Performance of the 2016 ACR/EULAR SS classification criteria in patients with secondary Sjögren's syndrome

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ABSTRACT

Objective. *To evaluate the performance of the 2016 ACR/EULAR classification Sjögren's syndrome (SS) criteria for classifying patients with secondary SS.*

Methods. *We randomly selected 300 patients with systemic lupus erythematosus, rheumatoid arthritis and scleroderma, as well as 50 with primary SS. SS diagnosis was established by two independent rheumatologists and was based on the combination of symptoms, signs, diagnostic tests and medical chart review. We evaluated the fulfillment of the 2002 AECG, 2012 ACR and 2016 ACR/EULAR criteria, and their performance using as the gold standard the clinical diagnosis.*

Results. *We identified 154 patients with a clinical (definitive/probable) SS diagnosis, 95 patients (61.7%) fulfilled the AECG, 96 patients (62.3%) the ACR and 90 (58.4%) the 2016 ACR/EULAR criteria. Among the subset with definitive SS clinical diagnosis (n=99), 83 patients (83.8%) fulfilled the AECG, 77 (77.7%) the ACR and 79 (79.7%) the 2016 ACR/EULAR criteria. The concordance rate between the clinical diagnosis (definitive/probable) and the AECG, ACR and 2016 ACR/EULAR criteria was κ=0.58, κ=0.55 and κ=0.60, respectively. The 2016 ACR/EULAR criteria showed the best AUCs results (0.87 definitive/probable diagnosis, 0.90 definitive diagnosis), followed by the AECG (0.82 definitive/probable diagnosis, 0.85 definitive diagnosis) and ACR (0.80 definitive/probable diagnosis, 0.79 definitive diagnosis) criteria. As a sensitivity analysis, the results were similar when excluding patients with primary SS.*

Conclusion. *Our study provides further evidence that the 2016 ACR/EULAR criteria are applicable in the setting of secondary SS.*

Introduction

Over the time, diverse sets of classification criteria have been developed in Sjögren's syndrome (SS) in order to identify a homogenous group of patients who can be included in clinical and interventional studies (1-2). The 2016 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria represents an international effort for a better classification of SS patients (3). These criteria combine items from both the 2002 American European Consensus Group (AECG) criteria (4) and the 2012 American College of Rheumatology (ACR) criteria (5), thus they closely resemble. However, the 2016 ACR/EULAR classification criteria are applicable in the setting of ocular or oral sicca symptoms or among patients with at least one systemic feature listed in the ESSDAI (EULAR SS Disease Activity Index). At their final validation cohort, they showed high specificity and sensitivity (95% and 96%, respectively) (3).

Although the 2016 ACR/EULAR Classification Criteria publication paper suggested their applicability in secondary SS (3), up to date only one validation cohort has included both primary and secondary SS (6). Herein, we evaluated the performance of the 2016 ACR/EULAR classification criteria for classifying patients with secondary SS from a well-characterised cohort of patients with connective tissue disease (CTD).

Methods

Briefly, using the methodology of our parent studies (7-8), we randomly included between February 2006 and July 2007, 100 patients with systemic lupus erythematosus (SLE) (9), 100 with scleroderma (SSc) (10) and 100 with rheumatoid arthritis (RA) (11), as well as 50 patients with primary SS.

We excluded patients under drugs that impaired salivary flow within 48 hours before the study, had history of hepatitis C or HIV infection, sarcoidosis, IgG4-related disease, lymphoma, graft *versus* host disease, or history of neck/head radiotherapy. Participants were asked to refrain from eating, drinking, chewing, smoking or having an oral hygiene procedure for at least 1 hour before the evaluation.

The study was approved by our Institutional Biomedical Research Board and all patients gave signed informed consent.

Sjögren's syndrome assessment

The patients were subjected to a 3-phase evaluation: screening, confirmatory, and lip biopsy. A muti-disciplinary team (Rheumatologist, Ophthalmologist and Dentist) participated in this assessment. We pursued the completeness of the evaluation according to the daily clinical approach and considering risk and benefits of each test.

a. Screening phase

Patients had a face-to-face interview with a single rheumatologist who applied a validated 6-item screening questionnaire for oral and ocular sicca symptoms (4) and performed the Schirmer-I test and the wafer test. We also obtained a peripheral blood sample for autoantibodies testing (anti-Ro/SSA, anti-La/SSA, rheumatoid factor and antinuclear antibodies). Patients with at least one affirmative response to the screening questionnaire, Schirmer-I test ≤5 mm in 5 minutes (4), or wafer test >4 minutes (8) were considered to have a positive screening.

b. Confirmatory phase

Patients with positive screening underwent fluorescein staining test and non-stimulated whole salivary flow rate (NSWSF). For the fulfillment of the 2002 AECG and the 2016 ACR/EULAR criteria, the fluorescein staining test was considered positive with a score ≥4 according to the van Bijsterveld scale (vBS) in at least one eye (3-4). For the fulfillment of the 2002 ACR criteria (5), as we lacked of ocular staining score (OSS), we substituted it by a vBS ≥3.

Table I. Clinical and serological features among patients with Sjögren's syndrome according with the clinical criteria.

Variable	Sjögren's syndrome (both primary and secondary) n=154
Age in years, mean±SD	51.2±14.2
Females, n (%)	151 (98.1)
Oral symptoms, n (%)	105 (68.2)
Ocular symptoms, n (%)	109 (70.8)
Parotid enlargement, n (%)	35 (22.7)
Abnormal Schirmer test, n (%)	112 (72.7)
Impaired NSWS, n (%)	139 (90.3)
Keratoconjuctivitis sicca, n (%)	97/148 (65.5)
van Bijsterveld scale, median (range)	4 (0-9)
Positive minor salivary gland biopsy, n (%)	62/84 (73.8)
Anti-Ro/La antibodies, n (%)	89 (57.7)
Rheumatoid factor, n (%)	70 (45.5)
ANA ≥1:320, n (%)	121 (61.7)

For the NSWSF collection, saliva was collected for 15 minutes using the spitting method and considered abnormal if ≤1.5 ml/15 minutes (4). The assessment protocol did not include scintigraphy or sialography, but some patients had these studies done as part of the regular clinical evaluation.

c. Minor salivary gland biopsy

Lip biopsy was proposed for all patients who had >2 of the following results: at least one affirmative answer to the oral component of the screening questionnaire; wafer test >4 min; presence of keratitis by fluorescein staining test; NSWSF ≤1.5 ml/15 min; and positive anti-Ro/La antibodies. Focal lymphocytic sialoadenitis was diagnosed based on a focal score of one or more lymphocytic foci (>50 lymphocytes per 4 mm^2 (4).

d. Diagnosis of Sjögren's syndrome (gold standard)

It was established by two independent rheumatologists and was based on the combination of symptoms, signs, and diagnostic tests. Each patient was diagnosed as Sjögren's syndrome (definitive or probable) or non-Sjögren's syndrome. The agreement among the two rheumatologists was 92.2% for definitive SS, and 79.1% for probable SS. In case of a discrepancy, a consensus was reached among them.

Statistical analysis

Our gold standard was the clinical diagnosis of SS. We applied the 2002 AECG, 2012 ACR and the 2016 ACR/EULAR criteria to each study participant including those with incomplete features for any set. We estimated the sensitivity, specificity, positive predictive value, negative predictive value, accuracy as area under the curve (AUC) for each criteria set. We used kappa statistic to evaluate the degree of agreement between the clinical diagnosis and each criteria set. All analyses were performed using SPSS for Windows 20.0

Results

The detailed description of the cohort though the three phases evaluation has been previously reported (6, 7). Overall, we identified 154 patients with SS (definitive n=99, probable n=55), of whom 107 had an associated CTD. Table I summarises the clinical and serological features of the patients with SS. Among the 154 patients with a clinical (definitive/probable) SS diagnosis, 95 patients (61.7%) fulfilled the 2002 AECG criteria, 96 patients (62.3%) the 2012 ACR criteria and 90 (58.4%) the 2016 ACR/EULAR criteria. Among the subset of patients with definitive SS clinical diagnosis (n=99), 83 patients (83.8%) fulfilled the 2002 AECG criteria, 77 (77.7%) the 2012 ACR criteria and 79 (79.7%) the 2016 ACR/EULAR criteria.

The concordance rate between the clinical diagnosis (definitive/probable) and the 2002 AECG, 2012 ACR and 2016 ACR/EULAR criteria was κ=0.58, κ=0.55 and κ=0.60, respectively. On the other hand, the agreement between the clinical diagnosis (definitive) and the 2002 AECG, 2012 ACR and 2016 ACR/EULAR criteria was κ=0.73, κ=0.60 and κ=0.73, respectively.

Table II shows the performance of each set of criteria, according to the population setting. The 2016 ACR/EULAR criteria showed the best AUCs results (0.87 definitive/probable diagnosis, 0.90 definitive diagnosis), followed by the 2002 AECG (0.82 definitive/probable diagnosis, 0.85 definitive diagnosis) and 2012 ACR (0.80 definitive/probable diagnosis, 0.79 definitive diagno-

Table II. Performance of AECG, ACR and EULAR/ACR classification SS criteria in patients with connective tissue diseases.

	SN 95% CI	SP 95% CI	PPV 95% CI	NPV 95% CI	LR+ 95% CI	LR- 95% CI	Accuracy	AUC 95% CI
Definitive/Probable diagnosis								
				Full population (n=350)				
AECG	61.6 53.5-69.4	94.3 90.1-97.1	89.6 82.1-94.7	75.8 69.9-81.0	10.9 6.1-19.7	0.41 0.3-0.5	80	0.82 (0.78-0.87)
ACR	62.3 54.1-70.0	91.3 86.4-94.8	84.9 77.0-90.9	75.5 69.5-80.8	7.19 4.4-11.5	0.41 0.34-0.51	78.5	0.80 (0.75-0.85)
ACR/EULAR	58.4 50.23-66.3	100 98.1-100	100 95.9-100	75.3 71.7-78.6	∞	0.42 0.34-0.50	81.7	0.87 (0.84-0.91)
				Patients with RA, SLE and scleroderma (n=300)				
AECG	50.5 40.6-60.2	94.3 90.0-97.1	83 71.7-82.6	77.4 71.5-82.6	8.8 4.8-16.2	0.53 0.43-0.64	78	0.80 (0.74-0.84)
ACR	59.8 49.8-69.1	91.1 86.2-94.7	79 68.5-87.2	80.3 74.4-85.4	6.7 4.2-10.9	0.44 0.35-0.56	80	0.79 (0.73-0.85)
ACR/EULAR	45.7 36.1-55.7	100 98.1-100	100 92.7-100	76.8 73.6-79.8	∞	0.54 0.46-0.61	80.6	0.88 (0.84-0.92)
Definitive diagnosis								
				Full population (n=350)				
AECG	61.6 53.5-69.4	94.3 90.1-97.1	89.6 82.1-94.7	75.8 69.9-81.0	10.9 6.1-19.7	0.41 0.3-0.5	80	0.85(0.80-0.90)
ACR	62.3 54.1-70.0	91.3 86.4-94.8	84.9 77.0-90.9	75.5 69.5-80.8	7.19 4.4-11.5	0.41 0.34-0.51	78.5	0.79 (0.73-0.85)
ACR/EULAR	79.8 70.8-87.2	95.6 92.2-97.7	87.7 79.9-92.8	92.3 89.2-94.6	18.2 10.1-32.7	0.21 0.14-0.31	91.1	0.90 (0.85-0.94)
				Patients with RA, SLE and scleroderma (n=300)				
AECG	50.5 40.6-60.2	94.3 90.0-97.1	83 71.7-82.6	77.4 71.5-82.6	8.8 4.8-16.2	0.53 0.43-0.64	78	0.80 (0.72-0.87)
ACR	59.8 49.8-69.1	91.1 86.2-94.7	79 68.5-87.2	80.3 74.4-85.4	6.7 4.2-10.9	0.44 0.35-0.56	80	0.75 (0.68-0.82)
ACR/EULAR	75.4 62.2-85.8	90.9 86.9-94.2	66.15 56-74.9	94.0 90.9-96.1	8.33 5.45-12.7	0.27 0.17-0.83	88	0.86 (0.79-0.93)

SN: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: likelihood ratio positive; LR-: likelihood ratio negative; AUC: area under the curve.

sis) criteria. As a sensitivity analysis, the results were similar when excluding patients with primary SS (Table II).

Discussion

In this cohort of patients with CTD, we previously described that the 2002 AECG and 2012 ACR criteria for SS performed similarly; however, the feasibility of the 2002 AECG criteria was better (7). Herein, now we observed that the 2016 ACR/EULAR criteria had the highest SP among the three sets of criteria, indeed for both primary and secondary SS population. This finding goes in agreement with the original 2016 ACR/EULAR validation cohort that reported a SP of 95% (3). Moreover, Billings *et al*. in the NIH cohort described SP=87.4% for both primary/secondary SS, 89.5% for primary SS and 99.6% for secondary SS (6). Nevertheless, it is important to highlight that the authors used the AECG criteria as their gold standard. In contrast, a lower SP was reported in primary SS in Asian (76.7–81.8%) (12-13) and Dutch population (83%) (14).

On the other hand, we observed a SN=79.8% for the 2016 ACR/EULAR criteria for both primary and secondary SS, and 75.4% for secondary SS; figures that are lower than previous studies in primary (87.4–96%) (3, 12-15) and secondary SS (83%) population (6). We observed moderate agreement (κ=0.66) between the 2016 ACR/EULAR criteria and the clinical diagnosis (definitive/probable), that raised to good agreement (κ=0.73) when we used a definitive clinical diagnosis. In their study, Van Nimwegen *et al*. (14) also used the expert opinion as the gold standard, among PSS population, and found a good agreement (κ=0.77). These discrepancies reflect that in some patients, the diagnosis of PSS is challenging even for the experts. Finally the 2016 ACR/EULAR criteria had the best results of AUC to classify patients with both primary and secondary SS.

We acknowledge some potential limitations and strengths of our study. First, most of the studies regarding classification criteria have used the 2002 AECG criteria as their gold standard. Herein, we used instead the clinical criteria. We considered that as the 2002 AECG criteria has been widely used over a decade, a potential circularity between clinical diagnosis and classification criteria is possible, biasing the results in its favor. Moreover, the comparison of clinical diagnosis *versus* the 2002 AECG and the 2012 ACR criteria are also part of their original publication. Second, as we did not have available SICCA OSS and we lacked of a study that compared its performance *versus* the vBS; we arbitrary substituted it with vBS≥3 in order to improve its specificity. Third, our results come from the experience of one single centre, hampering their external validity. Finally, although our sample of secondary SS was not so large, it came from a randomly selected population of patients with CTD and in whom we pursued the completeness of the assessment.

In conclusion, our study provides further evidence that the 2016 ACR/EULAR criteria are also applicable in the setting of secondary SS.

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