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Article type : Original Article

Comparison of Ultrasound Features of Major Salivary Glands in Sarcoidosis, Amyloidosis, and Sjögren's Syndrome

Running head: Salivary Gland Ultrasound Comparison

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/acr.24029

No financial support which would create potential conflicts of interest for any of the authors.

Abstract

Objectives:

While salivary gland ultrasound (SGU) has gained prominence for evaluating Sjögren's syndrome, little information exists on SGU appearance of sarcoidosis and amyloidosis, potential mimics of Sjögren's syndrome. Our goal is to estimate diagnostic accuracy of major SGU features in differentiating Sjögren's syndrome from sarcoidosis, amyloidosis, and controls.

Methods:

We enrolled consecutive adult ambulatory patients with clinical diagnosis of Sjögren's syndrome fulfilling 2016 American College of Rheumatology classification criteria; clinical diagnosis of sarcoidosis or AL amyloidosis, with histological confirmation from any tissue, and rheumatology outpatients without diagnoses affecting salivary glands. Subjects underwent major SGU using the Hočevar protocol, with resulting video clips reviewed blind to clinical diagnosis.

Results:

Sjögren's syndrome SGU score were greater than in the other groups, but there were no distinguishing salivary glands features from AL amyloid or sarcoidosis. None of the patients in the control group scored higher than 17, a cutoff previously suggested for Sjögren's syndrome, but 27% of AL amyloidosis and 19% of sarcoidosis patients scored higher than 17. Adding Hočevar SGUS of ≥17 to the 2016 ACR/EULAR criteria in parallel scheme increased the sensitivity for Sjogren's from 87 to 98%, while combining the two criteria in series increased specificity from 81 to 98%.

Conclusion:

Sjögren's syndrome, sarcoidosis and AL amyloidosis share common SGU features that can help distinguish these conditions from patients without systemic rheumatologic disease. Clinicians should carefully consider these potential mimics when interpreting salivary gland ultrasound results.

Significance and Innovations

- This is the first systematic evaluation of salivary glands from patient with AL amyloidosis and sarcoidosis using ultrasound
- Similarities in salivary gland ultrasound appearance between Sjögren's syndrome and both sarcoidosis and AL amyloidosis are described

Introduction:

Over the past decade, ultrasound imaging has emerged as a potential diagnostic test for the evaluation of salivary glands by rheumatologists. The reasonable use guidelines published by the American College of Rheumatology gave ultrasound use for salivary glands a "B" rating based on a comprehensive literature review[1]. There have been a number of ultrasound criteria published for establishing the diagnosis of Sjögren's syndrome[2, 3]. The Hočevar protocol was created based on a cohort of patients referred for Sjögren's syndrome, and concluded that an ultrasound score of 17 and above suggested a specificity (i.e., probability of a negative test outcome in a non-diseased person) of 98.7% and sensitivity (i.e., probability of a positive test outcome in a diseased person) of 58.8% for Sjögren's syndrome when the American-European Consensus group classification criteria was used as a clinical gold standard[4] (i.e., assumed to have a perfect sensitivity and specificity). However, the

underlying diagnosis of this study's cohort members without Sjögren's was not described resulting in difficulty of interpretation of results when differentiating Sjögren's syndrome from similar conditions. Other studies also suggested ultrasound imaging to be useful in differentiating Sjögren's syndrome from idiopathic sicca syndrome[5], drug-induced sicca syndrome[6], and undifferentiated connective tissue disease. There are infiltrative conditions occasionally encountered in rheumatology practice such as sarcoidosis and systemic immunoglobulin light chain (AL) amyloidosis that can also cause salivary gland enlargement and thus may be difficult to differentiate clinically from Sjögren's syndrome. Nonetheless, little literature exists on ultrasound imaging of these conditions in the salivary glands, or even on the prevalence of salivary gland involvement in patients with systemic sarcoidosis or AL amyloidosis. The purpose of this study is twofold: to examine the prevalence of salivary gland abnormalities by ultrasound in patients with clinically-diagnosed sarcoidosis or AL amyloidosis, and to estimate diagnostic accuracy of ultrasound assessment of the salivary glands in distinguishing these conditions and controls from patients with Sjögren's syndrome and from patients without known disease of the salivary glands.

Patients and methods

Study population

We conducted a single-center cross-sectional study at Boston Medical Center, a tertiary referral center in Boston, Massachusetts. The study enrolled consecutive adult clinic outpatients presenting at our center, between June 2017 and May 2018. Enrollment inclusion criteria included clinical diagnosis of Sjögren's syndrome fulfilling 2016 ACR/EULAR classification criteria[7] and all patients were either positive anti-SSA , anti-SSB or had a typical minor salivary gland biopsy; clinical diagnosis of sarcoidosis or AL amyloidosis, with histological confirmation (biopsy showing non-caseating granuloma or positive staining on

Congo red respectively) from any tissue; and rheumatology outpatients without these diagnoses or other autoimmune rheumatic disease.

Participants were asked to describe symptoms of dryness using a sicca symptom questionnaire[8]. Subjects underwent Schirmer's test, unstimulated salivary flow measurement, and bilateral parotid and submandibular salivary gland ultrasound by a single un-blinded investigator, using an ultrasound machine (Esaote MyLab™25Gold) with an 18-6 MHz ultrasound probe. Patients were examined in supine position with the neck extended and the head slightly turned contralaterally [9]. The parotid and submandibular glands were scanned in both the longitudinal and transverse planes, in both greyscale and Doppler views, and images were saved as video clips. Another investigator, blinded to underlying diagnosis and clinical evaluation, analyzed ultrasound video clip images for salivary gland ultrasound score (SGUS) per Hočevar protocol (parenchymal echogenicity, homogeneity, hypoechoic areas, hyperechoic foci, and border visibility)[10], Doppler signal, hyperechoic septae and in addition lymph node characteristics. Intra-glandular lymph nodes were evaluated for number, shape, size, group configuration, and pattern of Doppler flow[11, 12].

SGUS scores were compared between the 4 groups using analysis of variance (ANOVA) in addition to pairwise comparison between each group pair by two-sample Wilcoxon rank sum test, also known as the Mann-Whitney test, where a *p*-value less than 0.05 was considered statistically significant difference. Pearson's product-moment correlation coefficient was used to determine the correlation between clinical parameters and ultrasound findings.

We used a Bayesian latent class model to estimate the diagnostic sensitivity (Se) and specificity (Sp) of SGUS score to differentiate Sjögren's syndrome from controls, and also Sjögren's syndrome from a group comprised of controls, and subjects with either amyloidosis, or sarcoidosis. The Bayesian latent class approach does not require a perfect (i.e., Se and Sp = 100%) gold standard for verification in order to provide an unbiased estimate of the diagnostic accuracy of SGUS. Specifically, we implemented a Bayesian latent class multinomial model of "two diagnostic test, one population", as described in Branscum et al.[13]. This problem is unsolvable in a non-Bayesian setting because in the frequentist approach, unless additional restrictions are implemented, the number of unknown parameters (i.e., two sensitivities, two specificities, and prevalence parameters) is larger than the three degrees of freedom available.

The Bayesian approach is implemented by specifying probability distributions that summarize current expert opinion or past knowledge as well as our uncertainties on parameters such as Se, Sp, or probability of an event in a sample/population (i.e., sample/population prevalence). These probability distributions are referred to as priors and are then combined with the current study's collected data to derive updated probability distributions, known as posteriors, for the Se, Sp, and prevalence parameters. To elicit priors, the most likely value of a parameter (i.e., mode of a distribution) is extracted from past published works or from expert opinion in addition to some degrees of certainty or uncertainty that the mode is above or below a plausible value. Alternatively, when past knowledge is not available or a high degree of uncertainty regarding a parameter exists, priors can be specified to be diffuse (i.e., weakly informative) or non-informative, where all possible values for a parameter is considered to occur equally likely. For quantifies that are probabilities, for example Se, Sp, or prevalence, a beta prior is used because of its flexibility and a confinement between 0 and 1. For example, past published work reported a Sp = 0.874

for the ACR/EULAR criteria[5]. Using this reported value as the most likely value for Sp of ACR/EULAR (i.e., mode of the distribution of possible values for ACR/EULAR Sp) and assuming that the true mode is greater than 0.70 with a 95% certainty, we derived the beta probability distribution as Beta(18.74, 3.56). Similarly, beta priors were specified on all other parameters (Supplementary Table 1). In addition to the primary priors that we described in the Supplementary Table 1, we ran the models with two additional sets of priors for the purpose of sensitivity analysis. These alternative priors included a more informative prior specification on the Se and Sp of SGUS, that we called enthusiastic priors and consisted of a narrower probability distribution around the center of defined priors, and also a less informative prior specification for Se and Sp of SGUS, which we called skeptical priors and consisted of a wider probability distribution around the center of defined priors for Se and Sp of SGUS.

In addition to estimating the diagnostic Se and Sp of each criterion, i.e., ACR/EULAR and Hočevar score, we estimated diagnostic Se and Sp for combined testing in parallel scheme to maximize combined Se, where either criterion being positive is considered a positive outcome, and also in serial scheme to maximize combined Sp, where both criteria should indicate a positive result to consider a positive outcome.

Bayesian computations were done in JAGS software version 4.3.0 (Plummer M. JAGS version 4.3.0 user manual. Lyon, France: International Agency for Research on Cancer; 2017.) through "rjags" version 4-8 library (Martyn Plummer, rjags: Bayesian Graphical Models using MCMC 2018. https://cran.r-project.org/package=rjags) in R software version 3.5.2 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.r-project.org). The shape parameters of beta distributions that were specified for priors were calculated by the "epiR"

library version 0.9-99 (Mark Stevenson. epiR: Tools for the Analysis of Epidemiological Data. 2018. https://CRAN.R-project.org/package=epiR) in R software.

Informed consent was obtained from all participants, and the study was performed in accordance with the ethical standards set by the Declaration of Helsinki and were approved by the institutional internal review board.

Results:

Participant cohorts included 21 with Sjögren's syndrome, 27 with sarcoidosis, 22 with AL amyloidosis, and 16 controls without these diagnoses or other autoimmune rheumatic disease (Table 1). New and established patients with AL amyloidosis were included. They were slightly older, and had a higher male predominance than the Sjögren's syndrome cohort. Patients with Sjögren's syndrome had a higher dryness score than patients with sarcoidosis (3.7 vs. 1.4, $p<0.0001$), AL amyloidosis (3.7 vs. 1.6, $p<0.001$) or controls (3.7 vs. 2, $p<0.003$). In the control group, there was no correlation between age and SGUS score as suggested by the Pearson's correlation coefficient (coef. = 0.33, 95% CI: -0.20, 0.71). Furthermore, Pearson's correlation coefficients suggested no correlation between dryness score and the SGUS in any of the groups.

By Shapiro-Wilk test of normality, only the AL amyloidosis group slightly violated the assumption of normality. ANOVA of the mean SGUS showed significant difference among the four groups ($p<0.00008$). Sjögren's syndrome SGUS was significantly higher than sarcoidosis, AL amyloidosis, and control groups (20 vs. 11, 14, 9, respectively, all with $p<0.05$, Table 2, Figure 1). AL amyloidosis SGUS was higher than controls (14 vs. 9, $p<0.05$), but SGUS in the sarcoidosis group was not different from controls (11 vs. 9, p=NS).

Analysis done by salivary gland type also demonstrated that the parotid US score was greater in Sjögren's syndrome (10.4), AL amyloidosis (6.3), and sarcoidosis (4.7), than in controls (2.4) (p=0.004, 0.02, 0.0001) (Table 2, Figure 2). The Sjögren's syndrome parotid US score did not differ from AL amyloidosis, but was higher than the sarcoidosis group(p=0.005). The submandibular US score was higher in Sjögren's syndrome (10) than in controls (6.2) (p=0.02) but AL amyloidosis (8.1), and sarcoidosis (6.4) did not differ from controls (6.2) (Table 2, Figure 3). Furthermore, Sjögren's group submandibular US score once again did not differ from AL amyloidosis, but was greater than sarcoidosis (p=0.009).
It is notable that 27% (6) of AL amyloidosis patients and 19% (5) of sarcoidosis patients had a SGUS score >17 compared to 62% (13) of Sjögren's syndrome patients and none of the control patients (Figure 1).

Infiltrative hypoechoic lesions were significantly more common in Sjögren's syndrome (2.4) than in controls (1.1) (p=0.01), but were not different between sarcoidosis (1.8) or AL amyloidosis (1.8) and controls (1.1) (p=NS). Hyperechoic septae were more common in Sjögren's syndrome (1.6) and AL amyloidosis (1.8) than in controls (0.63) (p=0.04 and 0.01 respectively), but did not distinguish sarcoidosis (0.74) from controls (0.63) (p=NS). Of the ultrasound characteristics which were not part of the Hočevar protocol, neither Doppler signal nor intra-glandular lymph node number differentiated Sjögren's syndrome, sarcoidosis or AL amyloidosis groups from the control group. Doppler flow did not differ between the groups (p=NS). The mean number of intra-glandular lymph nodes did not differ between Sjögren's syndrome (4.1), sarcoidosis (3.9), AL amyloidosis (2.7), or controls (3.3) (p = NS). There were no particular ultrasound features which could distinguish the infiltrative conditions of sarcoidosis or AL amyloidosis from Sjögren's syndrome, although higher Hočevar scores favor Sjögren's syndrome.

Table 3 provides estimates of diagnostic sensitivity and specificity for ACR/EULAR criteria and Hočevar protocol. Both criteria suggested high sensitivity in differentiating Sjögren's syndrome from control, despite lower specificity for Hočevar protocol when used solely (Sp = 0.80, 95% Bayesian PI: 0.64, 0.93). When Sjögren's syndrome was assessed against controls in addition to sarcoidosis and AL amyloidosis, specificity of Hočevar protocol (Sp = 0.89, 95% Bayesian PI: 0.80, 0.96) was higher than ACR/EULAR criteria, despite similar sensitivity. When ACR/EULAR criteria and Hočevar protocol were combined in parallel scheme to maximize sensitivity, the parallel joint sensitivity reached 0.99 (95% Bayesian PI: 0.96, 0.99) and 0.98 (95% Bayesian PI: 0.94, 0.99) when sarcoidosis and AL amyloidosis were not and were included in differential diagnosis of Sjögren's syndrome, respectively (Table 3). Combination of ACR/EULAR criteria and Hočevar protocol in serial scheme to maximize specificity resulted in 0.98 (95% Bayesian PI: 0.94, 0.99) and 0.98 (95% Bayesian PI: 0.95, 0.99) specificities when Sjögren's syndrome was contrasted against controls only and controls in addition to sarcoidosis and AL amyloidosis, respectively (Table 3).

Discussion:

Our study is the first to compare the SGUS features in patients with sarcoidosis, AL amyloidosis and Sjögren's syndrome using a predefined scanning protocol and scoring methodology. We found that a substantial proportion of patients with systemic sarcoidosis and AL amyloidosis meet salivary gland ultrasound criteria previously suggested for Sjögren's syndrome. In patients with Sjogren's syndrome, a previous study reported a very strong agreement between the ultrasound Hočevar score and histology of 83% for parotid and 79% for minor salivary gland[14]. However, there was not a description of the diagnoses comprising the patients in the study who were not diagnosed with Sjogren's syndrome.

Available literature is limited to comparing Sjogren's syndrome salivary gland ultrasound with that of undifferentiated connective tissue disease (UCTD)[15] and IgG4 related disease[16]. Patients with UCTD may be similar to patients with Sjogren's syndrome in some of their extra-glandular disease manifestations, but would not be expected to have abnormalities of their salivary glands and UCTD is not an established cause of salivary gland enlargement. Thus, it is less compelling that salivary gland ultrasound has been found to distinguish between UCTD and Sjögren's syndrome. IgG4 disease on the other hand does cause salivary gland enlargement, and has been studied in comparison to Sjögren's syndrome by ultrasound. A "nodal" pattern was found in 60% of IgG4 cohort with gland involvement and this could distinguish IgG4 from Sjögren's. IgG4 also differed by its predilection for the submandibular glands (90%) over the parotid glands (35%) while Sjogren's affects the glands equally. While we looked for differences in nodal pattern and differences in parotid versus submandibular gland involvement in our study cohorts, we did not detect similar differences.

We used AL amyloidosis as the archetypal form of amyloidosis to obtain a homogeneous population of patients with amyloidosis, and because this is the most common form of systemic amyloidosis. To our knowledge, there is no published literature on the appearance of amyloidosis in major salivary gland ultrasound. We have shown that AL amyloid causes both hypoechoic lesions and hyperechoic septa in the salivary glands similar in appearance to patients with Sjögren's syndrome, and can have a Hočevar score above the range of control subject at least 27% of the time.

Previous literature indicated that the parotid gland can be affected by sarcoidosis (6-30%)[17] [18, 19]. Brantley et al. reported about 11 (58%) positive parotid gland biopsies in 19 patients with proven generalized sarcoidosis[20]. We found a Hočevar score above control range in about 19% of our sample, and 37% when using a cutoff score of 15 as suggested in some studies[14]. A case series described US findings of the parotid gland of six patients with histologically proven sarcoidosis of the parotid gland with sonographic features ranging from nodal enlargement to diffuse or partial involvement of the parotid gland with various degrees of echogenicity and vascularity[12]. However, we did not detect any differences in lymph nodes or vascularity among our cohorts, and we could not distinguish the glandular appearance of the sarcoidosis subjects with abnormal salivary glands from those with Sjögren's syndrome. Our data may be an under representation of salivary gland involvement in sarcoidosis as we recruited consecutive patients with sarcoidosis, many of which were already receiving treatment, which might resolve salivary gland lesions.

While there are various salivary gland ultrasound scoring systems available, we opted to use Hočevar protocol because there is more extensive literature to support its validity than others, and because it assesses for multiple parameters allowing for analysis of specific SGUS features in this exploratory hypothesis generating study. Unfortunately, there does not appear to be any specific salivary gland ultrasound findings to help distinguish Sjögren's syndrome from sarcoidosis and AL amyloidosis.

The prevalence of Sjögren's syndrome of 0.1%[21] is similar to that of sarcoidosis of about 0.1%[22] while AL amyloidosis is much less frequent at about 0.004%[23]. Since we found that ultrasound features of these conditions overlap substantially and do not contain pathognomonic findings for any of the three diseases, salivary gland ultrasound test

characteristics will depend substantially on the prevalence of these conditions in the patient population being evaluated. Dryness score and other clinical characteristics specific to these conditions may help distinguish these diagnoses.

A strength of our study was that we did not assume either of the two criteria, ACR/EULAR and Hočevar score, to be a perfect reference standard in order to derive accuracy measures of the two criteria when applied individually or in combination. Additionally, we incorporated 3 district sets of priors for sensitivity analysis where priors varied based on how strong or weak an investigators belief is with regard to the accuracy of Hočevar scoring, compared to the ACR/EULAR criteria. Our posterior estimates of Se and Sp for Hočevar scoring could be used to elicit priors for future studies. Another unique advantage of our Bayesian approach is that the provided probability intervals have exact probabilistic interpretation such that the probability that the truth exist within our calculated Bayesian probability interval is exactly 95 percent, as opposed to a frequentist approach where such probability is either 0 or 100 percent based on hypothetical repetitions of the study.

Limitations of our study include being based at a single-center that limited the number of patients enrolled. AL amyloidosis is a particularly rare condition that makes recruiting a larger sample size challenging. There is potential for bias as the physical obtaining the ultrasound images was not blinded to diagnoses. However, the ultrasound video clips were reviewed in a blinded manner, and we did not expect that the protocol driven acquisition of the ultrasound images would be affected by the lack of blinding of the physician obtaining the images.

Finally, an external validation study including direct comparison of salivary gland histology with ultrasound is needed.

While our results confirm the sensitivity and specificity of ultrasound assessment for Sjögren's syndrome overall, one must be aware of the substantial overlap between the ultrasound findings in the salivary glands of patients with Sjögren's syndrome and those with sarcoidosis and AL amyloidosis.

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Table 1. Baseline characteristics of research subjects

	Control	Sarcoidosis	AL Amyloidosis	Sjögren's Syndrome
Number of subjects	16	27	22	21
Female (%)	63	48	41	95
Age (mean)	58	55	66	49
Dryness Score (0-5)	1.6	1.4	2	3.7
Abnormal Schirmer's test (%)	38	65	86	57
Abnormal salivary flow (%)	25	4	32	62

Table 2. Salivary gland ultrasound findings for study cohorts. Number in bold are significantly different from control group. * Sjögren's syndrome salivary gland ultrasound score (SGUS) is significantly different from sarcoidosis and AL amyloidosis groups.

	Control	Sarcoidosis	AL Amyloidosis	Sjögren's Syndrome
Total SGUS	9	11	**14**	**20***
Parotid US	2.4	**4.7**	**6.3**	**10.4**
Submandibular US	6.2	6.4	8.1	**10**
Hypoechoic regions	1.1	1.8	1.8	**2.4**
Hyperechoic septa	0.6	0.74	**1.8**	**1.6**
Doppler signal	5.1	4.6	5.6	4.6
# intra-glandular lymph nodes	3.3	3.9	2.7	4.1

Table 3. Posterior medians and corresponding 95% Bayesian probability intervals for the accuracy of 2016 ACR/EULAR criteria and Hočevar score with a cut-off at 17 when used individually or jointly.

	Parameter	**Posterior Median (95% Bayesian Probability Interval)**		
In Sjögren's syndrome vs. control				
		With Primary Priors	Sensitivity Analysis 1 With Enthusiastic Priors for Hočevar	Sensitivity Analysis 2 With Skeptical Priors for Hočevar
ACR/EULAR	Se	0.85 (0.68, 0.96)	0.83 (0.67, 0.95)	0.86 (0.69, 0.96)
	Sp	0.90 (0.78, 0.97)	0.90 (0.78, 0.97)	0.90 (0.78, 0.97)
Hočevar	Se	0.92 (0.80, 0.98)	0.91 (0.85, 0.96)	0.92 (0.76, 0.99)
	Sp	0.80 (0.64, 0.93)	0.85 (0.77, 0.92)	0.76 (0.57, 0.93)
Parallel	Se	0.99 (0.96, 0.99)	0.99 (0.96, 0.99)	0.99 (0.95, 0.99)
combination	Sp	0.72 (0.55, 0.86)	0.76 (0.64, 0.86)	0.68 (0.49, 0.85)
Serial combination	Se	0.77 (0.60, 0.90)	0.75 (0.60, 0.87)	0.78 (0.59, 0.91)
	Sp	0.98 (0.94, 0.99)	0.99 (0.96, 0.99)	0.98 (0.93, 0.99)
In Sjögren vs. control, sarcoidosis, and AL amyloidosis				
		With Primary Priors	Sensitivity Analysis 1 With Enthusiastic Priors	Sensitivity Analysis 2 With Skeptical Priors

ACR/EULAR	Se	0.87 (0.71, 0.97)	0.88 (0.72, 0.97)	0.87 (0.71, 0.97)
	Sp	0.81 (0.71, 0.91)	0.80 (0.70, 0.88)	0.83 (0.72, 0.94)
Hočevar	Se	0.85 (0.65, 0.96)	0.90 (0.83, 0.95)	0.77 (0.52, 0.96)
	Sp	0.89 (0.80, 0.96)	0.88 (0.82, 0.93)	0.89 (0.79, 0.97)
Parallel	Se	0.98 (0.94, 0.99)	0.99 (0.97, 0.99)	0.97 (0.90, 0.99)
combination	Sp	0.72 (0.60, 0.83)	0.70 (0.60, 0.79)	0.73 (0.61, 0.85)
Serial combination	Se	0.73 (0.53, 0.88)	0.78 (0.64, 0.89)	0.66 (0.43, 0.86)
	Sp	0.98 (0.95, 0.99)	0.98 (0.96, 0.99)	0.98 (0.96, 0.99)

Figure 1: Unidimensional scatterplot of mean (horizontal line) and 95% CI (vertical line) of salivary gland ultrasound scores per Hočevar protocol amongst controls and patients with sarcoidosis, AL amyloidosis, and Sjögren's syndrome

Figure 2: Parotid salivary gland ultrasound images in A) control, B) sarcoidosis, C) AL Amyloidosis, D) Sjögren's syndrome

Figure 3. Submandibular salivary gland ultrasound images in A) control, B) sarcoidosis, C) AL Amyloidosis, D) Sjögren's syndrome