**Title**
Preliminary Screening Questionnaire for Sjögren's Syndrome in the Rheumatology Setting

**Permalink**
https://escholarship.org/uc/item/4wv257d9

**Journal**
JCR Journal of Clinical Rheumatology, 28(2)

**ISSN**
1076-1608

**Authors**
Yu, Kimberley
Ying, Gui-Shuang
Vivino, Frederick B
et al.

**Publication Date**
2022-03-01

**DOI**
10.1097/rhu.0000000000001760

Peer reviewed

# Preliminary Screening Questionnaire for Sjögren's Syndrome in the Rheumatology Setting

**Kimberley Yu, BA**[1], **Gui-Shuang Ying, PhD**[2], **Frederick B. Vivino, MD, MS**[3], **John A. Gonzales, MD**[4,5], **Mina Massaro-Giordano, MD**[2], **Vatinee Y. Bunya, MD, MSCE**[2]

[1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

[2]Department of Ophthalmology, Scheie Eye Institute, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

[3]Department of Rheumatology, Penn Presbyterian Medical Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

[4]Francis I. Proctor Foundation, University of California San Francisco, San Francisco, CA

[5]Department of Ophthalmology, University of California San Francisco, San Francisco, CA

## Abstract

**OBJECTIVE:** Sjögren's syndrome (SS) is frequently undetected or misdiagnosed as other rheumatologic diseases. We aimed to develop a SS screening questionnaire for the rheumatology practice.

**METHODS:** We developed the SS Screening Questionnaire (SSSQ) via secondary analysis of data from 974 participants referred by rheumatologists to the Sjögren's International Collaborative Clinical Alliance (SICCA) study. Participants answered 88 questions regarding symptoms, medical history, and demographics. They underwent ocular, dental, and serologic tests and were classified as SS or non-SS using the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria. We conducted univariate and multivariate logistic regression to identify questions most discriminative of SS, from which we derived an individual's likelihood of SS ("SSSQ score").

**RESULTS:** Five questions were significantly discriminative of SS in the multivariate analysis (p<0.05): 1) Can you eat a cracker without drinking a fluid/liquid? [No = OR 1.39 (95% CI 1.06–1.82)]; 2) How would you describe your dental and oral health in general? [Fair/Poor = OR 1.68 (1.04–2.75)]; 3) During the last week have you experienced tearing? [None of the time = OR 2.26 (1.23–4.34)]; 4) Are you able to produce tears? [No = OR 1.62 (1.12–2.37)]; and 5) Do you currently smoke cigarettes? [No = OR 2.83 (1.69–4.91)]. SSSQ score ≥ 7 (possible range 0–11) distinguishes SS from non-SS patients with 64% sensitivity and 58% specificity (Area under ROC curve=0.65).

**CONCLUSION:** The SSSQ is a simple 5-item questionnaire designed to screen for SS in clinical practice, with a potential impact to reduce delays in diagnosis.

Corresponding Author: Vatinee Y. Bunya, MD, MSCE, Scheie Eye Institute, 51 N. 39th Street, Philadelphia, PA 19104, Phone: 215-662-9791, Fax: 215-243-4696, vatinee.bunya@pennmedicine.upenn.edu.

**Keywords**

Sjögren's Syndrome; Dry Eye Syndromes; Keratoconjunctivitis Sicca; Surveys and Questionnaires; Mass Screening/methods

## INTRODUCTION

Sjögren's syndrome (SS) is a chronic, systemic autoimmune rheumatic disease characterized by lymphocytic infiltration of the lacrimal and salivary glands, causing dry eye and dry mouth [1]. Systemic manifestations often occur including fatigue, arthritis/arthralgias, myositis/myalgias, and skin rashes. SS leads to an increased risk for a wide range of serious long-term complications, including cardiovascular disease, kidney failure, interstitial lung disease, peripheral neuropathies, central nervous system involvement, and lymphoma [1–4]. The standardized incidence ratio for risk of non-Hodgkin's B-cell lymphoma among SS patients is significantly higher than the general population and ranges from 7.08 to 48.1 depending on the population-based study [4]. SS can occur alone ("primary SS") or in the presence of other autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) ("secondary SS") [5, 6]. SS is a relatively common autoimmune disease, with prevalence in the United States estimated to range from 0.4 to 3.1 million individuals [7]. About 1 in 10 patients with clinically significant dry eye have underlying SS [8–10].

Studies of patients with dry eye or mixed connective tissue disease have found that only 33–50% of patients with primary SS had been previously diagnosed, suggesting that SS could remain undiagnosed in more than half of affected adults [10, 11]. There are often significant delays in diagnosis due to the nonspecific and variable nature of the symptoms, the heterogeneity of clinical presentations, the slow progression of disease, and lack of access to care [12], with data suggesting an average 3.9-year delay before diagnosis [13]. The clinical and serologic manifestations of SS often overlap with those of other connective tissue disorders including RA and SLE [14]. The patient who presents with a constellation of vague symptoms such as malaise, fatigue, rash, cough and musculoskeletal pain will frequently present a significant diagnostic challenge to the practicing rheumatologist who is trying to differentiate between these diseases. In one study, patients who met criteria for primary SS were initially misdiagnosed with RA or SLE [15]. Delays in SS diagnosis can lead to irreversible organ damage, decreased quality of life, and potential delays in monitoring for serious complications like lymphoma. Better screening methods are therefore needed for earlier diagnosis of SS.

The three most recent sets of classification criteria commonly used for SS were all developed for research purposes and attempt to define homogeneous populations of patients for clinical trials and other studies. They include the 2002 American-European Consensus Group (AECG) criteria [16], the 2012 Sjögren's International Collaborative Clinical Alliance (SICCA)/American College of Rheumatology (ACR) criteria [17], and the 2016 ACR/European League Against Rheumatism (EULAR) criteria [18]. Common recommendations for the diagnostic evaluation of SS include ocular surface staining,

serological testing for autoantibodies, and labial minor salivary gland biopsies when indicated.

The 2002 AECG criteria also include six questions on ocular and oral symptoms. However, these questions were designed to standardize classification of SS patients for studies and were not intended for clinicians. Accordingly, the AECG criteria were created and validated using a homogenous population of European patients considered to have well-defined SS based on the clinical judgement of participating experts [19, 20]. This cohort was not intended to reflect the typical cadre of patients seen by the practicing rheumatologist. In the present study, however, an evidence-based screening tool was developed for office use to identify patients in real clinical settings with a high likelihood of meeting criteria for SS, and who warrant further diagnostic evaluation. Working up all patients with non-specific findings is prohibitively expensive and time-consuming for both patients and providers.

Due to the variety of SS symptom presentations, rheumatologists, ophthalmologists, oral care specialists, and primary care professionals are all positioned along the care pathway to screen for and diagnose the disease. Patients that present to each of these providers will likely display a tendency towards different symptoms. The greatest heterogeneity of presentations is likely seen by the rheumatologist and may include abnormal lab values, sicca symptoms, and significant extra-glandular manifestations that overlap with those of other rheumatic diseases [14]. In contrast, a SS patient may present primarily with severe dry eye symptoms to an ophthalmologist or significant dry mouth symptoms to a dentist or oral medicine specialist. Screening tools for SS should therefore reflect the appropriate practice setting.

The SICCA study was a longitudinal, multi-center, international study funded from 2003–2013 that is unique in its representation of 3514 ethnically diverse individuals uniformly evaluated for SS from 9 international sites. Its large cohort size referred from diverse sources, extensive symptom questionnaire data, and verified diagnostic workups provide a unique opportunity to create a screening tool for SS tailored to specific practice settings. The purpose of this study was to utilize data from the SICCA study to develop a screening questionnaire for SS in the rheumatology practice.

## PATIENTS AND METHODS

### Study population

The SICCA cohort consists of 3514 participants suspected of SS from 9 participating international research sites: University of Buenos Aires, German Hospital, Argentina (441); Peking Union Medical Collage Hospital, China (333), Copenhagen University Hospital, Denmark (610), Kanazawa Medical University, Japan (368), Aravind Eye Hospital, Madurai India (161), King's College London, United Kingdom (312), University of California, San Francisco, CA USA (718), University of Pennsylvania, Philadelphia, PA USA (266), and Johns Hopkins, Baltimore, MD USA (305). Participants could be referred to the study by a rheumatologist, SS clinic, dentist, ophthalmologist, other doctor, website/internet, advertisement, friend/relative, or other miscellaneous sources. To be eligible for enrollment in the SICCA study, participants had to be 21 years or older and fulfill at least one of the

following criteria: (1) complaint of dry eyes or dry mouth, (2) have a previous suspicion or diagnosis of SS, (3) have bilateral salivary gland enlargement, (4) have recent increase in dental caries, (5) have elevated anti-nuclear antibodies (ANA) or rheumatoid factor (RF) or anti-SSA/anti-SSB, or (6) have a diagnosis of rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) *and* any of the previous 5 criteria [21]. Enrolled participants answered baseline questions on symptoms, medical history, and demographics. They also underwent ocular exams for dry eye (ocular surface staining of the cornea and conjunctiva with vital dyes [fluorescein and lissamine green], tear break-up time [TBUT], and unanesthetized Schirmer's test), as well as dental and rheumatologic exams, serological testing, and a lip biopsy if not previously performed within the last year. All biopsies were reviewed by the same group of oral pathologists. Participants were classified as SS or non-SS following the 2016 ACR/EULAR classification criteria, meaning that they met eligibility criteria and had a weighted score of greater than or equal to 4 points from the following: (1) Anti-SSA/Ro positive (3 points); (2) labial salivary gland with focal lymphocytic sialadenitis and focus score of 1 foci/4mm$^2$ (3 points); (3) ocular staining score 5 (or van Bijsterveld score 4) in at least one eye (1 point); (4) Schirmer's test 5 mm/5 minutes in at least one eye (1 point); and (5) Unstimulated whole saliva flow rate 0.1 ml/minute (1 point) [18]. At baseline, 1578 participants were classified as SS and 1851 were classified as non-SS. For this study to develop an SS screening questionnaire for use in rheumatology practices, we conducted a secondary analysis of data from 974 patients (449 SS and 525 non-SS) referred by rheumatologists to the SICCA study.

### Instrument design and analysis

To develop a SS screening questionnaire for rheumatologists, we aimed to identify the questions from the SICCA baseline questionnaires that were most discriminative of SS vs. non-SS among rheumatologist-referred patients. We utilized 88 questions from the SICCA baseline questionnaires, covering patients' general physical and emotional health, symptoms, and medical history (Supplemental Table 1).

We first analyzed each candidate question individually using a chi-squared test and logistic regression. The chi-squared test was conducted to determine whether there is a significant difference in the proportions of SS across each possible response to a question (e.g. "yes" vs. "no" in response to a question from the SICCA baseline questionnaire, or "positive" vs. "negative" for an ocular test). Univariate logistic regression was conducted to evaluate the strength of association using odds ratio (OR) and the discriminating power using the area under the receiver operating characteristic (ROC) curve. Questions with responses that were significant (p< 0.05) and demonstrated an OR in the expected direction (as determined by an ophthalmologist and a rheumatologist with specialized expertise on SS) were included in the multivariate logistic regression analysis. A stepwise variable selection was performed to reach the final multivariate model by keeping only the statistically significant questions. As sensitivity analyses, variable selection using the Akaike Information Criterion (AIC) and Lasso regression were also performed. The same final multivariate model was reached when performing stepwise, forward, or backward variable selection using the AIC (AIC=1274) or Lasso regression (optimal lambda=0.004 by cross-validation). To evaluate our model for multicollinearity between predictors, we computed variance inflation factor (VIF) scores,

where the lowest possible VIF value is 1 and values greater than 5 are suggestive of problematic multicollinearity.

We created a simple risk-point scoring system to compute a patient's likelihood of SS ("SSSQ score") from their responses to the selected questions, following the approach developed by Sullivan [22]. Questions were weighted based on their regression coefficients from our final multivariate models. We evaluated the discriminative power of SSSQ score for SS using area under ROC curve (AUC). Sensitivities and specificities at different cut points of the SSSQ score and their 95% confidence intervals (CI) were calculated. In addition, we determined the optimal cut point for the SSSQ score that maximized Youden's J index (sensitivity + specificity – 1). Positive and negative predictive values (PPV and NPV, respectively) corresponding to potential SS prevalence rates among patients suspected of SS by their rheumatologist were calculated following the method by Altman [23]. A subgroup analysis was performed with age stratified into quartiles to evaluate if model performance varies with age.

## RESULTS

Among the 974 rheumatologist-referred patients of the SICCA study eligible for the analysis, 93.4% were female and approximately half (52%) were Caucasian. The median age was 52 years (IQR=42–60). Forty-six percent (n=449) had SS and 54% (n=525) did not have SS after baseline evaluation. 79% of SS patients were positive for anti-SSA/Ro, while 4% of non-SS patients were positive for anti-SSA/Ro. Additional demographics are summarized in Supplemental Table 2.

In our final multivariate regression model, we identified five questions as being significant for discriminating SS from non-SS: 1) Can you eat a cracker without drinking a fluid/liquid? [No = OR 1.39 (95% CI 1.06–1.82)]; 2) How would you describe your dental and oral health in general? [Fair or Poor = OR 1.68 (95% CI 1.04–2.75)]; 3) During the last week have you experienced tearing? [None of the time = OR 2.26 (95% CI 1.23–4.34)]; 4) Are you able to produce tears? [No = OR 1.62 (95% CI 1.12–2.37)]; and 5) Do you currently smoke cigarettes? [No = OR 2.83 (1.69–4.91)] (Table 1). VIF values were low (1.05, 1.05, 1.01, 1.07, and 1.01 for the five questions, respectively), indicating that multicollinearity between predictors is minimal. The discriminative ability of these five questions individually in univariate logistic regression is also reported in Supplemental Table 3.

A simple risk-point-based scoring system was developed to calculate a "SSSQ score", which reflects a patient's likelihood of SS given their responses to the questions on the SSSQ (Table 2). Questions were given different point values based on the magnitude of association with SS in the multivariate logistic regression model, with a total maximum score of 11. SS diagnosis was associated with a higher SSSQ score, with the fraction of patients classified as SS increasing with increasing SSSQ score (Figure 1). The AUC of the SSSQ score is 0.65 (95% CI 0.62–0.69) (Figure 2).

A SSSQ score of 7 was determined to be the optimal cut point for distinguishing SS from non-SS patients, with sensitivity of 64.3% (95% CI: 59.6–68.7%), specificity of 58.4%

(95% CI: 54.0–62.7%), and Youden's J index of 0.23. The PPV and NPV at this optimal sensitivity and specificity were 27.9% and 86.7%, respectively, assuming the SS prevalence among the clinical screening population was 20%.

A subgroup analysis with age stratified into quartiles was performed. The AUC as well as the sensitivities and specificities of the model using the optimal SSSQ cut point of 7 was calculated for each age group (Table 3). The model had the highest AUC, sensitivity, and specificity for ages 21 to 42 (AUC = 0.71, sensitivity = 67%, specificity = 62%) and ages 43 to 52 (AUC = 0.71, sensitivity = 67%, specificity = 67%), in comparison to ages 53 to 60 (AUC = 0.65, sensitivity = 62%, specificity = 57%) and ages 61 to 90 (AUC = 0.63, sensitivity = 60%, specificity = 48%).

## DISCUSSION

We describe the first evidence-based screening algorithm developed for rheumatologists to screen patients for suspected SS in clinical practice. The SSSQ is simple, easy-to-use, and fast, consisting of only 5 questions. A score on the SSSQ of greater than or equal to 7 out of 11 points can discriminate SS from non-SS patients with 64% sensitivity and 58% specificity (AUC=0.65). Patients with a high SSSQ score greater than or equal to 7 are recommended to undergo further diagnostic evaluation for SS with ocular, salivary gland, and serologic tests.

As expected, a mix of both dry eye and dry mouth symptoms are significant at discriminating SS from non-SS in our models. It is interesting to note that "Can you eat a cracker without drinking a fluid/liquid?" and "How would you describe your dental and oral health in general?" are significantly discriminative, while other dry mouth questions like "Does your mouth feel dry?" and "Do you have difficulty swallowing any foods?" are not. This suggests that the former two questions are more specific to SS, whereas the latter two questions may receive positive answers for both SS and non-SS patients. For example, a non-SS patient with a different rheumatologic disease like SLE may have difficulty swallowing due to esophageal dysmotility or gastrointestinal reflux [24], without associated difficulty eating a cracker without drinking a fluid. Similarly, "During the last week have you experienced tearing?" and "Are you able to produce tears?" are significant at discriminating SS vs. non-SS while "Do your eyes feel dry?" is not, suggesting that the latter question is too non-specific to distinguish SS from other non-SS dry eye patients.

Additionally, it is interesting to note that an answer of "No" to "Do you currently smoke cigarettes?" is discriminative of SS when used in combination with the other questions. Several other studies have suggested that cigarette smoking is associated with lower SS prevalence rates [25, 26], as well as less severe focal lymphocytic sialadenitis in lower lip biopsies among patients with primary SS [27]. It is unclear whether this is due to protective immunomodulatory effects of tobacco on salivary gland tissue, greater deterrence to smoking among SS patients with dry mouth, or a combination of factors.

A cut point of 7 was considered optimal to indicate a positive SSSQ score warranting further diagnostic evaluation for SS (sensitivity = 64.3%, specificity = 58.4%, Youden's J index

= 0.23). The positive predictive value (PPV) and negative predictive value (NPV) of the screening tool will vary depending on the prevalence of SS in the population being screened. For example, if we assume a SS prevalence rate of approximately 20% as reported by Sánchez-Guerrero et al. in a study of 181 rheumatology patients [28], the PPV is 27.9% and the NPV is 86.7% for SSSQ score 7. In contrast, in a population where the SS prevalence rate is as low as 4% as seen by Sánchez-Guerrero et al. among 119 internal medicine patients [28], the PPV is 6.0% and the NPV is 97.5%. The SSSQ's high NPV despite a lower PPV is ideal for use of the SSSQ as a screening tool, where the goal is to identify all patients who should be further evaluated for SS using diagnostic exams indicated in the ACR/EULAR classification criteria. A high NPV means that patients who receive a low SSSQ score have a low likelihood of being diagnosed with SS and may not warrant further workup. This would reduce the burden of testing all patients with non-specific dry eye and dry mouth symptoms.

While a cut point of 7 maximizes Youden's J index (sensitivity + specificity – 1), the SSSQ cut point can be adapted to accommodate the desired level of sensitivity or specificity for SS screening. For example, if a rheumatologist desires to screen with a higher sensitivity, they can choose a lower cut point, such as 4. In this case, the SSSQ will have a sensitivity of 94.8%, a specificity of 13.1%, a PPV of 21.4%, and a NPV of 91.0% at a 20% SS prevalence rate, indicating that a lower cut point would allow for fewer false negatives at the expense of more false positives.

The SSSQ was developed using a population of patients evaluated by rheumatologists for signs or symptoms suggestive of SS, in order to enable rheumatologists to quickly identify patients who should receive further diagnostic evaluation. While the SSSQ's sensitivity of 64% and specificity of 58% may not seem that high, it should be appreciated in the context of the current study population. In this context, the SSSQ's sensitivity and specificity is impressive, supporting its potential use to help differentiate SS patients from patients with similar symptoms due to other rheumatologic diseases or other causes of dry eye or dry mouth. Furthermore, it is notable that the individual diagnostic tests used for the 2016 ACR/EULAR classification criteria are themselves variable in sensitivity and specificity. Labial minor salivary gland biopsies have demonstrated variable sensitivities (63.5–93.7%) and specificities (61.2–100%) in different studies [29]. Anti-SSA/Ro is detected in only 50–70% of SS patients depending on the assay [30]. In comparison, the SSSQ is somewhat less sensitive and specific, yet much faster and easier to use, offering a standardized and evidence-based single method for rapid SS screening across rheumatology practices that can be followed up with a full diagnostic evaluation. By screening patients with the SSSQ, clinicians could detect SS patients who may normally be missed while decreasing medical costs and unnecessary workups for those with a low likelihood of having SS. Additionally, the SSSQ performed best in younger individuals ages 21 to 52, with an AUC of 0.71, a sensitivity of 67%, and a specificity of 62–67%. The average age of onset of SS has been reported to be 40 to 60 years old [31], and thus the SSSQ's improved performance in this younger age range is ideal for its use as a screening tool.

The SSSQ was designed to represent patients presenting to a rheumatologist, since this population often presents with a constellation of clinical and serologic findings overlapping

with other rheumatic diseases that make recognition of SS challenging for the practicing rheumatologist. Indeed, patients with primary SS are frequently initially misdiagnosed with RA or SLE [15]. Still, the SSSQ could have the potential to be used for patients suspected of SS in other care settings, such as primary care. Longitudinal validation should be performed to determine if the SSSQ can be used for patients suspected of SS by other providers.

The SSSQ is notable for being, to the best of our knowledge, the only evidence-based screening questionnaire for SS designed for use in clinical practice. While the 2002 AECG classification criteria similarly includes six questions on oral and ocular symptoms, these questions were designed to define a homogenous population of patients comparable across institutions for research purposes [16, 19]. They are not appropriate for screening in clinical practice. In the AECG studies, only patients considered to have well-defined SS based on the judgement of participating clinicians were labeled as SS cases, and only European and Israeli centers were represented. The AECG questions' sensitivities >60% and specificities >80% in a validation study [20] are at least partially attributable to the homogenous, well-defined nature of its study population. In contrast, patients labeled as SS in the SICCA cohort were classified with the newer ACR/EULAR classification criteria using ocular, oral, and serologic testing for SS, capturing patients with more diverse symptomology and more up-to-date SS classification than those considered to have SS in the AECG studies. Furthermore, the SICCA cohort is more diverse in its representation of 9 international research sites including North America, South America, Europe, East Asia, and South Asia.

Limitations of our study include possible over- or under-representation of certain populations. While the SICCA study was designed to be diverse and includes patients recruited from 9 different international sites, approximately half of the 974 rheumatologist-referred patients were Caucasian and the majority were female, limiting the generalizability of the SSSQ in other races or in men. Longitudinal studies are needed to validate the SSSQ in these populations. Additionally, the SSSQ is designed to be used in English, and may not be applicable in other cultures where terms like "cracker" may be uncommon or interpreted differently. Furthermore, the recruitment protocol may have varied at different sites. It is possible that some study sites may have chosen to refer patients to the SICCA study only if there was strong suspicion of SS, while others may have referred patients with any level of suspicion. This could potentially confound the predictive ability of some questions. Additionally, our screening questionnaire would be unlikely to identify SS patients who present with systemic manifestations without any sicca symptoms. A final limitation of our study is lack of information on duration of illness of patients in the SICCA cohort, since the study included evaluation of both patients with known SS and unknowns with a variety of phenotypes. Accurate identification of disease onset is difficult because some individuals have a prodrome before diagnosis during which autoantibodies appear but the patient remains asymptomatic [32]. Even after symptom onset, patients have different thresholds for experiencing symptoms before presenting to a clinician. To address the limitations of our study, we plan to complete a longitudinal study to determine the practical utility of the instrument.

In summary, the SSSQ is a simple, easy-to-use, and cost-effective preliminary 5-item questionnaire designed to enable rheumatologists to quickly screen patients suspected of SS.

To our knowledge, it is the first evidence-based screening questionnaire for SS designed for clinical practice. If the SSSQ predicts a high likelihood of SS, a full diagnostic evaluation for SS is recommended. The SSSQ's potential impacts include improving differential diagnosis of rheumatologic diseases with overlapping presentations, decreasing long delays in SS diagnosis, and reducing the burden of testing all patients with possible symptoms. The next steps are to perform longitudinal studies to validate the SSSQ in a new cohort of patients in rheumatology and potentially other practice settings.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

## REFERENCES

1. Fox RI. Sjögren's syndrome. The Lancet. 2005;366(9482):321–31.

2. Delalande S, De Seze J, Fauchais A-L, et al. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine. 2004;83(5):280–91. [PubMed: 15342972]

3. Bartoloni E, Baldini C, Schillaci G, et al. Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. J Intern Med. 2015;278(2):185–92. [PubMed: 25582881]

4. Baer A, Ambinder R. Lymphoproliferative disease in Sjögren's syndrome. In: Vivino F, ed. Sjögren's Syndrome: A Clinical Handbook. Amsterdam: Elsevier, Inc; 2020. p. 129–52.

5. Heaton J. Sjögren's syndrome and systemic lupus erythematosus. Br Med J. 1959;1(5120):466. [PubMed: 13629021]

6. He J, Ding Y, Feng M, et al. Characteristics of Sjögren's syndrome in rheumatoid arthritis. Rheumatology. 2013;52(6):1084–9. [PubMed: 23382356]

7. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. Arthritis Rheum. 2008;58(1):15–25. [PubMed: 18163481]

8. Zhang M, Kim E, Akpek EK. Prevalence and predictors of Sjögren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. Br J Ophthalmol. 2012;96(12):1498–503. [PubMed: 23001257]

9. Henrich CF, Ramulu PY, Akpek EK. Association of dry eye and inflammatory systemic diseases in a tertiary care–based sample. Cornea. 2014;33(8):819–25. [PubMed: 24977987]

10. Akpek EK, Klimava A, Thorne JE, et al. Evaluation of patients with dry eye for presence of underlying Sjögren's syndrome. Cornea. 2009;28(5):493. [PubMed: 19421051]

11. Usuba FS, Lopes JB, Fuller R, et al. Sjögren's syndrome: An underdiagnosed condition in mixed connective tissue disease. Clinics. 2014;69(3):158–62. [PubMed: 24626939]

12. Manthorpe R. Primary Sjogren's syndrome: diagnostic criteria, clinical features, and disease activity. J Rheumatol. 1997;24:8–11.

13. Beckman KA, Luchs J, Milner MS. Making the diagnosis of Sjögren's syndrome in patients with dry eye. Clinical ophthalmology (Auckland, NZ). 2016;10:43.

14. Vivino FB. Sjogren's syndrome: clinical aspects. Clin Immunol. 2017;182:48–54. [PubMed: 28428095]

15. Rasmussen A, Radfar L, Lewis D, et al. Previous diagnosis of Sjögren's syndrome as rheumatoid arthritis or systemic lupus erythematosus. Rheumatology. 2016;55(7):1195–201. [PubMed: 26998859]

16. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61(6):554–8. [PubMed: 12006334]

17. Shiboski S, Shiboski C, Criswell L, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken). 2012;64(4):475–87. [PubMed: 22563590]

18. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/ European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis & Rheumatology. 2017;69(1):35–45. [PubMed: 27785888]

19. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1993;36(3):340–7.

20. Vitali C, Moutsopoulos HM, Bombardieri S. The European Community Study Group on diagnostic criteria for Sjögren's syndrome. Sensitivity and specificity of tests for ocular and oral involvement in Sjögren's syndrome. Ann Rheum Dis. 1994;53(10):637–47. [PubMed: 7979575]

21. Daniels TE, Criswell LA, Shiboski C, et al. An early view of the international Sjögren's syndrome registry. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2009;61(5):711–4.

22. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. Stat Med. 2004;23(10):1631–60. [PubMed: 15122742]

23. Altman DG, Bland JM. Statistics Notes: Diagnostic tests 2: predictive values. BMJ. 1994;309(6947):102. [PubMed: 8038641]

24. Ebert EC, Hagspiel KD. Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. J Clin Gastroenterol. 2011;45(5):436–41. [PubMed: 21422947]

25. Stone DU, Fife D, Brown M, et al. Effect of tobacco smoking on the clinical, histopathological, and serological manifestations of Sjögren's syndrome. PLoS One. 2017;12(2):e0170249. [PubMed: 28166540]

26. Olsson P, Turesson C, Mandl T, et al. Cigarette smoking and the risk of primary Sjögren's syndrome: a nested case control study. Arthritis Res Ther. 2017;19(1):50. [PubMed: 28270185]

27. Manthorpe R, Benoni C, Jacobsson L, et al. Lower frequency of focal lip sialadenitis (focus score) in smoking patients. Can tobacco diminish the salivary gland involvement as judged by

histological examination and anti-SSA/Ro and anti-SSB/La antibodies in Sjögren's syndrome? Ann Rheum Dis. 2000;59(1):54–60. [PubMed: 10627428]

28. Sánchez-Guerrero J, Pérez-Dosal M, Cárdenas-Velázquez F, et al. Prevalence of Sjögren's syndrome in ambulatory patients according to the American–European Consensus Group criteria. Rheumatology. 2005;44(2):235–40. [PubMed: 15509625]

29. Guellec D, Cornec D, Jousse-Joulin S, et al. Diagnostic value of labial minor salivary gland biopsy for Sjögren's syndrome: a systematic review. Autoimmunity reviews. 2013;12(3):416–20. [PubMed: 22889617]

30. Fayyaz A, Kurien BT, Scofield RH. Autoantibodies in Sjögren's syndrome. Rheumatic Disease Clinics. 2016;42(3):419–34. [PubMed: 27431345]

31. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med. 2004;164(12):1275–84. [PubMed: 15226160]

32. Jonsson R, Theander E, Sjöström B, et al. Autoantibodies present before symptom onset in primary Sjögren syndrome. JAMA. 2013;310(17):1854–5. [PubMed: 24193084]
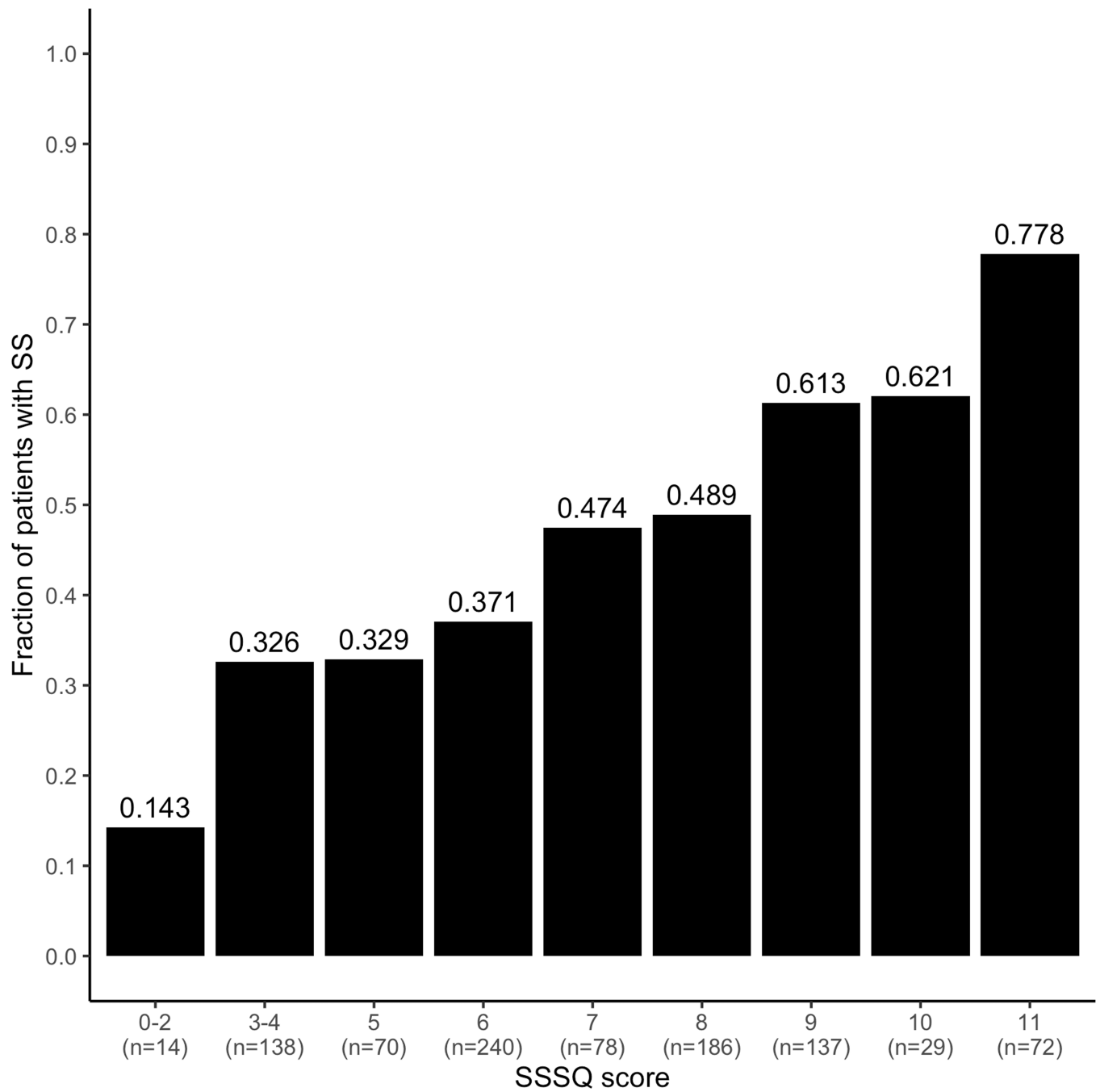
**Figure 1.**
The fraction of patients with Sjögren's syndrome (SS) increases as the Sjögren's Syndrome
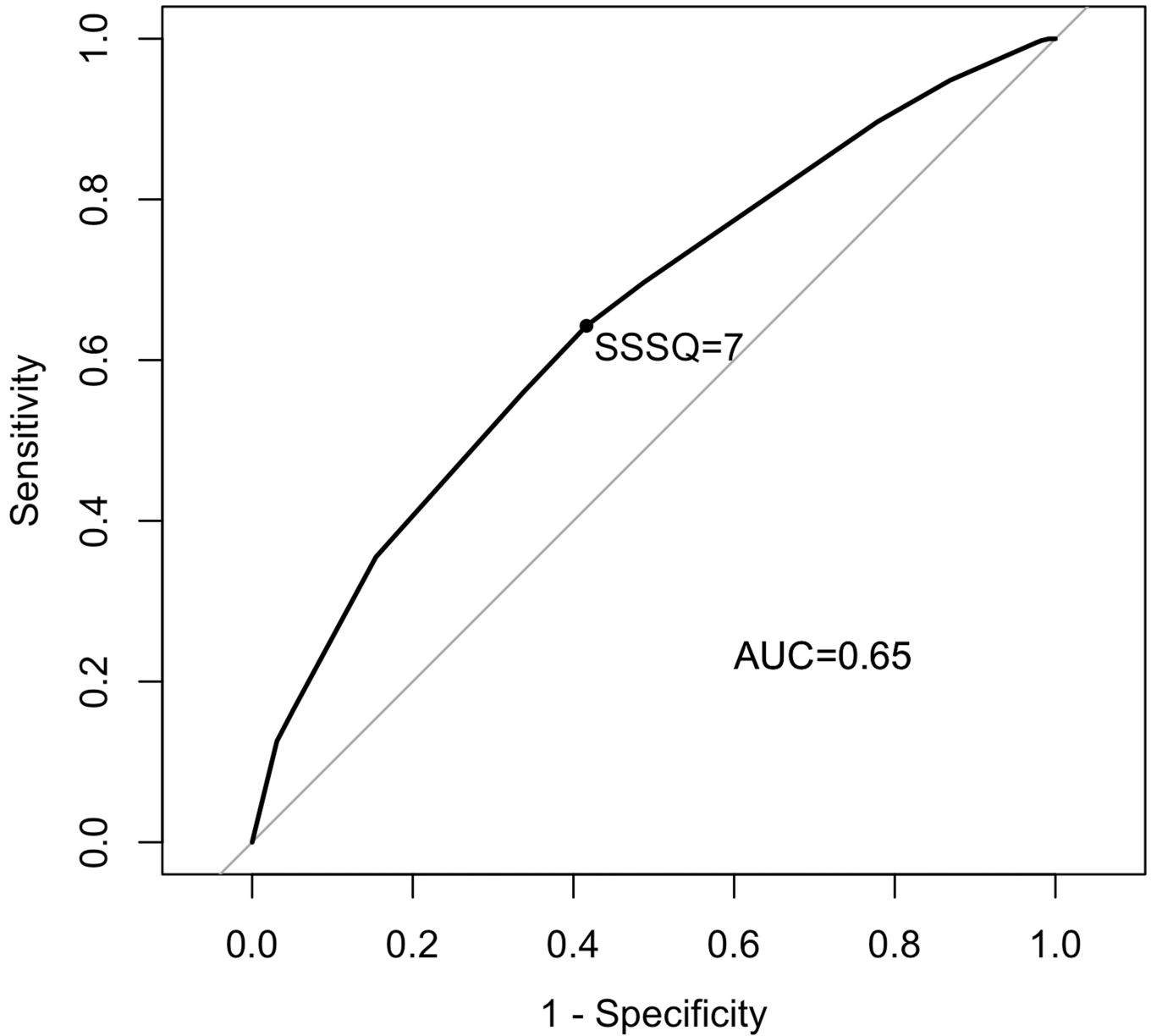Screening Questionnaire (SSSQ) score increases.

**Figure 2.**
The Sjögren's Syndrome Screening Questionnaire (SSSQ) score discriminates Sjögren's syndrome (SS) vs. non-SS with an AUC of 0.65. An SSSQ score cut point of 7 maximizes Youden's J index (sensitivity + specificity – 1), with sensitivity=0.643, specificity=0.584, and Youden's J index=0.227.

**Table 1.**

Five questions significantly discriminated Sjögren's syndrome (SS) vs. non-SS in the multivariate logistic regression model.

| | Number of responders | # of responders with SS (%) | Regression coefficient | OR (95% CI) | p-value |
|---|---|---|---|---|---|
| **Can you eat a cracker without drinking a fluid/liquid?** | | | | | |
| Yes | 520 | 220 (42.3%) | | 1.00 | |
| No | 453 | 229 (50.6%) | 0.33 | 1.39 (1.06–1.82) | 0.017 |
| **How would you describe your dental and oral health in general?** | | | | | |
| Excellent | 85 | 32 (37.6%) | | 1.00 | |
| Good | 318 | 123 (38.7%) | 0.085 | 1.09 (0.66–1.82) | 0.74 |
| Fair or Poor | 571 | 294 (51.5%) | 0.52 | 1.68 (1.04–2.75) | 0.035 |
| **During the last week have you experienced tearing?** | | | | | |
| None of the time | 701 | 361 (51.5%) | 0.82 | 2.26 (1.23–4.34) | 0.011 |
| Some of the time | 221 | 72 (32.6%) | 0.13 | 1.14 (0.59–2.26) | 0.71 |
| More than some of the time | 52 | 16 (31.4%) | | 1.00 | |
| **Are you able to produce tears?** | | | | | |
| Yes | 816 | 351 (43.0%) | | 1.00 | |
| No | 155 | 98 (63.2%) | 0.48 | 1.62 (1.12–2.37) | 0.011 |
| **Do you currently smoke cigarettes?** | | | | | |
| Yes | 80 | 22 (27.5%) | | 1.00 | |
| No | 894 | 427 (47.8%) | 1.04 | 2.83 (1.69–4.91) | 0.0001 |
| **AUC (95% CI)** | | 0.65 (0.62–0.69) | | | |

**Table 2.**

Sjögren's Syndrome Screening Questionnaire (SSSQ) scoring system.

| Question | Response | Score |
|---|---|---|
| 1. Can you eat a cracker without drinking a fluid/liquid? | Yes | 0 |
| | No | 1 |
| 2. How would you describe your dental and oral health in general? | Excellent | 0 |
| | Good | 0 |
| | Fair/Poor | 2 |
| 3. During the last week have you experienced tearing? | None of the time | 3 |
| | At least some of the time | 0 |
| 4. Are you able to produce tears? | Yes | 0 |
| | No | 2 |
| 5. Do you currently smoke cigarettes? | Yes | 0 |
| | No | 3 |
| **TOTAL** | | (Max 11) |

**Table 3.**

Performance of the Sjögren's Syndrome Screening Questionnaire (SSSQ) for all subjects and stratified by age.

| Age range | N | # with SS (%) | Sensitivity (95% CI) | Specificity (95% CI) | AUC (95% CI) |
|---|---|---|---|---|---|
| All ages (21–90) | 974 | 449 (46.1%) | 0.64 (0.60–0.69) | 0.58 (0.54–0.63) | 0.65 (0.62–0.69) |
| 21–42 | 249 | 128 (51.4%) | 0.67 (0.59–0.76) | 0.62 (0.52–0.70) | 0.71 (0.64–0.77) |
| 43–52 | 253 | 109 (43.1%) | 0.67 (0.57–0.75) | 0.67 (0.59–0.75) | 0.71 (0.65–0.77) |
| 53–60 | 229 | 106 (46.3%) | 0.62 (0.52–0.71) | 0.57 (0.47–0.66) | 0.65 (0.58–0.72) |
| 61–90 | 243 | 106 (43.6%) | 0.60 (0.50–0.69) | 0.48 (0.39–0.57) | 0.63 (0.56–0.70) |

*
Stratified ages are divided into quartiles. The sensitivity and specificity of the SSSQ using a cut point of 7 was calculated for each age group. The AUC of the multivariate regression model is reported for each age group.