Applying the ACR/EULAR Systemic Sclerosis Classification Criteria to the Spanish Scleroderma Registry Cohort

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ABSTRACT. ***Objective.*** To compare American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for systemic sclerosis (SSc) with previous American Rheumatology Association (ARA) criteria.

Methods. This was a cross-sectional multicenter study comparing sensitivity of both criteria in the cutaneous subsets in the Spanish scleroderma registry (RESCLE) cohort.

Results. In 1222 patients with SSc, the most prevalent items were Raynaud phenomenon (95%), skin thickening (91%), and abnormal capillaroscopy (89%). ARA criteria classified as SSc 63.5% of all patients, and 63%, 100%, 11.2%, and 0% in the limited, diffuse, sine, and pre-SSc subsets, respectively. ACR/EULAR criteria classified 87.5% of all patients and 98.5%, 100%, 41.8%, and 15.9% in the same subsets, respectively.

Conclusion. ACR/EULAR criteria are more sensitive than ARA criteria, especially in limited, sine, and pre-SSc subsets. (J Rheumatol First Release October 15 2015; doi:10.3899/jrheum.150144)

Key Indexing Terms:
SYSTEMIC SCLEROSIS CLASSIFICATION CRITERIA

The 1980 American Rheumatology Association (ARA)[1] classification criteria for systemic sclerosis (SSc) have shown low sensitivity for the diagnosis of the disease in its early and limited subsets[2,3,4]. Other sets of criteria have tried to improve this low sensitivity for the diagnosis of SSc[5,6,7].

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) supported an international working group to revise the classification criteria for SSc. After an initial approach, a Delphi and nominal group technique[8,9], 8 criteria were selected, with a different weight given to each one. Patients achieving a score of 9 or more are classified as having SSc. This system was tested in both "derivation" and "validation" samples of patients with SSc and controls ("mimickers"). The new set

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of criteria showed greater sensitivity and specificity than the 1980 ARA and 2001 LeRoy and Medsger criteria, in both samples[10,11].

We compared the new ACR/EULAR criteria with the old 1980 ARA ones, focusing on their performance in a large series of patients in the Spanish scleroderma registry (RESCLE) cohort. The objectives of our study were (1) to find the prevalence of each of the 8 items of the ACR/EULAR classification criteria in the RESCLE cohort and in its pre-SSc subset; and (2) to compare the sensitivity of the new 2013 ACR/EULAR criteria with the 1980 ARA criteria, in all the patients with SSc and in their cutaneous subsets.

MATERIALS AND METHODS

The RESCLE is a nationwide, cross-sectional registry created in 2006 to study a large series of Spanish patients with SSc[12]. The registry was approved and created within the Spanish Society of Internal Medicine and its Group of Autoimmune Diseases. Twenty Spanish centers have recruited patients since 2006, using the LeRoy-Medsger classification criteria[6], to avoid excluding patients with SSc who did not fulfill the preliminary ARA classification criteria. The registry includes epidemiological, clinical (visceral involvement), laboratory, immunological, and capillaroscopic data, according to a designed standard protocol. Disease onset is defined with the first self-reported symptom [Raynaud phenomenon (RP) in most patients].

The patients are classified at entry into the registry, according to LeRoy and Medsger's subsets[6]:

1. Pre-SSc: RP, capillaroscopic changes, and/or specific autoantibodies without skin thickening.
2. Limited cutaneous SSc (lcSSc): skin sclerosis confined distally to the elbows and knees or the face.
3. Diffuse cutaneous SSc (dcSSc): skin thickening extended proximally to the elbows and knees, or including the trunk.
4. Systemic sclerosis sine scleroderma (ss-SSc): RP, SSc clinical features, and SSc-specific autoantibodies without skin sclerosis.

Capillaroscopic study of each patient, if available, was classified in active or slow pattern, according to Maricq's classification[13]. Antibodies included in the RESCLE were antinuclear antibodies, anticentromere, anti-PM-Scl, and antibodies to extractable nuclear antigens, or ENA (SSA/Ro, SSB/La, Sm, RNP, and topoisomerase I).

All the patients included in the registry on April 30, 2013, were analyzed for the study, a few months after the ACR/EULAR criteria were presented at the 2012 ACR meeting. First, each of the 8 items included in the classification criteria[8] was studied. Then, patients fulfilling the 1980 ARA classification criteria and the 2013 ACR/EULAR classification criteria were compared.

It is worth noting that the ACR/EULAR classification criteria should not be applied to patients who have an SSc-like disease that better explains their manifestations, and patients who have skin thickening sparing the fingers (exclusion criteria).

Statistical analysis. Clinical, epidemiological, and laboratory data were collected at each center and included in the RESCLE database. The analysis was performed using contingency tables with patients fulfilling the 1980 ARA criteria and the 2013 ACR/EULAR criteria and then with the different cutaneous subtypes of SSc, according to the LeRoy-Medsger classification. All statistical analyses were performed with SPSS 15.0 for Windows (SPSS). A p level < 0.05 was considered significant.

RESULTS

By April 2013, 1222 patients from the RESCLE cohort were included in the analysis; 65 were withdrawn for incomplete data. Most patients were women (89%) and their mean age was 45 years at disease onset and 52 years at diagnosis. RP was the first SSc symptom in 83% of patients, and 96% had it at any moment of the disease. As for cutaneous subsets, there were 60.5% lcSSc, 25.2% dcSSc, 8.3% ss-SSc, and 5.8% pre-SSc. The median followup in April 2013 was 5 years. Within those 5 years, 17% of patients in the registry had died.

Table 1 shows the proportion of SSc and pre-SSc patients fulfilling each of the ACR/EULAR classification criteria in the RESCLE cohort. Only telangiectasia and digital pitting scars were found in a few patients with pre-SSc[14]. In this group, the 1980 ARA criteria were unable to classify those patients as SSc: 0% versus 15.9% with the 2013 ACR/EULAR criteria.

Table 2 shows the cross-tables comparing each set of criteria in the whole sample and in its cutaneous SSc subsets. In patients with dcSSc, both sets of criteria achieve 100% of patients. Differences begin in patients with lcSSc: 98.5% and 63.5% with the 2013 ACR/EULAR and the 1980 ARA criteria, respectively, and fewer in the ss-SSc (41.8% and 11.2%, respectively). This means 34.5% more patients with lcSSc, 31.6% more patients with sine-SSc, and 15.9% more patients with pre-SSc might now be classified as SSc with the new criteria.

Table 3 shows the number and percentage of patients classified as SSc with both sets of criteria, in their different cutaneous subsets. These results show significant differences in the limited cutaneous subsets and in the whole sample, with better performance of the 2013 ACR/EULAR criteria than with the 1980 ARA criteria. In the dcSSc subset, both criteria classify all the patients as SSc.

DISCUSSION

This study compares the performance of the 1980 ARA and

Table 1. ACR/EULAR SSc classification criteria in the RESCLE cohort (whole sample and pre-SSc subset).

Item ACR/EULAR	SSc (%), n = 1151	Pre-SSc (%), n = 71	p
Cutaneous sclerosis, proximal to MCP	309/1151 (27)	0/71 (0)	< 0.001
Puffy fingers	24/1055 (2.3)	0/69 (0)	0.324
Presence of scleroderma (skin thickening)	1048/1151 (91)	0/71 (0)	< 0.001
Fingertip ulcers/pitting scars	498/1150 (43)	16/71 (23)	0.001
Telangiectasia consistent with SSc	727/1150 (63)	16/71 (23)	< 0.001
Abnormal nailfold capillary pattern	764/856 (89)	48/68 (71)	< 0.001
PH or ILD	561/1149 (49)	0/71 (0)	< 0.001
Raynaud phenomenon	1096/1150 (95)	71/71 (100)	< 0.001
Scleroderma-related antibodies	689/1111 (62)	40/71 (56)	0.340

MCP: metacarpophalangeal; SSc: systemic sclerosis; PH: pulmonary hypertension; ILD: interstitial lung disease; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; RESCLE: Spanish Scleroderma Registry.

Table 2. Proportion of patients fulfilling 1980 SSc and 2013 ACR/EULAR classification criteria in the whole sample and in each cutaneous subset of systemic sclerosis.

Total Patients with SSc		2013 ACR/EULAR Criteria		Total
		n < 9 points (%)	n ≥ 9 points (%)	N (%)
1980 ARA criteria	Not fulfilled	118 (27.8)	290 (68.4)	408 (100) (34.6)
	Fulfilled	7 (0.9)	742 (98.1)	749 (100) (63.5)
Total		125 (13.5)	1032 (87.5)	1157 (100)
Patients with lcSSc		2013 ACR/EULAR Criteria		Total
		n < 9 points (%)	n ≥ 9 points (%)	N (%)
1980 ARA criteria	Not fulfilled	8 (3.2)	244 (96.8)	252 (100) (37)
	Fulfilled	2 (0.5)	427 (99.5)	429 (100) (63)
Total		10 (1.5)	671 (98.5)	681 (100)
Patients with dcSSc		2013 ACR/EULAR Criteria		Total
		n < 9 points (%)	n ≥ 9 points (%)	N (%)
1980 ARA criteria	Not fulfilled	0 (0)	0 (0)	0 (0)
	Fulfilled	0 (0)	309 (100)	309 (100)
Total		0	309 (100)	309
Patients with ss-SSc		2013 ACR/EULAR Criteria		Total
		n < 9 points (%)	n ≥ 9 points (%)	N (%)
1980 ARA criteria	Not fulfilled	52 (59.8)	35 (40.2)	87 (100) (88.8)
	Fulfilled	5 (45.5)	6 (54.5)	11 (100) (11.2)
Total		57 (58.2)	41 (41.8)	98
Pre-SSc patients		2013 ACR/EULAR Criteria		Total
		n < 9 points (%)	n ≥ 9 points (%)	N (%)
1980 ARA criteria	Not fulfilled	58 (84.1)	11 (15.9)	69 (100)
	Fulfilled	0 (0)	0 (0)	0 (0)
Total		0	11 (15.9)	69

SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ss-SSc: sine scleroderma SSc; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; ARA: American Rheumatism Association.

Table 3. Patients classified as SSc with both sets of criteria in their different cutaneous subsets.

	1980 ARA, n (%)	Only 2013 ACR/EULAR Criteria Fulfilled, n (%)	p
lcSSc	429/681 (63.0)	671/681 (98.5)	< 0.001
dcSSc	309/309 (100)	309/309 (100)	—
pre-SSc	0/69 (0)	11/69 (15.9)	0.001
ss-SSc	11/98 (11.2)	41/98 (41.8)	< 0.001
Total	749/1157 (64.7)	1032/1157 (89.2)	< 0.001

SSc: systemic sclerosis; 1980 ARA: 1980 American Rheumatism Association preliminary classification criteria for SSc; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ss-SSc: sine scleroderma SSc.

the 2013 ACR/EULAR classification criteria for SSc in the RESCLE cohort. The new ACR/EULAR criteria classify as SSc up to 24.5% more RESCLE patients than the old ARA classification criteria. This difference rises to 31.6% in ss-SSc and 34.5% in lcSSc subsets. Even 15.9% of pre-SSc patients are now classified as SSc with the new criteria, because these patients only present RP, abnormal nailfold capillaroscopy, and/or specific SSc autoantibodies. In patients with dcSSc, both criteria are fulfilled in 100% of patients, because proximal skin thickening is the major and sufficient criterion in the 1980 ARA and scores a threshold of 9 in the 2013 ACR/EULAR criteria.

More patients can now be classified as SSc (1032 vs 749 patients out of 1157). This is 283 (24.5%) more patients that would not have been included under the old criteria. The new criteria should allow classification of more patients as having SSc. That would allow including them earlier in clinical trials, earlier treatment, and perhaps improved prognosis by enlarging the "window of opportunity."

Johnson, *et al*[15] reviewed up to 14 classification criteria for SSc that used 2 to 5 different subsets, according to their cutaneous extension. LeRoy-Medsger's was not only the most used and referenced classification — it also had good performance. All patients included in the RESCLE cohort fulfilled these LeRoy-Medsger criteria.

Few studies compare these 2 sets of criteria. A Swedish

population study[16] found that applying the ACR/EULAR classification criteria to patients with RP and SSc resulted in about 30–40% higher estimates of SSc prevalence and incidence compared to the 1980 ARA criteria. These results seem similar to those found in our study.

Hoffmann-Vold, *et al* applied both sets of criteria to 425 patients with suspected SSc and 178 patients from the Norwegian Mixed Connective Tissue Disease (MCTD) Cohort[17]. They found that 96% of patients with SSc fulfilled the ACR/EULAR classification criteria versus only 75% fulfilling the 1980 ARA criteria. They concluded that the new criteria are more sensitive but do not completely segregate SSc from MCTD, because 10% of these patients also fulfilled the ACR/EULAR SSc classification criteria.

Alhajeri, *et al* applied both sets of criteria to 724 patients with SSc from the Canadian Scleroderma Research Group cohort[18]. As in our study, they concluded that the ACR/EULAR classification criteria are more sensitive than the old ARA criteria (98.3% compared to 88.3% for the 1980 criteria), most strikingly in limited SSc (98.8% vs 85.6%) and ss-SSc (74.1% vs 11.1%). Both sets of criteria classify 100% of patients with dcSSc.

A limitation of our study is that the RESCLE cohort was not designed to compare classification criteria, although including patients fulfilling the LeRoy-Medsger criteria allowed us to also study patients who would not have entered the registry with the 1980 ARA criteria. As a consequence, we cannot work out specificity, predictive values, and likelihood ratios. The RESCLE cohort started in 2006, when the ACR/EULAR criteria had not yet been developed. This fact could have underestimated some of them, such as the "puffy fingers," which shows very low numbers in our registry (2.3% as an "initial" sign). A better recognition of these items could have classified more patients as SSc, showing perhaps even bigger differences.

The strength of our study lies in using a multicentric registry, confirming the findings of other similar studies. It is the largest study, to our knowledge, to test the new SSc classification criteria in a big sample of patients with SSc and pre-SSc.

The new ACR/EULAR classification criteria for SSc show better accuracy than the old ARA criteria, classifying a greater number of patients with SSc, especially in the lcSSc, ss-SSc, and pre-SSc subsets.

Using these new criteria should allow identification and treatment of patients with SSc in earlier stages, and perhaps improve their prognosis.

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APPENDIX

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