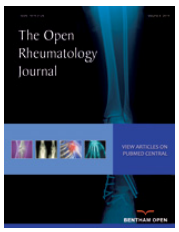

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RESEARCH ARTICLE

Noninvasive Score in Classification Diagnosis of Sjögren's Syndrome

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Abstract:

Background:

To develop simple, practical classification criteria for Sjögren's Syndrome (SS) without Labial Salivary Gland Biopsy (LSGB).

Methods:

In the new criteria (noninvasive score, NIS) set, classification as "definite SS" is based on the ocular and oral symptoms and signs, autoantibodies and the existence of autoimmune thyroid disease, which were calculated. Patients with a score ≥5 were classified as having definite SS and patients with a score <4 were supposed to be excluded from SS. For the patients with a score of 4, LSGB was suggested.

Result:

76 patients with suspected SS were recruited between April 2013 and September 2014, 42 of which were definitive diagnosis of SS and 34 were excluded from SS. Sensitivity and specificity for the NIS criteria in the diagnosis of SS were 97.6% and 94.1%, respectively. The Negative Predictive Value (NPV) and Positive Predictive Value (PPV) to detect SS were 97.0% and 95.3% respectively, and the diagnostic accuracy was 96.1%. The area under the ROC curves (AUC; 95% CI) for NIS criteria was 0.959 (0.905-1.000), which performed better than the American-European Consensus Group's (AECG) criteria and LSGB in the diagnosis of SS ($P < 0.05$).

Conclusion:

The NIS criteria are an alternative to the AECG criteria in classification diagnosis of SS, which are with high diagnostic efficiency. We recommend using a score <4 and ≥5 to rule out or to diagnose SS respectively. For the patients with a score of 4, LSGB is necessary and able to diagnose SS.

Keywords: Classification criteria, Diagnosis, Noninvasive, Score, Sjögren's syndrome, PPV.

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1. INTRODUCTION

Sjögren's Syndrome (SS) is a systemic chronic inflammatory disease characterized by lymphocytic infiltrates in exocrine organs. Its main clinical features are ocular and oral dryness due to hypofunction of lachrymal and salivary glands, parotid gland enlargement, thyroid dysfunction, hyperimmunoglobulinemia, and a variety of serum autoantibodies positive [1]. There are many other diseases that can also cause sicca symptoms [2], and there are no specific examinations for SS, for example the lack of specific autoantibodies and even Labial Salivary Gland Biopsy (LSGB) cannot be used as a single gold standard. All the above reasons lead to difficulty in a definite diagnosis of SS.

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The American-European Consensus Group's (AECG) criteria for the classification of SS were proposed in 2002 and were the most commonly used criteria for the diagnosis of SS in the past, which were with high sensitivity of 97.2% but low specificity of 48.6% in the diagnosis of primary SS (PSS), and with high specificity of 97.2% but low sensitivity of 64.7% in the diagnosis of secondary SS (SSS) [3 - 5]. A new set of classification criteria has been developed by the Sjögren's Syndrome International Collaborative Clinical Alliance (SICCA) and accepted as a provisional criteria set by the American College of Rheumatology (ACR) in 2012 in order to improve the efficiency of diagnosis. The ACR criteria have higher sensitivity and specificity which are 93% and 95% respectively. And the new criteria do not distinguish between PSS and SSS [6, 7]. The disadvantage of the ACR criteria is heavily reliant on LSGB. So, we propose to develop simple,

practical classification criteria of SS to reduce reliance on LSGB, which are defined as new noninvasive score (NIS criteria) in classification diagnosis of SS. We undertook this study to compare the NIS criteria to the AECG criteria in patients with suspected SS that have been carefully evaluated for SS.

2. PATIENTS AND METHODS

2.1. Participant Recruitment

Patients with suspected SS at the University of Hong Kong-Shenzhen Hospital between April 2013 and September 2014 were recruited in this study. These patients were referred to rheumatology clinic by the family physician, internist, dentist or ophthalmologist if SS was suspected due to sicca complaints, major salivary gland swelling, suggestive extra-glandular features or suggestive autoantibodies.

2.2. Clinical Evaluation and Laboratory Tests

Schirmer's I test was considered abnormal if ≤5 mm/5 min while vital dye staining ≥4 according to van Bijsterveld's scoring system, and the unstimulated whole salivary flow (UWSF) < 1.5Ml/ 15 min. Indirect Immunofluorescence (IIF), Immunoblotting Test (IBT) and Enzyme-Linked Immuno-absorbent Assay (ELISA) were employed to detect Anti-Nuclear Antibody (ANA), Anti-Extractable Nuclear Antigen (ENA) Antibody and anti-double strand DNA (dsDNA) antibody, respectively, and Rheumatoid Factor (RF, IgM and IgA isotypes) using in-house enzyme-linked immunosorbent assays. A positive LSGB should have a focus score of at least 1 focus/4 mm2 [8]. A focus is defined as the presence of a cluster of at least 50 lymphocytes per 4 mm2 glandular tissue adjacent to normal appearing mucous acini [8]. For the patients who were suspected for the existence of autoimmune thyroid disease, thyroid function and thyroid autoantibodies were also detected.

2.3. Classification

Each patient was classified according to both the AECG criteria [9, 10] and the newly proposed NIS criteria [7, 11]. We eliminated from the analysis, the patients who did not have results for all the features of both classification systems with the exception of sialography and scintigraphy (Table **1**).

2.4. Definite Diagnosis of SS

The evaluating rheumatologist was asked to define the most probable diagnosis in his opinion for each patient, without referring to specific classification criteria, but based on the ocular and oral symptoms and signs, autoantibodies, the positive result of LSGB, and late follow-up result. All cases were reviewed by three rheumatologists (including one consultant and two attending doctors) to reach consensus.

2.5. Statistical Analysis

Statistical Package for the Social Sciences (version 19.0, SPSS Inc, Chicago, IL, USA) and MedCalc for Windows (version 11.4.2.0, MedCalc Software, Mariakerke, Belgium) were used to perform data analyses. Quantitative variables were described as mean ± standard deviation and qualitative variables as number (%). A chi-square test was performed to determine qualitative variables. Receiver Operating Characteristic Curves (ROC) were plotted to evaluate the diagnostic efficiency of NIS criteria, AECG criteria and LSGB by determining the area under the curve (AUC), and sensitivity, specificity, positive predictive value (PPV), Negative Predictive Value (NPV), mistake diagnostic rate, omission diagnostic rate and diagnostic accuracy were also calculated. The Wilcoxon z-test was used to analyze the statistical significance of the differences among AUC of the 3 ROC curves. A value of $P < 0.05$ was considered significant.

3. RESULTS

3.1. Patient Characteristics

76 patients with suspected SS were recruited, 42 of which were definitive diagnosis of SS and 34 were excluded from SS (non-SS). There were 70 females and 6 males; their ages ranged from 16 to 88 years and the mean (±SD) age was 47.5 (±14.0) years. Of the 42 SS patients, there were 40 females (95.2%) and 2 males (4.8%), and the mean age was 51.5 (±14.3) years. Clinical characteristics of patients are presented in Table **2**.

3.2. The Results of Diagnostic Tests of NIS Criteria in SS Patients

In Table **3**, the results of the various diagnostic tests of NIS criteria in the patients with a final diagnosis of SS and non-SS are shown. The differences of ocular and oral symptoms, ocular and oral signs, the existence of autoimmune thyroid disease and results of LSGB were all statistically significant, while the difference of autoantibodies was not statistically significant.

Table 1. Comparison of the AECG Criteria and NIS Criteria for SS.

AECG Criteria	NIS Criteria	Weight/Score
Item	Item	–
I. Ocular symptoms	I. Ocular symptoms	1
II. Oral symptoms	II. Oral symptoms	1
III. Ocular signs: a. Schirmer's I test b. Fluorescein vital staining	III. Ocular signs: a. Schirmer's I test b. Fluorescein vital staining	1 2 (only count the higher score)
IV. Histopathology: LSGB		
V. Oral sign: UWSF	IV. Oral sign: UWSF	1

(Table 1) contd.....

AECG Criteria	NIS Criteria	Weight/Score
VI. Autoantibodies: presence in the serum of the following autoantibodies: a. Positive anti-SSA or anti-SSB antibodies	V. Autoantibodies a. Positive anti-SSA or anti-SSB or anti-RO52 antibodies b. ANA titre ≥1:160 (Speckeld pattern) or positive anti-centromere B antibodies and negative anti-dsDNA and anti-Sm antibodies	2 1 (only count the higher score)
	VI Addition item: existence of autoimmune thyroid disease	2
Classification rules	Classification rules	
For PSS: Presence of any four of the six items with at least item IV or VI, or presence of any three of the four objective items (items III, IV, V and VI)	The total score is determined by adding the maximum weight (score) in each category. A. Patients with a score ≥5 are classified as having definite SS B. Patients with a score <4 were supposed to be excluded from SS C. Patients with a score of 4, LSGB was suggested. a. LSGB positive: definite SS b. LSGB negative: non-SS	
For Secondary SS: In patients with a potentially associated disease, the presence of item I or item II plus any 2 from among items III, IV and V.	Eliminated the distinction between PSS and SSS	
Exclusion criteria	Exclusion criteria	
1. Past head and neck radiation treatment 2. Hepatitis C infection 3. AIDS 4. Pre-existing lymphoma 5. Sarcoidosis 6. Graft versus host disease 7. Use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug)	Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: 1. History of head and neck radiation treatment 2. Hepatitis C infection 3. AIDS 4. Sarcoidosis 5. Amyloidosis 6. Graft versus host disease 7. IgG4-related disease	

Table 2. Clinical characteristics of SS and non-SS patients.

Item	–	SS (n=42)	Non-SS (n=34)	Total (n=76)
Ocular symptoms	positive	30	10	40
	negative	12	24	36
Oral symptoms	positive	37	13	50
	negative	5	21	26
Ocular signs:				
Schirmer's I test	positive	20	11	31
	negative	22	23	45
Fluorescein vital staining	positive	14	2	16
	negative	28	32	60
Histopathology: LSGB	positive	29	5	34
	negative	13	29	42
Oral sign: UWSF	positive	17	5	22
	negative	25	29	54
Autoantibodies				
Positive anti-SSA or anti-SSB or anti-RO52 antibodies	positive	35	28	63
	negative	7	6	13
ANA titre ≥1:160 (Speckeld pattern) and negative anti-dsDNA and anti-Sm antibodies	positive	20	10	30
	negative	22	24	46
positive anti-centromere B antibodies and negative anti-dsDNA and anti-Sm antibodies	positive	4	0	4
	negative	38	34	72
Autoimmune thyroid disease	positive	9	1	10
	negative	33	33	66
AECG criteria	positive	31	6	37
	negative	11	28	39

(Table 2) contd.....

Item	–	SS (n=42)	Non-SS (n=34)	Total (n=76)
NIS criteria	positive	41	2	43
	negative	1	32	33

Table 3. The results of diagnostic tests of NIS criteria in SS patients.

Item in NIS Criteria	Number of Positive Results in SS Patients (n=42)	Number of Positive Results in non-SS Patients (n=34)	P-value
I. Ocular symptoms	30 (71.43%)	10 (29.41%)	0.0006
II. Oral symptoms	37 (88.10%)	13 (38.24%)	<0.0001
III.Ocular signs (a and/or b)	29 (69.05%)	11 (32.35%)	0.0031
IV. Oral signs	17 (40.48%)	5 (14.71%)	0.0272
V. Autoantibodies (a and/or b)	39 (83.33%)	28 (82.35%)	0.2927
VI. Existence of autoimmune thyroid disease	9 (21.43%)	0 (0%)	0.0118
LSGB	29 (69.05%)	5 (14.71%)	<0.0001

Table 4. Comparison of the diagnostic efficiency of ROC curves.

Diagnostic Method	AUC (95% CI)	P-value	Sensitivity	Specificity	PPV	NPV	Mistake Diagnostic Rate, α	Omission Diagnostic Rate, β	Diagnostic Accuracy
NIS criteria	0.959 (0.905-1.000)*	0.000	97.6%	94.1%	95.3%	97.0%	5.9%	2.4%	96.1%
AECG criteria	0.781 (0.673-0.889)^{NS}	0.000	73.8%	82.4%	83.8%	71.8%	17.6%	26.2%	77.6%
LSGB	0.772 (0.663-0.881)	0.000	69.0%	85.3%	85.3%	69.0%	14.7%	31.0%	76.3%

Note: * $P < 0.05$, compared to AECG criteria and LSGB; ^{NS} $P > 0.05$, compared to LSGB.

Table 5. NIS criteria in diagnosis of SS.

Group	Score ≥5	Score =4		Score <4
		LSGB positive	LSGB negative	
SS group	36	5	0	1
Non-SS group	1	1	10	22

3.3. Diagnostic Efficiency

ROC curves were plotted to evaluate the diagnostic efficiency of NIS criteria, AECG criteria and LSGB, which are presented in Table **4**. All of the three diagnostic methods were statistically significant in the diagnosis of SS ($P < 0.05$). The area under the ROC curves (AUC; 95% CI) for NIS criteria was 0.959 (0.905-1.000), which performed best in the diagnosis of SS ($P < 0.05$). Sensitivity and specificity in the diagnosis of SS were, respectively, 97.6% and 94.1% for the NIS criteria, while the NPV and PPV to detect SS were 97.0% and 95.3% respectively, and the diagnostic accuracy was 96.1%.

The details of NIS criteria in the diagnosis of SS are shown in Table **5**. There were 16 patients with a score of 4, of which 6 had a positive LSGB result while the other 10 had a negative result. Five of the 6 LSGB-positive patients turned out to be SS, while all of the 10 LSGB-negative patients turned out to be non-SS.

4. DISCUSSION

This retrospective analysis is the first study to develop a noninvasive classification criteria for SS. SS primarily affects women, with a female-male ratio of 20:1 in this study, slightly higher than the previous reported 9:1 [12], and may occur in patients of all ages but typically has its onset in the fourth to sixth decades of life [12]. In the present study, there were statistical differences of ocular and oral symptoms and signs between the SS group and non-SS group, which suggested us to take these items into account of the new set criteria. In fact, these items were already included in the AECG criteria. The ACR Ocular Staining Score (OSS) was not considered in the new criteria because of low specificity.

Unexpectedly, the differences in autoantibodies were not statistically significant. But the serological items were still retained in the new criteria considering a variety of auto-antibodies, because these autoantibodies are sensitive in the diagnosis of SS although with low specificity [1]. Positive RF plus ANA ≥1:320 was not considered as one of the serological items, because ANA pattern was not distinguished in this item and also because it was observed in the study that for most patients with positive RF plus ANA ≥1:320, anti-SSA or anti-SSB or anti-RO52 antibodies were mostly positive.

SS along with thyroid disease diagnosed with laboratory data and clinical presentation were reported and the most common thyroid disease found was autoimmune thyroiditis and

the most common hormonal pattern was subclinical hypothyroidism [13, 14]. In this study, the existence of autoimmune thyroid disease between the two groups was statistical significance. Considering the low sensitivity, it was included as an additional item.

Positive rate of LSGB was significantly higher in the SS group than the non-SS group in the present study. The specificity of LSGB in the diagnosis of SS was high and the mistake diagnostic rate was only 14.7%, but the sensitivity was not that high and the omission diagnostic rate was up to 31.0%. These results were somewhat similar to a previous study, in which there was an even higher specificity of 100% and the sensitivity was 75.0% [15]. Considering the specificity and sensitivity, although LSGB was very important in the diagnosis of SS, it should not be used as a single gold standard. The diagnostic accuracy of the AECG criteria was only 77.6%, and the mistake diagnostic rate and omission diagnostic rate were 17.6% and 26.2%, respectively. It was not superior to using LSGB as a single standard.

The NIS criteria performed best in the diagnosis of SS, with high sensitivity and specificity. The sensitivity and specificity of the NIS criteria were both better than that of the AECG criteria, indicating that the NIS criteria were superior to the AECG criteria in the classification diagnosis of SS. Moreover, the PPV and NPV of the NIS criteria were both up to above 95.0% in our series, indicating the excellent ability of the NIS criteria in classification diagnosis of SS in addition to its high specificity and sensitivity.

In the present study, there were a total of 76 patients with suspected SS. Retrospectively analyzing the diagnosis applying the NIS criteria, only 16 (21.1%) patients with a score of 4 needed further LSGB examination and the results showed that LSGB was able to diagnose SS for these patients. So, the application of the NIS criteria could avoid about 80% suspected SS patients from the invasive LSGB examination.

The one with a score of 5 who turned out to be a non-SS was a female autoimmune liver disease patient with positive anti-SSA and anti-SSB. Further examinations showed positive Schirmer's I test, Fluorescein vital staining and UWSF. The LSGB examination was also positive. But this patient was clinically asymptomatic without ocular or oral symptoms. This case indicated that SS should be diagnosed circumspectly for clinical asymptomatic patients. However, the present study still has a few limitations. First and foremost, it was a single-center study, and bias may inevitably exist here. A multi-centric clinical study is needed to further confirm the conclusions of the present study. Secondly, the ACR OSS scoring was not available in our hospital, the diagnostic efficiency of the ACR criteria could not be evaluated. Further comparison of the ACR criteria and NIS criteria must be carried out. Thirdly, there were a comparatively small number of cases combined with autoimmune thyroid disease included in this study, leading to the difficulty to make sure whether the addition item "existence of autoimmune thyroid disease" is necessary for the new set criteria. Further research focusing on the relationship between SS and the existence of autoimmune thyroid disease is planned to be conducted.

CONCLUSION

In conclusion, the new set of noninvasive NIS criteria is an alternative to the AECG criteria in classification diagnosis of SS, which are with high diagnostic efficiency. We recommend using the score <4 and ≥ 5 to rule out or to diagnose SS, respectively. For the patients with a score of 4, LSGB is necessary to diagnose SS.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board of the University of Hong Kong-Shenzhen Hospital.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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Declared none.

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