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Original Article

Application of classification criteria of Sjogren syndrome in patients with sicca symptoms: Real-world experience at a medical center

Yu-Hsiang Chiu [a], Tony Szu-Hsien Lee [b], En Chao [c], I-Feng Chen [d], Feng-Cheng Liu [a], Chung-Hsin Chiu [d], Hsiang-Cheng Chen [a], Deh-Ming Chang [a,e], Shi-Jye Chu [a], San-Yuan Kuo [a], Chun-Chi Lu [a,*]

[a] *Division of Rheumatology/Immunology/Allergy, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[b] *Department of Health Promotion and Health Education, National Taiwan Normal University, Taiwan*
[c] *Medical Service Office, Tri-Service General Hospital Songshan Branch, National Defense Medical Center, Taipei, Taiwan*
[d] *Department of Nuclear Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[e] *Division of Allergy, Immunology, Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

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KEYWORDS
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Background: Patients who have symptoms of sicca, such as dry eyes and mouth, may have Sjögren's syndrome (SS). However, the conservative culture makes patients hesitate to undergo an invasive biopsy, which contributes to the difficulty of confirming a diagnosis. We aimed to identify the characteristics of patients with sicca symptoms to develop a better predictive value for each item included in the three different diagnostic criteria for SS and clarify the best diagnostic tools for the local population.
Methods: This is a single-center retrospective case-control study from January 2016 to December 2017. Patients who underwent sialoscintigraphy because of clinical symptoms of xerostomia and xerophthalmia at one medical center were reviewed via the patients' electronic medical records.
Results: Of 515 patients enrolled, the severity of results for sialoscintigraphy and Schirmer's test was correlated with a diagnosis of SS and generated receiver operator characteristic

* Corresponding author. Division of Rheumatology/Immunology and Allergy, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec 2, Cheng-Gong Rd, Neihu Dist., 114, Taipei, Taiwan. Fax: +886 2 87927136.
E-mail address: jameslutaiwan@gmail.com (C.-C. Lu).

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curve. The area under curve (AUC) was 0.603 for positive Schirmer's test, 0.687 for positive anti-Ro/La results, 0.893 for a positive salivary gland biopsy. The AUC was 0.626 and 0.602 for Schirmer's test which is redefined as <10 mm/5 minutes in either eye and according to 2016 the American College of Rheumatology/ European League Against Rheumatism criteria, respectively.

Conclusion: Our results indicate the cut-off point for defining a positive test result in the Schirmer's test is worth modified to <10 mm/5 minutes in either eye.

Introduction

Sjögren's syndrome (SS) is the result of autoimmune-mediated inflammation in exocrine glands. Some patients with SS also present with extraglandular manifestations including lymphoma, fatigue, cutaneous, muscular, articular, pulmonary, vascular, renal, neurological, and hematological abnormalities.[1,2] The current applied classification criteria are the 2002 American–European consensus group (AECG) criteria, the 2012 American College of Rheumatology (ACR) criteria and the 2016 ACR/the European League Against Rheumatism (EULAR) criteria.[3–5]

Patients who encounter symptoms of sicca, such as xerostomia and xerophthalmia, may have SS and would consult a rheumatologist. In our recent clinical practice, most of these patients undergo evaluation according to the 2002 AECG criteria, including a blood test for anti-Ro/La, sialoscintigraphy, and referral to an ophthalmologist for a Schirmer's test. If a patient is negative for anti-Ro/La autoantibodies but positive on either sialoscintigraphy or Schirmer's test, they are referred to an oral surgeon for labial salivary gland biopsy. However, the conservative culture in Taiwan makes patients hesitate to undergo an invasive biopsy, which contributes to the considerable difficulty of confirming a diagnosis of SS. Therefore, it is challenging to allocate a therapeutic plan for seronegative patients with sicca, especially when they have comorbidities related to extraglandular symptoms. We aimed to identify the characteristics of patients with sicca symptoms to develop better predictive value for each item included in the three different diagnostic criteria for SS and clarify the best diagnostic tools for the local population.

Methods

Study design

This single-center retrospective case-control study has been approved by the Institutional Review Board of Tri-Service General Hospital with waiving of the informed consent form, No. 1-107-05-036. Patients who underwent sialoscintigraphy because of xerostomia and xerophthalmia were recruited from January 2016 to December 2017. We reviewed the electronic medical records of the enrolled patients. Patient demographics including sex and age at the time of sialoscintigraphy were recorded. Patients under the age of 20 were excluded. The diagnosis of SS was determined by a rheumatologist in the follow-up period using the 2002 AECG classification criteria.[3] Comorbidities such as ischemic stroke, hypertension, diabetes mellitus, malignancy, status postradiotherapy, and psychological disorders such as insomnia, anxiety disorder, panic disorder, mood disorder, and schizophrenia were recorded.

Tear function was evaluated from the results of Schirmer's tests obtained from the ophthalmologists' records. A positive Schirmer's test was defined as a score of ≤5 mm/5 min in both eyes and a negative test as a score ≥10 mm/5 min in both eyes. The Schirmer's test results that did not fit either the positive or negative classifications were defined as equivocal. The results of sialoscintigraphy were reviewed by two experienced nuclear medicine physicians. Labial salivary gland biopsy results reporting a sialadenitis focus score of ≥1 were defined as positive.[3]

The results of serum immunological evaluations, including antinuclear antibody (ANA; EUROIMMUN), anti-Ro/La antibody, and rheumatoid factor (RF; Thermo Fisher Scientific) were collected. The reference ranges for anti-Ro, anti-La, and RF were defined according to the manufacturer's instructions. This study was approved by the Institutional Review Board of Tri-Service General Hospital.

Statistical analysis

We used the chi-squared test to compare distributions of categorical variables and baseline comorbidities between the SS and non-SS groups. Age as a continuous variable was tested using Student's *t*-test. An association between the results of sialoscintigraphy and Schirmer's test was evaluated using the Pearson chi-squared test with Cramer's V. Factors correlating with a diagnosis of SS were evaluated using an odds ratio (OR) with 95% confidence interval (CI). The predictive value of these factors was calculated using the area under the curve (AUC) of a receiver operating characteristic (ROC). P values < 0.05 were considered significant. Statistical analyses were conducted using the "dplyr," "vcd," "epitools," and "Epi" packages of R software (version 3.5.2).[6–13]

Results

Overall, 516 patients underwent sialoscintigraphy at one medical center between 2016 and 2017. One patient aged under 20 years old was excluded. The mean age of participants was 55.6 years. Women constituted 85.4% of the patients. Based on 2002 AECG criteria, 247 patients (48.0%) were diagnosed with SS, including 12 with secondary SS

Table 1 Demographic data.

	Total n (%)	Sjogren syndrome	Non-Sjogren syndrome	p-value
All	515	247 (48.0)	268 (52.0)	0.213
Age (years, mean ± SD)	55.6 ± 14.9	56.6 ± 14.7	54.7 ± 15.0	0.133
Female	440 (85.4)	219 (88.7)	221 (82.5)	0.062
Sialoscintigraphy				0.010
markedly	207 (40.2)	112 (45.3)	95 (35.5)	Cramer's V 0.149
moderately	222 (43.1)	102 (41.3)	120 (44.8)	
mildly	58 (11)	27 (11)	31 (12)	
negative	28 (5)	6 (2)	22 (8)	
Schirmer's test				<.001
Positive	184 (43.7)	124 (52.8)	60 (32.3)	Cramer's V 0.236
Equivocal	159 (37.8)	83 (35.3)	76 (40.9)	
Negative	78 (19)	28 (12)	50 (27)	
Schirmer's test (2016)				<.001
Positive	256 (60.8)	164 (69.8)	92 (49)	Phi 0.207
Negative	165 (39.2)	71 (30)	94 (51)	
Anti-Ro positive	225 (44.1)	156 (63.2)	69 (26)	<.001
Anti-La positive	59 (12)	47 (19)	12 (5)	<.001
Anti-Ro or Anti-La positive	226 (44.3)	157 (63.6)	69 (26)	<.001
ANA positive (>1:80)	228 (45.2)	135 (55.6)	93 (36)	<.001
RF positive	107 (22.2)	55 (24)	52 (21)	0.436
Stroke	14 (3)	9 (4)	5 (2)	0.333
Hypertension	102 (19.8)	55 (22)	47 (18)	0.217
Diabetes mellitus	53 (10)	26 (11)	27 (10)	0.981
Psychologic disorder	55 (11)	29 (12)	26 (10)	0.545
Malignancy	35 (7)	12 (5)	23 (9)	0.133
Status post radiotherapy	15 (43)	5 (42)	10 (44)	1

during the follow-up period. Of the 515 patients who underwent sialoscintigraphy because of decreased peak vascular perfusion or secretion velocity, 207 (40.2%) were reported as having marked delay, 222 (43.1%) as having moderate delay, 58 (11%) as having mild delay, and 28 patients (5%) were reported as negative. There were 421 patients who underwent a Schirmer's test: 184 (43.7%) were positive, 159 (37.8%) were equivocal, and 78 (19%) were negative. In the SS group, 51.1% of patients were positive for both Schirmer's test and sialoscintigraphy; in the non-SS group, the figure was 30.7% ($P < 0.001$). When the 2016 ACR/EULAR classification criteria were applied, a Schirmer's test result of ≤5 mm/5 min in at least one eye was redefined as positive,[5] meaning that 256 patients of 421

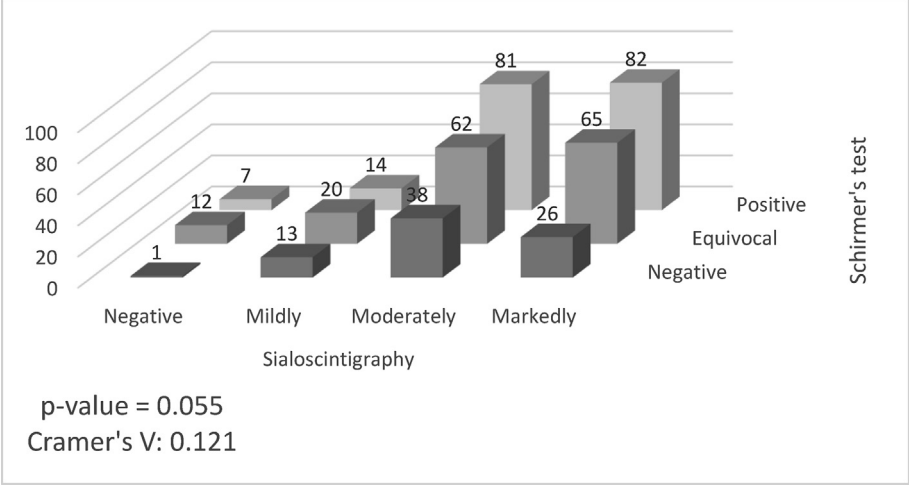

Figure 1 The association between Sialoscintigraphy and Schirmer's test.

Table 2 Correlation of items to the diagnosis of Sjögren syndrome.

Factor	Odds ratio	confidence interval	p
Sialoscintigraphy			
markedly	4.323	1.683–11.102	0.001
moderately	3.117	1.217–7.983	0.015
mildly	3.194	1.129–9.033	0.033
negative	1		
Schirmer's test			
Positive	3.690	2.117–6.434	<.001
Equivocal	1.950	1.117–3.406	0.019
Negative	1		
Schirmer's test (2016)	2.360	1.582–3.521	<.001
Anti-Ro positive	4.820	3.305–7.029	<.001
Anti-La positive	4.915	2.539–9.516	<.001
Anti-Ro or Anti-La positive	4.905	3.362–7.155	<.001
ANA positive (>1:80)	2.184	1.528–3.123	<.001
RF positive	1.202	0.782–1.847	0.443
RF positive and ANA ≥1:320	2.541	1.252–5.158	0.011
Anti-Ro or Anti-La positive or [RF positive and ANA ≥1:320]	4.636	3.191–6.736	<.001

patients (60.8%) were now positive. There were 225 patients (44.1%) who were positive for anti-Ro, 59 (11.6%) positive for anti-La, 226 (44.3%) positive for anti-Ro or anti-La, and 228 (45.2%) with an ANA of ≥1:80. Demographic information is shown in Table 1. Among 70 patients with positive salivary biopsy, 25 (35.7%) patients had an equivocal on Schirmer's tests. Two of four patients with positive anti-Ro and salivary biopsy presented an equivocal Schirmer's test. 100 out of 291 (34.4%) patients with the presence of anti-Ro or inflammation on salivary biopsy had an equivocal Schirmer's test.

The correlation between sialoscintigraphy and Schirmer's test results for all 421 participants is illustrated in Fig. 1, showing a *P*-value of 0.055 and Cramer's V of 0.121. The correlation of sialoscintigraphy with decreased vascular perfusion or delayed secretion velocity in patients with SS was significant, with an OR 4.323 (95% CI 1.683–11.102, $P = 0.001$) in patients with marked delay, OR 3.117 (95% CI 1.217–7.983, $P = 0.015$) in those with moderate delay, and OR 3.194 (95% CI 1.129–9.033, $P = 0.033$) in those with mild delay. The correlation between either a positive or equivocal Schirmer's test and a diagnosis of SS was significant, with ORs of 3.690 (95% CI 2.117–6.434, $P < 0.001$) and 1.95 (95% CI 1.117–3.406, $P = 0.019$), respectively. Based on the 2016 ACR/EULAR criteria, the correlation between a positive Schirmer's test and SS is significant with an OR of 2.36 (95% CI 1.582–3.521, $P < 0.001$). Positive anti-Ro or anti-La results were also significantly correlated with SS (OR 4.905, 95% CI 3.362–7.155; $P < 0.001$). Positive anti-Ro or anti-La results with simultaneously positive RF IgM and ANA ≥1:320 had an OR of 4.636 (95% CI 3.191–6.736, $P < 0.001$) for SS (Table 2).

The AUC was 0.563 for positive sialoscintigraphy, 0.603 for positive Schirmer's test, 0.687 for positive anti-Ro/La results, 0.893 for a positive salivary gland biopsy, 0.632 for the combination of positive sialoscintigraphy and positive Schirmer's test, 0.713 for the combination of positive sialoscintigraphy and positive anti-Ro/La results, 0.746 for the combination of positive Schirmer's test and positive anti-Ro/La results, 0.761 for the combination of positive sialoscintigraphy, positive Schirmer's test, and positive anti-Ro/La results (Fig. 2), 0.531 for a positive RF and ANA > 1:320, 0.681 for either positive anti-Ro or anti-La results or simultaneously positive RF and ANA ≥1:320. The AUC was 0.626 and 0.602 for Schirmer's test which is redefined as <10 mm/5 min in either eye and according to 2016 ACR/EULAR criteria, respectively (Table 3).

Discussion

The 2002 AECG classification criteria are the most commonly used in the health care system of Taiwan to classify primary SS, with an initial trial reporting a sensitivity of 89.5% and a specificity of 95.2%.[3] Clinical application of the criteria requires performance of sialoscintigraphy for objective salivary gland involvement and Schirmer's test for objective ocular signs, as well as performing a serum screen for anti-Ro/La. Therefore, biopsy of a salivary gland or a positive anti-Ro/La result is required to fulfill the diagnostic criteria. Many Taiwanese patients are hesitant to undergo salivary gland biopsy due to conservative culture, which makes fulfilling the criteria for the diagnosis of SS difficult.

Of the 515 included patients, 247 (48.0%) were diagnosed with SS. Positive Schirmer's test results were more strongly associated with SS than were the results of sialoscintigraphy, with the Cramer's Vs being 0.236 and 0.149, respectively. The more serious the disease detected on the objective xerophthalmia and xerostomia examination, the higher the possibility and the greater the odds of confirming a diagnosis of SS. Nonetheless, objective xerostomia was more prevalent than objective xerophthalmia, with 94.6% positive results for sialoscintigraphy and 43.7% positive results for Schirmer's test. Age was also a contributing factor for positive and equivocal results of the Schirmer's test. According to the interpretation of Schirmer's test used in

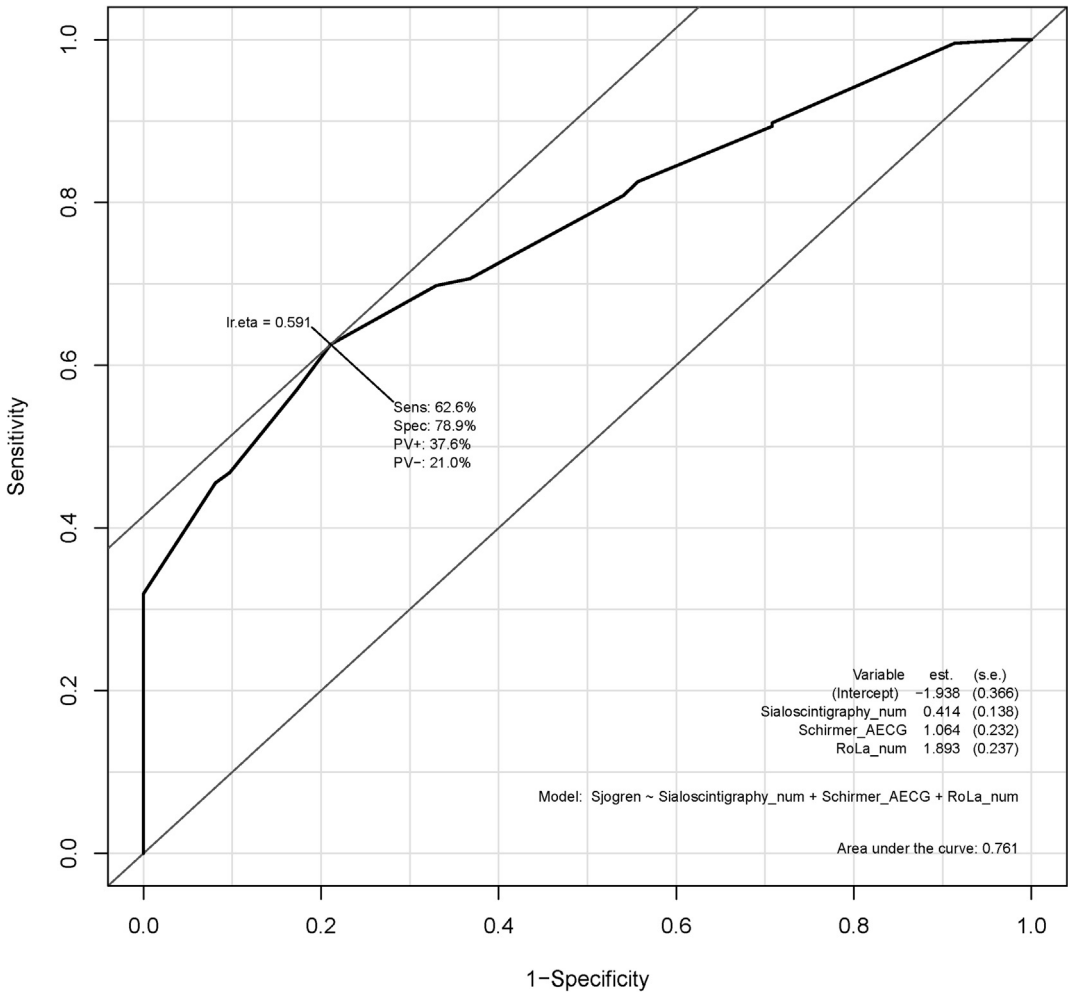

Figure 2 The receiver operating characteristic curve of the combination of sialoscintigraphy and positive anti-Ro/La results in the diagnosis of Sjögren syndrome.

Table 3 The area under the receiver operator characteristic curve of each factor.

	Area Under Curve
Sialoscintigraphy	0.563
Schirmer's test	0.603
Schirmer's test (2016)	0.602
Schirmer's test (redefined)	0.626
Positive anti-Ro/La	0.687
Positive ANA (>1:80)	0.600
Salivary gland biopsy	0.893
Sialoscintigraphy + Schirmer's test	0.632
Sialoscintigraphy + Positive anti-Ro/La	0.713
Schirmer test + Positive anti-Ro/La	0.746
Sialoscintigraphy + Schirmer's test + Positive anti-Ro/La	0.761
Positive RF and ANA > 1:320	0.531
Positive anti-Ro/La or [positive RF and ANA >1:320]	0.681

the 2002 AECG criteria, a result of <5 mm tears/5 min in both eyes is positive. An equivocal result on Schirmer's test does not contribute any points in the 2002 AECG classification criteria; however, in our data, it has an OR of 1.95 for a diagnosis of SS. A mild to marked delay in uptake, reduced concentration, and/or delayed excretion on sialoscintigraphy score one point for the objective evidence of salivary gland involvement.[3] We would suggest that the

application of the 2002 AECG classification criteria to our local population might be modified because the cut-off point for a positive diagnostic criterion for Schirmer's test might be an "equivocal" result, which would help accurately diagnose patients with SS. Sialoscintigraphy and Schirmer's test results show a trend towards positive association, with a Cramer's V of 0.121; however, the *P*-value of 0.055 did not reach significance in the study population. Double-positivity for sialoscintigraphy and Schirmer's test occurred more frequently in the SS group than in the non-SS group.

Apart from autoimmune exocrinopathy, previously reported contributors to dry eyes and mouth include age, sex, nutrition, allergies, thyroid disease, systemic disease (such as metabolic syndrome, diabetes mellitus, chronic kidney disease), medications, contact lens wearing, exposure to visual display terminals, humidity, head and neck radiotherapy, infection (such as with human immunodeficiency virus), and graft-versus-host disease.[14–22] Older age was also associated with more severe xerophthalmia on Schirmer's test in our study. Age, sex, and comorbidities such as stroke, hypertension, diabetes mellitus, psychologic disorders, malignancy, and radiotherapy did not differ significantly between the SS and non-SS groups in our study population. Except for other objective evaluations of ocular sicca including tear film breakup time and ocular staining, Schirmer's test has been the most practicing methodology in our clinic. Either tear film breakup time, conjunctival staining or Schirmer's test was achieved significant difference from patients with non-SS dry eye disease to SS dry eye disease.[23,24]

A positive anti-Ro/La or minor salivary gland pathology with a focus score of $\geq$1 are the necessary factors to allow the use of the 2002 AECG classification criteria. Our results are compatible with these criteria because the AUCs of anti-Ro/La or salivary gland biopsy were 0.687 and 0.893, respectively. A positive salivary gland biopsy showed a sensitivity of 98.6% and specificity of 80% for the diagnosis of SS.

The 2012 ACR classification enrolled either positive serum anti-Ro/La or positive RF and ANA titer $>$1:320 into diagnostic criteria.[4] Serum rheumatoid factor and ANA could be identified in many diseases in addition to autoimmune diseases, such as infectious diseases and malignancy. Although RF and high-titer ANA emerged in the 2012 ACR criteria, this combination had only a low diagnostic value in our local population. A positive RF did not even achieve a statistically significant difference between SS and non-SS group in our cohort. Few individuals were fulfilling the 2012 ACR criteria with negative for anti-Ro/La but positive for ANA and RF in the Oklahoma Medical Research Foundation cohort.[25] The ACR/EULAR consensus excluded ANA and RF in the 2016 criteria generation process.[5] Thus, the percentage of detected RF in SS is almost the same as in sicca patients without SS.

However, Schirmer's test is still enrolled in the criteria, which emphasized the importance of Schirmer's test. Sialoscintigraphy is a functional qualitative methodology, and the result is still not consistency dependent on the skill of different nuclear medicine physicians. We are working on a quantitative method through time activity curves for salivary gland activity which is capable of quantitating sialadenitis with more accuracy. Ocular staining is not as convenient and prevalent as the Schirmer's test in current clinical practice, and rose Bengal dye has been reported to be toxic to the cornea.[26,27]

There was a low predictive value for sialoscintigraphy, which is consistent with a previous study, an AUC $<$0.6.[28] Sialoscintigraphy was included in the item generation but did not remain through multi-criteria decision analysis of 2016 ACR/EULAR criteria.[5] However, Schirmer's test is still enrolled in the criteria, which emphasized the importance of Schirmer's test. Sialoscintigraphy is a functional qualitative methodology and the result is still not consistence dependent on the skill of different nuclear medicine physicians. A quantitative method through time activity curves for salivary gland activity has been launched in our study, which is capable of quantitating sialadenitis with more accuracy.

Patient acceptance of an invasive procedure, such as a labial salivary gland biopsy, is another critical problem in using the 2012 ACR and 2002 AECG criteria. Currently, the application of the 2002 AECG criteria is more suitable for our local population than that of the 2012 ACR criteria, based on the conservative culture. The ACR and EULAR developed new classification criteria in 2016 that incorporated modifications to the 2002 AECG and 2012 ACR criteria.[5] The Schirmer's test was reclassified as positive with a result of $\leq$5 mm/5 min in at least one eye rather than in both eyes. Positive serology included only anti-Ro, whereas anti-La, ANA, and RF were dropped from the criteria. Xerostomia was measured via the collection of unstimulated whole saliva rather than by sialoscintigraphy.[29] A positive score for more than 4 of 5 items was classified as indicating SS. This provides the possibility of diagnosing SS in seronegative patients who refuse a labial biopsy. The exclusion criteria of the 2016 ACR/EULAR criteria were added IgG4-related disease and allowed for pre-existing lymphoma.

The treatment for SS mainly involves lifestyle modification and symptom-revealed medications (such as artificial tears, pilocarpine, and cevimeline).[1] In the current consensus, initial immunomodulation is not suggested except in cases with extraglandular presentations, although in our population-based cohort study, it reduced the risk of developing lymphoma.[30] Our retrospective analysis of the real-world clinical experience help clinicians identify patients who have a high risk of developing SS and reduce the morbidity. Defining the severity of oral and ocular sicca by unstimulated whole saliva flow rate, sialoscintigraphy, ocular staining score or Schirmer's test are essential in patients with sicca symptoms in addition to comprehensive medical history collection. The immunological survey with serum anti-Ro stands for its autoimmune feature and is crucial in each of the classification criteria. Labial salivary gland biopsy is inevitable in seronegative patients with objective ocular and oral sicca. Based on our data, extended Schirmer's test helps identify more sicca patients who need treatments.

This study has some limitations. This is a retrospective case-control analysis based on the electronic medical record. Some sicca patients who might be at high risk of SS were lost follow-up or declined the lip biopsy. All participants were classified based on the 2002 AECG criteria

initially. Few patients received ocular staining in the current practicing in our cohort. Isreb and colleagues have reported a Pearson's correlation 0.751 between Schirmer's test with anesthesia and fluorescein break-up time,[31] which indicates a positive Schirmer's test could be representative of ocular sicca. The unstimulated whole saliva flow rate measurement was not routinely performed in the follow-up period. How to engage the 2016 ACR/EULAR criteria in the real-world clinical practice is still warranted in the future.

Conclusion

These results report the application of classification criteria for SS in our local population, for which the 2002 AECG criteria and 2016 ACR/EULAR criteria are more suitable than the 2012 ACR criteria. However, the cut-off point for defining a positive test result in the Schirmer's test would suggest modified: i.e., a positive Schirmer's test could be defined as $<$10 mm/5 min in either eye. The further application to patients with sicca symptoms and the association with developing extraglandular complications worth further investigation. The complete evaluation of patients with sicca symptoms should involve the cooperation of rheumatologists, ophthalmologists, and dentists.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2019.06.012.

References

1. Saraux A, Pers JO, Devauchelle-Pensec V. Treatment of primary Sjogren syndrome. *Nat Rev Rheumatol* 2016;**12**(8):456—71.
2. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjogren syndrome. *Nat Rev Rheumatol* 2018;**14**(3):133—45.
3. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;**61**(6):554—8.
4. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, et al. American college of rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort. *Arthritis Care Res (Hoboken)* 2012;**64**(4):475—87.
5. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American college of rheumatology/European league against rheumatism classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017;**76**(1):9—16.
6. Carstensen B, Plummer M. Using lexis objects for multi-state models in R. *J Stat Softw* 2011;**38**(6):1—18.
7. Carstensen B, Plummer M, Laara E, Hills M. *Epi: a package for statistical analysis in epidemiology*. 2018.
8. Meyer D, Zeileis A, Hornik K. The strucplot framework: visualizing multi-way contingency tables with vcd. *J Stat Softw* 2006;**17**(3):1—48.
9. Meyer D, Zeileis A, Hornik K. *Vcd: visualizing categorical data*. 2017.
10. Plummer M, Carstensen B. Lexis: an R class for epidemiological studies with long-term follow-up. *J Stat Softw* 2011;**38**(5):1—12.
11. Wickham H, Francois R, Henry L, Muller K. *Dplyr: a grammar of data manipulation*. 2017.
12. Zeileis A, Meyer D, Hornik K. Residual-based shadings for visualizing (conditional) independence. *J Comput Graph Stat* 2007;**16**(3):507—25.
13. Aragon TJ. *Epitools: epidemiology tools*. 2017.
14. Kawashima M, Uchino M, Yokoi N, Dogru M, Uchino Y, Komuro A, et al. Decreased tear volume in patients with metabolic syndrome: the Osaka study. *Br J Ophthalmol* 2014;**98**(3):418—20.
15. Kaido M, Kawashima M, Yokoi N, Fukui M, Ichihashi Y, Kato H, et al. Advanced dry eye screening for visual display terminal workers using functional visual acuity measurement: the Moriguchi study. *Br J Ophthalmol* 2015;**99**(11):1488—92.
16. Uchino Y, Uchino M, Yokoi N, Dogru M, Kawashima M, Okada N, et al. Alteration of tear mucin 5AC in office workers using visual display terminals: the Osaka study. *JAMA Ophthalmol* 2014;**132**(8):985—92.
17. Wang MTM, Craig JP. Comparative evaluation of clinical methods of tear film stability assessment: a randomized crossover trial. *JAMA Ophthalmol* 2018;**136**(3):291—4.
18. Paulsen AJ, Cruickshanks KJ, Fischer ME, Huang GH, Klein BE, Klein R, et al. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. *Am J Ophthalmol* 2014;**157**(4):799—806.
19. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. *Support Care Cancer* 2010;**18**(8):1039—60.
20. Furness S, Bryan G, McMillan R, Birchenough S, Worthington HV. Interventions for the management of dry mouth: non-pharmacological interventions. *Cochrane Database Syst Rev* 2013;**3**(9):CD009603. https://doi.org/10.1002/14651858.CD009603.pub.
21. Thomson WM. Dry mouth and older people. *Aust Dent J* 2015;**60**(Suppl. 1):54—63.
22. Kang YS, Lee HS, Li Y, Choi W, Yoon KC. Manifestation of meibomian gland dysfunction in patients with Sjogren's syndrome, non-Sjogren's dry eye, and non-dry eye controls. *Int Ophthalmol* 2018;**38**(3):1161—7.
23. Yang S, Lee HJ, Kim DY, Shin S, Barabino S, Chung SH. The use of conjunctival staining to measure ocular surface inflammation in patients with dry eye. *Cornea* 2019. https://doi.org/10.1097/ICO.0000000000001916.
24. Kuo MT, Fang PC, Chao TL, Chen A, Lai YH, Huang YT, et al. Tear proteomics approach to monitoring sjogren syndrome or dry eye disease. *Int J Mol Sci* 2019;**20**(8).
25. Rasmussen A, Ice JA, Li H, Grundahl K, Kelly JA, Radfar L, et al. Comparison of the American-European Consensus Group Sjogren's syndrome classification criteria to newly proposed American college of rheumatology criteria in a large, carefully characterised sicca cohort. *Ann Rheum Dis* 2014;**73**(1):31—8.
26. Lee YC, Park CK, Kim MS, Kim JH. In vitro study for staining and toxicity of rose bengal on cultured bovine corneal endothelial cells. *Cornea* 1996;**15**(4):376—85.
27. Tabery HM. Toxic effect of rose bengal dye on the living human corneal epithelium. *Acta Ophthalmol Scand* 1998;**76**(2):142—5.

28. Nadal M, Levy M, Bakhsh A, Joly A, Maruani A, Vaillant L, et al. Salivary scintigraphy for Sjogren's syndrome in patients with xerostomia: a retrospective study. *Oral Dis* 2018;**24**(4):552—60.
29. Navazesh M, Kumar SK, University of Southern California School of D. Measuring salivary flow: challenges and opportunities. *J Am Dent Assoc* 2008;**139**(Suppl):35S—40S.
30. Chiu YH, Chung CH, Lin KT, Lin CS, Chen JH, Chen HC, et al. Predictable biomarkers of developing lymphoma in patients with Sjogren syndrome: a nationwide population-based cohort study. *Oncotarget* 2017;**8**(30):50098—108.
31. Isreb MA, Greiner JV, Korb DR, Glonek T, Mody SS, Finnemore VM, et al. Correlation of lipid layer thickness measurements with fluorescein tear film break-up time and Schirmer's test. *Eye (Lond)* 2003;**17**(1):79—83.