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Comparative Analysis of the 2016 ACR-EULAR and the 2002 AECG Classification Criteria for Sjögren's Syndrome: Findings from the NIH cohort

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Abstract

Introduction—The introduction of new classification criteria for Sjögren's Syndrome, known as the 2016 American College of Rheumatology/European League against Rheumatism Classification Criteria (ACR-EULAR), created a need for the evaluation of its performance in an external cohort. The purpose of this study was to compare the performance of the 2016 ACR-EULAR classification set with the widely used American-European Consensus Group Classification criteria (AECG) in the cohort at the National Institutes of Health, USA and to compare the performance of the sets in classifying both primary and secondary Sjögren's Syndrome (pSS and sSS).

Methods—The study cohort at the NIH (N=1303) was enrolled for clinical suspicion of SS. Participants were classified as SS, pSS, and sSS according to both classification sets. Performance of 2016 ACR-EULAR and AECG sets were compared holding each as gold standard to the other. Statistical analysis of test diagnostics and agreement between the two sets were undertaken.

Results—By the AECG set, 701 were classified as having SS (627 pSS, 74 sSS) and 714 were classified with SS (647 pSS, 67 sSS) by the 2016 ACR-EULAR set. Sensitivity and specificity of the two sets were comparable in classifying SS, pSS, and sSS. There was high agreement between the two sets for classifying SS ($K = 0.79$), pSS ($K = 0.81$), and sSS ($K = 0.87$). The specificity of the 2016 ACR-EULAR set was significantly higher for classifying sSS than pSS, while the sensitivity was similar for the two disease groups. However, this pattern was also exhibited by the AECG set.

Conclusion—There was high agreement between the two classification sets with comparable performance diagnostics. There was no evidence of superior performance value by the new 2016 ACR-EULAR set over the AECG set and the two sets were found to be equivalent. Findings from our cohort indicate that 2016 ACR-EULAR classification could be extended to classification of sSS.

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Conflicts of Interest

None to declare

Introduction

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disorder that affects exocrine glands leading to dryness of mucosal surfaces, with oral and ocular dryness predominantly manifesting. In addition, the syndrome may present with numerous extraglandular manifestations. Such diverse manifestations make SS a complex pathology to characterize and gives rise to variability in disease classification, making comparability of research findings a challenge. Therefore, the need for a uniform, standardized set of criteria to classify individuals to have SS is imperative. There have been 13 classification criteria systems for SS from 1965 to 2016 (Bloch et al., 1965, Shearn, 1971, Daniels et al., 1975, Ohfuji, 1977, Manthorpe et al., 1981, Homma et al., 1986, Skopouli et al., 1986, Fox et al., 1986, Vitali et al., 1993, Vitali et al., 2002, Shiboski et al., 2012, Shiboski et al., 2017, Fujibayashi, 2000). The 2002 American-European Consensus Group Classification criteria (AECG) has been the most widely used classification set with over 1500 citations (Rasmussen et al., 2014). This set employed 6 domains of assessment, of which, 2 were subjective (ocular and oral dryness) and 4 were objective (ocular signs, oral signs, histopathology, and autoantibodies)(Vitali et al., 2002). However, in 2012 a new classification system known as the American College of Rheumatology (ACR) Classification Criteria for SS was proposed to improve specificity that would consequently limit the exposure of individuals (falsely classified as SS) to biologics of uncertain safety in clinical trials (Shiboski et al., 2012). This system eliminated symptoms of oral and ocular dryness and the objective sign of hyposalivation, and was based exclusively on objective signs of positive focus score, serology and ocular staining score. When the performance of this system was evaluated, it was found to be comparable with the AECG classification system in terms of sensitivity, specificity, and other test diagnostics and did not provide increased value over the existing AECG set (Rasmussen et al., 2014).

The 2012 ACR classification was replaced by another system proposed by the International Sjögren's Syndrome Criteria Working Group, known as the 2016 American College of Rheumatology/European League against Rheumatism Classification Criteria (ACR-EULAR) (Shiboski et al., 2017). This set incorporated criteria from both the AECG and ACR sets and gave weighted points for the four objective signs of focus score 1 foci/4mm² (3 points), anti-SSA/Ro-positive (3 points), ocular staining score 5/Van Bijsterveld score 4 (1 point), and Schimer's test 5mm/5min (1 point) and unstimulated whole saliva flow rate 0.1 ml/min (1 point). A total score of 4 points classified someone as having primary SS (pSS) (Shiboski et al., 2017).

A recent study conducted with a Japanese cohort reported that the sensitivity of 2016 ACR-EULAR set was higher but the specificity was lower than that of the AECG, Japanese (JPN), and ACR sets. In addition, there was low agreement between the 2016 ACR-EULAR and the 3 other sets (Tsuboi et al., 2017). These findings contradicted previously reported performance estimates of the 2016 ACR-EULAR set (Shiboski et al., 2017). It has been suggested that the 2016 ACR-EULAR set developed for classification of pSS is also applicable to classify secondary SS (sSS). However, evidence confirming such an assumption is lacking and further research is needed, which has been acknowledged by the developers of the classification set (Shiboski et al., 2017). The study by Tsuboi et al (2017)

with the Japanese cohort also restricted their analysis to pSS. Consequently, the performance of the 2016 ACR-EULAR in classifying sSS remained unknown. Therefore, given the contradictory performance estimates and existing lack of evidence of application of the 2016 ACR-EULAR set to sSS, the purpose of this study was not only to compare the performance of the 2016 ACR-EULAR classification criteria with the widely used AECG classification criteria in the cohort at the National Institutes of Health, USA, but also to compare the performance of the 2016 ACR-EULAR set with the AECG set in classifying both pSS and sSS.

Methods

Study Population

The NIDCR Sjögren's Syndrome and Salivary Gland Dysfunction Unit (SSGDU) has been evaluating and enrolling participants with dry mouth symptoms and/or clinical suspicion of SS since 1984, making the NIDCR/NIH SS cohort one of the largest in the US. To investigate the proposed objectives, data from the source cohort comprising participants enrolled before August 27, 2015 were analyzed. Details of the source cohort have been previously published (Billings et al., 2016).

Classification

In this study, participants were classified according to both classification sets, the AECG and 2016 ACR-EULAR sets. They were classified as SS (pSS & sSS) and non-SS by applying the AECG Classification Criteria (inclusion and exclusion criteria). They were also classified by applying the 2016 ACR-EULAR Classification Criteria (screening, inclusion and exclusion criteria) for pSS and those with a potentially associated disease (such as a well-defined connective tissue disease), but otherwise met the 2016 ACR-EULAR criteria, were classified as sSS by this set. The sum of the number of pSS and sSS cases yielded the number of SS cases. Details of the clinical procedures have been previously published (Billings et al., 2016). All study participants provided Informed Consent prior to the initiation of any study procedures and clinical protocols were approved by an NIH Institutional Review Board, conforming to the standards indicated by the Declaration of Helsinki.

Statistical Analysis

Performance of the 2016 ACR-EULAR set was evaluated holding the AECG as gold standard. Conversely, performance of the AECG set was evaluated against the 2016 ACR-EULAR as gold standard in test diagnostics. Sensitivities and specificities of the classification sets were compared and tested by McNemar's test, Kappa statistic was computed, and receiver operating curves (ROC) were generated with area under the curve (AUC). Statistical significance was assessed on a set two-tailed p-value of 0.05. All statistical analyses were performed using STATA 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

The NIH cohort was comprised of participants with clinical suspicion of SS. When the AECG classification criteria were applied to this cohort (N=1303), 701 were classified as having SS and 602 did not meet criteria for SS. Of those with SS, 627 were classified as pSS and 74 as sSS (Table 1). When participants were classified according to the 2016 ACR-EULAR classification criteria (N=1303), there were 714 SS cases and 589 did not meet criteria. Of those with SS, 647 were pSS and 67 were sSS. Of the 698 subjects who were classified as pSS by either set, 576 (83%) met both classification sets. Similarly, of the 79 subjects who were classified as sSS by either set, 62 (78%) met both classification sets.

The agreement between the two classification sets that is higher than what is expected by chance alone is estimated by the Kappa statistic. The agreement between the two sets in classifying SS was substantial ($K = 0.79$) which further improved for classifying pSS ($K = 0.81$) and sSS ($K = 0.87$).

Performance of the two sets was evaluated in comparison with the other; with both held as gold standard in turns. The sensitivities, specificities, positive and negative predictive values of the classification sets are summarized in Table 2. The test diagnostics for classification of SS by the two classification sets were found to be comparable. The sensitivity of the 2016 ACR-EULAR was 91.0% (95%CI: 88.6%–93.0%) and that of the AECG was 89.4% (95%CI: 86.9%–91.5%). There was no statistically significant difference in sensitivities between the two sets ($p\text{-value} = 0.31$). The 2016 ACR-EULAR had a slightly lower specificity of 87.4% (95%CI: 84.5%–89.9%) but it was comparable with that of AECG (89.3%, 95%CI: 86.5%–91.7%, $p\text{-value} = 0.31$).

The 2016 ACR-EULAR classification set had a similar performance for the classification of pSS. The sensitivity of the set was 91.9% (95%CI: 89.4%–93.9%), which was comparable with the sensitivity of AECG (89.0%, 95%CI: 86.4%–91.3%, $p\text{-value} = 0.09$). Specificities of the two sets were also comparable with the 2016 ACR-EULAR having a specificity of 89.5% (95%CI: 86.9%–91.7%) and the AECG with a specificity of 92.20% (95%CI: 89.9%–94.2%, $p\text{-value} = 0.09$).

The performance of the 2016 ACR-EULAR for classification of sSS was also evaluated. The classification set had a slightly lower sensitivity in detecting sSS than pSS with estimates of 83.80% (95%CI: 73.4%–91.3%) and 91.90% (95%CI: 89.4%–93.9%) respectively, though not statistically significantly different. However, the set had a significantly higher specificity for sSS (99.60%, 95%CI: 99.1%–99.9%) than pSS (89.50%, 95%CI: 86.9%–91.7%). Test diagnostics of the 2016 ACR-EULAR and AECG for sSS when compared, were found to be comparable ($p\text{-value} = 0.14$). The sensitivity of the AECG for sSS was 92.50 (95%CI: 83.4%–97.5%) and the specificity was 99.0% (95%CI: 98.3%–99.5%).

The area under the curve (AUC) for the new classification was estimated. The AUC for 2016 ACR-EULAR classification for SS was 0.89 (95%CI: 0.87–0.91), for pSS was 0.91 (95%CI: 0.89–0.92), and for sSS was 0.92 (0.87–0.96) and the three estimates were similar (Figure 1).

We then increased the cut off of the 2016 ACR-EULAR classification criteria from a total score of 4 to 5 and evaluated its performance in classification of SS, particularly pSS. It was found that the sensitivity of the classification set for SS significantly dropped from 91% (95%CI: 88.6%–93.0%) to 67.9% (95%CI: 64.3%–71.3%) ($p<0.001$) but the specificity significantly increased from 87.4% (95%CI: 84.5%–89.9%) to 96.5% (95%CI: 94.7%–97.8%) ($p<0.001$). Consequently, the classification's AUC for SS significantly decreased from 0.89 (95% CI: 0.87–0.91) to 0.82 (95%CI: 0.80–0.84). For pSS, when the cut off was increased to 5, the sensitivity significantly dropped from 91.9% (95%CI: 89.4%–93.9%) to 68.7% (95%CI: 64.9%–72.4%) ($p<0.001$) and the specificity significantly increased from 89.5% (95%CI: 86.9%–91.7%) to 97.2% (95%CI: 95.6%–98.3%) ($p<0.001$). Here again, the AUC significantly decreased from 0.91 (95%CI:0.89–0.92) to 0.83 (95%CI: 0.81–0.85).

Discussion

Classification criteria are used to define a disease class for clinical trials and epidemiologic studies, and thereby to facilitate standardization and comparability of findings across studies. The closer the percentage of sensitivity (true positive rate) and specificity (true negative rate) of the criteria are to 100%, the higher the diagnostic value of the criteria. However, due to the lack of uniformity in signs and symptoms in a disorder marked with heterogeneity of manifestations, development of classification criteria is challenging. This is particularly the case with Sjögren's syndrome, a complex autoimmune, systemic disorder.

The AECG introduced in 2002 originated from a revised version of the European criteria by the American-European Consensus Group (Vitali et al., 2002). It was found that the sensitivity of the AECG set was 97.4% and specificity was 89.4% for pSS when any four of the six domains were applied. Further, when obligatory criteria were applied, with exclusion of cases in which both serology and histopathology were negative, the sensitivity dropped to 89.5% and specificity increased to 95.2%. As a higher specificity was more desirable for the purpose of classification, the obligatory criteria were introduced (Vitali et al., 2002).

In 2012 a new classification set (ACR) was proposed. However, when the performance of this new set was evaluated in external cohorts, it was found to be comparable with the existing AECG set and no increased value was exhibited by the new set (Rasmussen et al., 2014). The study conducted on a cohort of 646 individuals in Oklahoma and Minnesota, found the sensitivity of the ACR set in classifying SS was 87% (95%CI: 83%–91%) and the specificity was 93% (95%CI: 90%–96%), while the sensitivity of the AECG set was 91% (95%CI: 87%–94%) and specificity was 91% (95%CI: 87%–93%). The study found no statistically significant difference in these diagnostic values ($p=0.19$) and there was strong agreement between the two sets ($K=0.81$) (Rasmussen et al., 2014).

The 2012 ACR set was replaced by the revised 2016 ACR-EULAR set. This revised set was recently evaluated on a cohort of 499 (383 sub-cohort) Japanese patients for classification of pSS (Tsuboi et al., 2017). The study found that the sensitivity (94.1%, 95%CI: 90.8%–96.4) of the 2016 ACR-EULAR set was significantly higher than that of the AECG (85.7%, 95%CI: 82.1%–88.7%), but the specificity (76.7, 95%CI: 73.0%–79.3%) was significantly lower than that of the AECG (86.1%, 95%CI: 82.0%–89.4%), ($p<0.001$) (Tsuboi et al.,

2017). The low agreement between the two sets was contrary to previously published estimates (Shiboski et al., 2017). These controversial findings were attributed to the difference in prevalence estimates in Japan as opposed to geographic settings where the classification set was developed and to insufficient investigation of sicca symptoms in the cohort (Vitali & Del Papa, 2017).

To evaluate the performance of the 2016 ACR-EULAR classification set in comparison to AECG, we undertook a comparative analysis in an external cohort at the NIH, USA with detailed evaluation of sicca symptoms and objective signs mandated by both sets of classification. In our study cohort (N=1303), the performance of the two sets was comparable in classifying SS, pSS and sSS with very high agreement. Although we could see the pattern indicated by the Japanese study of higher sensitivity and lower specificity of the 2016 ACR-EULAR set compared to that of the AECG, it was not of statistical significance. The reason for a pattern of increased sensitivity (though not significant in our cohort) could be potentially explained by the influence of weights attributed by the 2016 ACR-EULAR set, and because the 2016 ACR-EULAR set only requires two objective signs, with either histopathology or serology being positive, while the AECG requires four positive criteria. For example, an individual with only a focus score ≥ 1 foci/4mm² and whole unstimulated salivary flow 1.5 ml/15min will be assigned a total score of 4, which classifies the person as SS with the 2016 ACR-EULAR set. Yet this is insufficient to classify as SS by AECG, which would require an additional two signs or symptoms.

This study undertook evaluation of the 2016 ACR-EULAR set in classifying not only pSS but also sSS, which has not been evaluated thus far. The findings indicate that the sensitivity of 2016 ACR-EULAR for pSS and sSS were comparable. However, the specificity of 2016 ACR-EULAR for sSS was statistically significantly higher than the set's specificity for pSS. Nevertheless, such a pattern was also exhibited by the AECG set. The sensitivity and specificity for sSS between the two sets were comparable, indicating that the 2016 ACR-EULAR set could be applied to classification of sSS.

Finally, as the study with the Japanese cohort found that the 2016 ACR-EULAR set had a low specificity compared to other classifications, we explored the impact of increasing the classifying cutoff of the 2016 ACR-EULAR from 4 to 5. We found that when the cut off increased to ≥ 5 , the specificity of the 2016 ACR-EULAR increased but its sensitivity decreased and the overall test performance was lower compared to its performance with a cut off of ≥ 4 . Therefore, the cut off of ≥ 4 recommended by the developers of the classification set showed to be more efficient than a cut off of ≥ 5 .

In conclusion, in the NIH cohort, the evaluation of the 2016 ACR-EULAR classification set had a comparable performance to the AECG set. Test diagnostics such as sensitivity and specificity of the 2016 ACR-EULAR set were not significantly different from that of the AECG set. Further research to attain the objective of developing improved classification criteria with increased specificity is needed. In that respect, the assessment of the effect of increasing the existing focus score cut off of 1 foci/4mm², continuing research in understanding the underlying etiopathogenesis and possibly incorporating genetic and

genomic alterations might prove beneficial in constructing improved criteria for this complex disorder.

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Figure 1.
Receiver Operating Curves (ROC) of 2016 ACR-EULAR Classification of SS, pSS and sSS.

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Table 1

Classification of NIH cohort by AECC and 2016 ACR-EULAR sets

Classification Criteria	Classification Status				Total*
	SS	pSS	sSS	Non-SS	
AECC	701	627	74	602	1303
2016 ACR-EULAR	714	647	67	589	1303

* Sum of SS and non-SS.

Table 2

Test Diagnostics of Classification Criteria for SS, pSS, and sSS

A. Classification for SS						
	2016 ACR-EULAR			AECG ^T	P-value	
	SS	Non-SS	Total			
AECG						
SS	638	63	701			
Non-SS	76	526	602			
Total	714	589	1,303			
Test Diagnostics	2016 ACR-EULAR *			AECG ^T	P-value	
	Estimate	95% CI	Estimate			
Prevalence	53.80%	51.0%–56.5%	54.80%	52.0%–57.5%		
Sensitivity	91.00%	88.6%–93.0%	89.40%	86.9%–91.5%		0.31
Specificity	87.40%	84.5%–89.9%	89.30%	86.5%–91.7%		
ROC area	0.89	0.87–0.91	0.89	0.88–0.91		
Likelihood ratio (+)	7.21	5.84–8.91	8.35	6.61–10.56		
Likelihood ratio (–)	0.1	0.08–0.13	0.12	0.10–0.15		
Odds ratio	70.09	49.25–99.75	70.09	49.25–99.75		
Positive predictive value	89.40%	86.9%–91.5%	91.00%	88.6%–93.0%		
Negative predictive value	89.30%	86.5%–91.7%	87.40%	84.5%–89.9%		
B. Classification for pSS						
	2016 ACR-EULAR			AECG ^T	P-value	
	pSS	Non-pSS	Total			
AECG						
pSS	638	63	701			
Non-pSS	76	526	602			
Total	714	589	1,303			
Test Diagnostics	2016 ACR-EULAR *			AECG ^T	P-value	
	Estimate	95% CI	Estimate			
Prevalence	48.10%	45.4%–50.9%	49.70%	46.9%–52.4%		

A. Classification for SS				
AECG	2016 ACR-EULAR			Total
	SS	Non-SS		
Sensitivity	91.90%	89.4%–93.9%	89.00%	86.4%–91.3%
Specificity	89.50%	86.9%–91.7%	92.20%	89.9%–94.2%
ROC area	0.91	0.89–0.92	0.91	0.89–0.92
Likelihood ratio (+)	8.75	7.01–10.91	11.45	8.79–14.93
Likelihood ratio (–)	0.09	0.07–0.12	0.12	0.10–0.15
Odds ratio	96.24	66.02–140.28	96.24	66.02–140.28
Positive predictive value	89.00%	86.4%–91.3%	91.90%	89.4%–93.9%
Negative predictive value	92.20%	89.9%–94.2%	89.50%	86.9%–91.7%
C. Classification for sSS				
AECG	2016 ACR-EULAR			Total
	sSS	Non-sSS		
sSS	62	12	74	
Non-sSS	5	1,224	1,229	
Total	67	1,236	1,303	
Test Diagnostics				
	2016 ACR-EULAR*			AECG [†]
	Estimate	95% CI	Estimate	
Prevalence	5.70%	4.5%–7.1%	5.10%	
Sensitivity	83.80%	73.4%–91.3%	92.50%	0.14
Specificity	99.60%	99.1%–99.9%	99.00%	
ROC area	0.92	0.87–0.96	0.96	
Likelihood ratio (+)	205.94	85.38–496.73	95.31	
Likelihood ratio (–)	0.16	0.10–0.27	0.08	
Odds ratio	1264.8	440.60–3603.06	1264.8	
Positive predictive value	92.50%	83.4%–97.5%	83.80%	
Negative predictive value	99.00%	98.3%–99.5%	99.60%	

* Performance of 2016 ACR-EULAR with AECG as gold standard |

[†] Performance of AECG with 2016 ACR-EULAR as gold standard |

p-value by Mc Nemar's test.

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