compatible with SjD, the possibility of a coexisting mucosa-associated lymphoid tissue (MALT) lymphoma, should not be dismissed (Fig. 4). In such instances, it is imperative to consider additional clini-

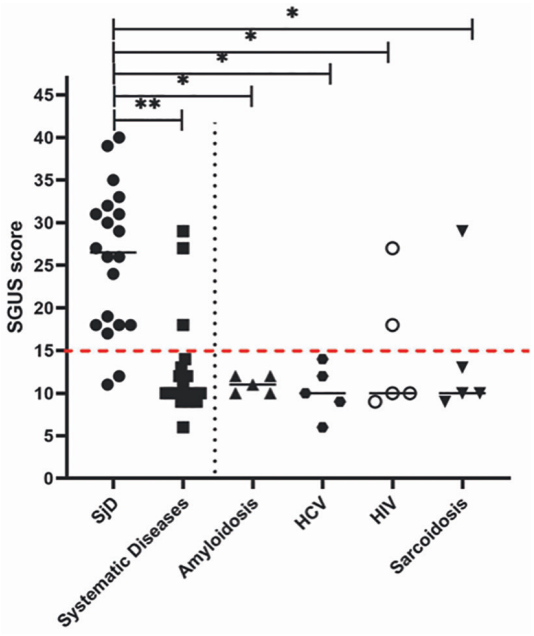

Fig. 3. SGUS score in patient (sub-)groups. The intermittent red horizontal line shows the cut-off value of 15, which was applied to define positive or negative ultrasound for SjD. The intermittent black vertical line separates the two major patient groups (SjD *vs*. other systemic diseases) from the subgroups of patients with a specific systemic disease (amyloidosis, HCV, HIV and sarcoidosis). **indicate $p<0.001$ and * indicates $p<0.05$. Black horizontal lines indicate median values.

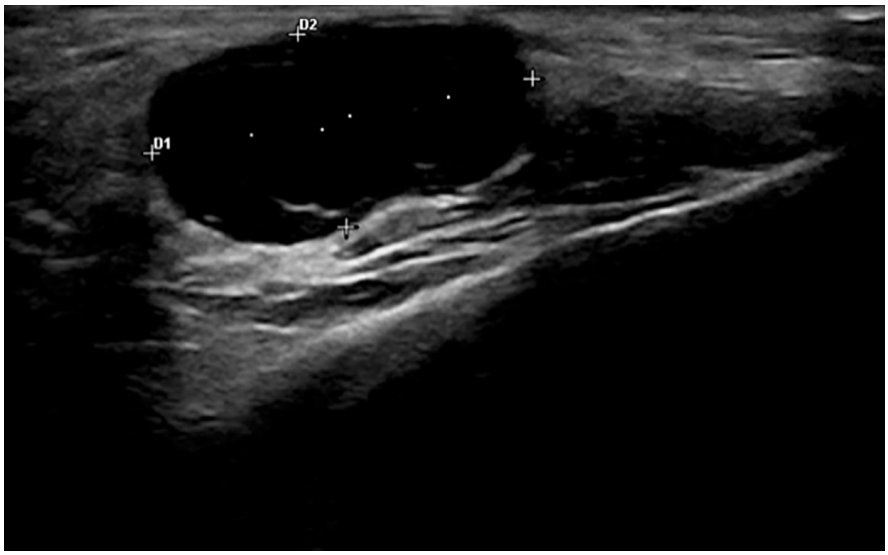

Fig. 4. Ultrasonographic image of parotid gland with a histologically proven MALT lymphoma showing a nearly anechoic space-occupying lesion.

cal and serological parameters, particularly when there is a heightened suspicion of MALT lymphoma, *e.g.* in case of unilateral salivary gland enlargement, as well as in case of potential presence of other systemic symptoms such as sudden fever, night sweats, and unexplained weight loss. At present, specific cohorts and comprehensive studies focusing on patients with MALT lymphomas, other than SjD patients suspected for a co-existing MALT lymphoma (25), and their corresponding SGUS data are notably lacking. The eagerly awaited research in this area aims to unveil the most prevalent ultrasonographic lymphoma findings in major salivary (and lacrimal) glands. Such research should also seek to provide clinical guidelines to facilitate accurate interpretation, to assess the efficacy of SGUS in comparison with other imaging modalities, and to explore the potential of SGUS in post-treatment follow-up of lymphomas. Furthermore, these studies target to investigate the utility of SGUS in differentiating active lymphomas from cases in remission.

As far as the cut-off value to define positive or negative SGUS for SjD is concerned, Law *et al*. proposed to add SGUS scores of ≥17 to the 2016 ACR/EULAR classification criteria (20). After testing both cut-off values of ≥17 and 15, we showed that a cut-off ≥15 improves the diagnostic accuracy of SGUS, since it retains the same specificity as with a cut-off ≥17, but at the same time it improves the sensitivity by 5%. Our results are in agreement with the study of Mossel *et al*., who also showed that in a cohort of 103 consecutive outpatients with clinically suspected SjD, SGUS diagnostic accuracy compared to the ACR-EULAR criteria is higher when a cut-off ≥15 (or 16) is used (9).

The most important strength of the current study is that we included consecutive patients diagnosed with SjD or another systemic disease visiting an outpatient clinic, avoiding possible selection bias. Moreover, we focused on the Hocevar scoring system (3). We chose to use this extensive scoring system as it is one of the most detailed ultrasound scoring systems used today and it can easily be transformed to almost any of the existing ones (26). The scoring system proposed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group is gaining more attention and should be also tested in future studies to assess if it can accurately discriminated SjD from its major mimickers (27). Both scoring systems were shown, however, to be comparable in terms of diagnostic accuracy (28). Additionally, we recruited patients with HIV and chronic HCV, whose salivary glands until now have not been comprehensively examined with ultrasound in the current literature nor compared with the ultrasonographic findings in patients with SjD.

The number of included patients was limited and thus data should be interpreted cautiously. Patients with a systemic disease were probably at different stages of the disease, *i.e.* some were just diagnosed while others were being in a long term follow up and thus salivary glands might be affected at a different degree. However, this exploratory analysis provides a first step in the evaluation of the diagnostic accuracy of SGUS to differentiate SjD from other systemic diseases.

Conclusion

This study indicates that SGUS has a potentially high diagnostic accuracy to discriminate SjD from associated systemic diseases with salivary gland involvement, like sarcoidosis, amyloidosis, HIV infection and chronic HCV infection. Further studies including more patients with different stages of systemic diseases are required to confirm and elucidate our findings.

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