RHEUMATOLOGY
doi:10.1093/rheumatology/keu530
Advance Access publication 11 March 2015

Concise report

Performance of the new ACR/EULAR classification criteria for systemic sclerosis in clinical practice

Suzana Jordan[1], Britta Maurer[1], Martin Toniolo[1], Beat Michel[1] and Oliver Distler[1]

Abstract

Objective. The preliminary classification criteria for SSc lack sensitivity for mild/early SSc patients, therefore, the new ACR/EULAR classification criteria for SSc were developed. The objective of this study was to evaluate the performance of the new classification criteria for SSc in clinical practice in a cohort of mild/early patients.

Methods. Consecutive patients with a clinical diagnosis of SSc, based on expert opinion, were prospectively recruited and assessed according to the EULAR Scleroderma Trials and Research group (EUSTAR) and very early diagnosis of SSc (VEDOSS) recommendations. In some patients, missing values were retrieved retrospectively from the patient's records. Patients were grouped into established SSc (fulfilling the old ACR criteria) and mild/early SSc (not fulfilling the old ACR criteria). The new ACR/EULAR criteria were applied to all patients.

Results. Of the 304 patients available for the final analysis, 162/304 (53.3%) had established SSc and 142/304 (46.7%) had mild/early SSc. All 162 established SSc patients fulfilled the new ACR/EULAR classification criteria. The remaining 142 patients had mild/early SSc. Eighty of these 142 patients (56.3%) fulfilled the new ACR/EULAR classification criteria. Patients with mild/early SSc not fulfilling the new classification criteria were most often suffering from RP, had SSc-characteristic autoantibodies and had an SSc pattern on nailfold capillaroscopy. Taken together, the sensitivity of the new ACR/EULAR classification criteria for the overall cohort was 242/304 (79.6%) compared with 162/304 (53.3%) for the ACR criteria.

Conclusion. In this cohort with a focus on mild/early SSc, the new ACR/EULAR classification criteria showed higher sensitivity and classified more patients as definite SSc patients than the ACR criteria.

Key words: classification criteria, systemic sclerosis, early SSc.

CLINICAL SCIENCE

Rheumatology key messages

- The new ACR/EULAR classification criteria for SSc are applicable in clinical practice.
- The new ACR/EULAR classification criteria have increased sensitivity compared with the previous ACR criteria.
- Some patients with features of early SSc are not covered by the new classification criteria.

Introduction

SSc is a heterogeneous disease that varies greatly between individual patients, resulting in differences in organ involvement, treatment and prognosis. There are particular challenges in recognizing mild and early forms of the disease. Classification criteria for SSc are important for the uniformity of disease cohorts, e.g. in clinical trials, but also for the early detection of SSc to guide timely decisions on treatment interventions. Several different classifications have been proposed, most often based on the degree of skin involvement [1–7]. The preliminary ACR classification criteria for SSc were the first to be externally validated in a large population of patients [8]. They have been applied successfully for many years. However, the ACR criteria are limited by their lack of sensitivity for mild and early cases of SSc.

This unmet need for greater sensitivity initiated revision of the classification criteria by a joint effort of the EULAR

[1]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland

Submitted 26 May 2014; revised version accepted 9 December 2014

Correspondence to: Oliver Distler, Division of Rheumatology, University Hospital Zurich, Gloriastr. 25, 8091 Zurich, Switzerland.
E-mail: Oliver.Distler@usz.ch

and the ACR. Through a specific, predefined process of item generation, item reduction and item validation, a final set of clinical and laboratory features was chosen as the new ACR/EULAR classification criteria [9–12]. These new criteria now have to be applied and tested in clinical practice to show whether the limitations of the old criteria have been successfully addressed. Therefore the aim of our study was to evaluate the performance of the new ACR/EULAR classification criteria for SSc in our real-life cohort with a particular focus on mild and early SSc patients.

Methods

This was a single-centre observational study performed in accordance with good clinical practice. All patients signed informed consent according to the Declaration of Helsinki, and the Cantonal Ethics Committee Zurich approved the study. Consecutive patients with a clinical diagnosis of SSc were prospectively recruited and assessed according to EULAR Scleroderma Trials and Research group (EUSTAR) and very early diagnosis of SSc (VEDOSS) recommendations [13, 14]. The clinical diagnosis of SSc was based on the expert opinion of two experienced rheumatologists (O.D. and B.M., 18 years and 5 years of experience in SSc assessment, respectively) from our tertiary care university centre. Data from all patients were prospectively collected in the database. Definitions of items and data collection in this cohort are highly standardized. More than 90% of patients are seen by the same two physicians with long-term experience in SSc (B.M. and O.D.). Data are collected directly during the visit on paper and are afterwards transferred into the online local database by a data entry clerk (N.S.). There is also regular external independent monitoring for consistency of key parameters with primary source data. As the new ACR/EULAR criteria are cumulative, all available visits of the patients were included in the analysis where appropriate. Some items such as pitting scars and telangiectasia, which were not collected prospectively, were retrieved from the patient's charts. Patients with missing data on the classification items were excluded from the analysis ($n = 4$).

The ACR criteria were used to classify patients into established SSc (old ACR criteria fulfilled) or mild/early SSc (old ACR criteria not fulfilled) [8]. Afterwards, the new ACR/EULAR criteria were applied to these groups of established and mild/early SSc [11, 12]. Scores for each patient were calculated automatically using Excel software (Microsoft, Redmond, WA, USA). Patients with a total score $\geqslant 9$ were classified as definite SSc patients according to new ACR/EULAR classification criteria. Distribution of the data was analysed by the d'Agostino and Pearson omnibus normality test for continuous variables. Non-parametric data are shown as median and interquartile range (IQR) if not indicated otherwise. Frequencies are shown as percentage. Comparison of sensitivity between ACR and ACR/EULAR criteria was done by Fisher's exact test.

Results

There were 308 patients with a clinical expert diagnosis of SSc reported in the database. We excluded four patients because of missing data on classification items that were unavailable from patients' charts. The final set of data for analysis contained 304 patients. The final set was divided into a group of 162 patients with established SSc who fulfilled the ACR criteria and a group of 142 patients with mild/early SSc who did not fulfil the ACR criteria. Baseline characteristics and a comparison of these two groups of patients are shown in Table 1. Demographics and clinical characteristics were defined according to EUSTAR definitions [15, 16].

We next applied the ACR/EULAR classification criteria to both groups. All patients in the established group fulfilled the new criteria. In the group of mild/early SSc patients, 80/142 (56.3%) fulfilled the new criteria, whereas 62/142 (43.7%) did not.

We further characterized the 80 patients who fulfilled the new ACR/EULAR criteria, but not the old ACR criteria (Table 2). Their median age was 58 years (range 48–70), disease duration was 6 years (range 3–16); 32/80 patients (40%) had skin fibrosis with a median modified Rodnan skin score (mRSS) of 0 (range 0–2) and a median score with the new classification criteria of 10 (IQR 10–14). Of these 80 patients, 78 (97.5%) had RP, 71 (88.8%) had SSc-related antibodies, 66 (82.5%) had abnormal nailfold capillaries, 44 (55.0%) had puffy fingers and 34 (42.5%) had telangiectasia (Table 2). In this group, 18/76 patients (23.6%) had a disease duration of <3 years and 38/80 (47.5%) had gastrointestinal involvement.

We were also interested in characterizing the 62 patients with a clinical expert diagnosis of SSc who did not fulfil the new ACR/EULAR classification criteria for SSc (Table 2). Their median age was 54 years (range 38–66), disease duration was 6 years (range 2–12) and none of them had skin fibrosis [median mRSS 0 (range 0–0)]. Of these 62 patients, 58 (93.5%) had RP, 45 (72.6%) had abnormal nailfold capillaroscopy findings, 37 (59.6%) had SSc-related antibodies, 11 (17.7%) had puffy fingers and 4 (6.4%) had telangiectasia. Pulmonary arterial hypertension, interstitial lung disease, digital ulcers and pitting scars occurred in only one patient (1.6%) (Table 2). Thus the median score of those patients according to the ACR/EULAR criteria was 7 (IQR 5–8). In this group, 22/54 patients (40.7%) had disease duration of <3 years and 26/62 (41.9%) had gastrointestinal involvement. Taken together, we found that in this cohort of 304 SSc patients with a focus on mild/early SSc, 162 (53.3%) fulfilled the previous criteria and 242 (79.6%) fulfilled the new ACR/EULAR classification criteria for SSc. Thus, in our cohort, the new ACR/EULAR classification criteria showed significantly increased sensitivity compared with the ACR criteria ($P < 0.0001$). Patients with an expert diagnosis of SSc who did not fulfil the new ACR/EULAR criteria most often had RP, an SSc pattern on nailfold capillaroscopy, SSc-related antibodies and puffy fingers.

Table 1 Baseline characteristics of patients with established SSc and mild/early SSc

	Established SSc	Mild/early SSc	*P*-value
Analysed patients, *n*/*N* (%)	162/304 (53.3)	142/304 (46.7)	
Age, median (IQR), years	61 (51–69)	56 (43–68)	0.0003
dcSSc subset, *n*/*N* (%)	66/162 (40.7)	0/142	<0.0001
Sex, female, *n*/*N* (%)	132/162 (81.5)	126/142 (88.7)	0.1
mRSS, median (IQR) (minimum–maximum)	8 (4–16) (0–37)	0 (0–0) (0–6)	<0.0001
Disease duration, median (IQR), years	6 (3–13)	6 (2–13)	0.6
ANA status, *n*/*N* (%)	155/159 (97.5)	142/142 (100.0)	0.1
ACA, *n*/*N* (%)	51/159 (32.1)	89/142 (62.6)	<0.0001
Anti-Scl-70, *n*/*N* (%)	51/161 (31.7)	13/139 (9.3)	<0.0001
Anti-PM/Scl, *n*/*N* (%)	14/110 (12.7)	3/120 (2.5)	0.004
Anti-U1-snRNP[a], *n*/*N* (%)	3/115 (2.6)	5/128 (3.9)	0.7
Anti-RNA polymerase III, *n*/*N* (%)	14/112 (12.5)	6/128 (4.6)	0.03
Digital ulcers, *n*/*N* (%)	67/162 (41.4)	6/142 (4.2)	<0.0001
SSc pattern on nailfold capillaroscopy, *n*/*N* (%)	91/162 (56.2)	111/142 (78.1)	<0.0001
RP, *n*/*N* (%)	153/159 (96.2)	136/142 (95.8)	1.0
Interstitial lung disease, *n*/*N* (%)	73/161 (45.3)	12/142 (8.4)	<0.0001
PAH, *n*/*N* (%)	17/162 (10.5)	0/142 (0)	<0.0001
Renal crisis, *n*/*N* (%)	4/162 (2.5)	1/142 (0.7)	0.4
GI involvement, *n*/*N* (%)	112/162 (69.1)	64/142 (45.1)	<0.0001

Interstitial lung disease diagnosed by CT or, where not available, X-ray or forced vital capacity <70% without other explanation; pulmonary arterial hypertension (PAH) diagnosed by right heart catheterization, which was performed when PAH was suspected by expert opinion; renal crisis per the EUSTAR definition and confirmed by expert opinion; gastrointestinal (GI) involvement diagnosed if there was involvement of the oesophagus, stomach or intestine, as per EUSTAR definition [15]. Demographics and clinical characteristics were defined according to EUSTAR definitions [16] and are provided in supplementary Table S1 (available at *Rheumatology* Online). [a]Autoantibodies were measured and interpreted according to local standards. GI: gastrointestinal; IQR: interquartile range (25th–75th percentile); mRSS: modified Rodnan skin score; anti-Scl 70: anti-topoisomerase 1 antibodies; anti-PM/Scl: antibodies against a nucleolar macromolecular complex of peptides of 75 kDa and 100 kDa; anti-U1-snRNP: anti-U1 small nuclear ribonucleoprotein antibodies; PAH: pulmonary arterial hypertension.

Table 2 Characterization and comparison of mild/early patients who fulfilled and did not fulfil the new ACR/EULAR classification criteria

Criteria	Subcriteria	Patients who fulfilled the new ACR/EULAR classification criteria, *n*/*N* (%)	Patients who did not fulfil the new ACR/EULAR classification criteria, *n*/*N* (%)	*P*-value
Skin thickening of the fingers (count the higher of the two)	Puffy fingers	44/80 (55.0)	11/62 (17.7)	<0.0001*
	Whole finger, distal to MCP	30/80 (37.5)	0/62	<0.0001*
Fingertip lesions (count the higher of the two)	Digital ulcers	5/80 (6.3)	1/62 (1.6)	0.2
	Pitting scars	7/80 (8.7)	1/62 (1.6)	0.07
Telangiectasia		34/80 (42.5)	4/62 (6.4)	<0.0001*
Abnormal NFC		66/80 (82.5)	45/62 (72.6)	0.02
Lung involvement	PAH (on RHC)	3/80 (3.8)	1/62 (1.6)	0.6
	ILD (on HRCT)	11/80 (13.8)	1/62 (1.6)	0.001*
RP		78/80 (97.5)	58/62 (93.5)	0.4
SSc-related antibodies	Any of ACA, anti-Scl-70,[a] anti-RNA polymerase III	71/80 (88.8)	37/62 (59.6)	0.0001*

[a]Autoantibodies were measured and interpreted according to local standards. HRCT: high-resolution CT; ILD: Interstitial lung disease; NFC: nailfold capillaroscopy; PAH: pulmonary arterial hypertension; RHC: right heart catheterization; anti-Scl 70: anti-topoisomerase 1 antibody. *Statistically significant ($P < 0.005$).

Discussion

The objective of this study was to evaluate the performance of the new ACR/EULAR classification criteria for SSc in a cohort that reflects everyday clinical practice and has a focus on mild and early SSc. This focus on mild patients is an important difference from the cohorts that were used to validate the classification criteria in the initial approach [10].

We have chosen the term mild/early for this group, because this was a mixed group of patients with mild SSc and longer disease duration (median 6 years) and a group of early patients that did not (yet) fulfil ACR criteria [e.g. 13/54 patients (24.1%) had disease duration <2 years from non-RP symptoms and 22/54 (40.7%) had disease duration <3 years]. Thus mild/early SSc is a more correct term than early SSc for this cohort. This is an important result of our study and should be considered in the current discussion of patients with early SSc [14, 17, 18]. In fact, the current definition of patients with very early SSc might be a heterogeneous group of patients with mild and early SSc, which is probably paralleled by a different prognosis and clinical course of the disease. Thus our data indicate that cohorts of patients with early SSc should be analysed separately from patients with mild SSc.

In a recent analysis, application of the new ACR/EULAR classification criteria in southern Sweden resulted in a 30–40% higher prevalence and incidence of SSc compared with the 1980 ACR criteria [19]. We found that 53.3% of SSc patients fulfilled the previous criteria and 79.6% the new criteria and could thus show that the new ACR/EULAR classification criteria allowed classification of ~26% more patients in our cohort compared with the ACR criteria. These newly classified patients were exclusively patients with mild and early disease, and accordingly, 56% of patients with mild/early disease that could not be classified with the old criteria met the new classification criteria. Therefore this study confirms that the main aim of the new classification criteria, i.e. increased sensitivity, was achieved. Furthermore, our results showed that the new classification criteria are applicable in clinical practice. Although we confirmed that the new ACR/EULAR criteria have increased sensitivity, one should be cautious about overdiagnosing, because there are important psychological, financial and other health consequences for patients diagnosed with early SSc, but who do not develop disease over time.

However, it has to be emphasized that the new ACR/EULAR criteria represent classification criteria and should not be misinterpreted as diagnostic criteria. Along this line, there were 62 patients (43.7% of the early/mild cohort) in our cohort with a clinical expert diagnosis of SSc who still did not fulfil the new criteria. These patients were characterized most often by a combination of RP, SSc-characteristic antibodies and an SSc pattern on nailfold capillaroscopy. These combinations of clinical features resemble cases that were proposed to be named early or limited SSc by LeRoy and Medsger [5]. Indeed, patients with these clinical features can truly be named SSc patients, as recent studies have shown that up to 65.9% of those patients develop definite SSc with additional clinical manifestations at the 5 year follow-up [20]. Another more frequent clinical feature of this patient group was puffy fingers, which has recently been proposed as a pivotal sign for the suspicion of SSc in patients with very early disease [14].

A limitation of our study was the inability to measure the specificity of the new classification criteria in our cohort. Since our registry does not contain SSc mimicker diseases or patients with primary RP, we were unable to measure the specificity of the test (the fraction of those without disease correctly identified as negative by test). Also, while most data were collected prospectively, some data, such as pitting scars and telangiectasia, had to be collected retrospectively. Furthermore, expert diagnosis is standard for this kind of study, and both experts have long-standing experience, but expert diagnosis might have been different with experts from other centres.

Taken together, this study shows that the new ACR/EULAR classification criteria for SSc are applicable in clinical practice and have increased sensitivity compared with the previous ACR classification criteria. This allows the inclusion of patients with mild and early disease in SSc cohorts and clinical studies. Our results also demonstrate that despite their increased sensitivity, the new classification criteria are not diagnostic criteria. In particular, patients with RP, SSc-characteristic antibodies and an SSc pattern on nailfold capillaroscopy might still be diagnosed with early SSc despite not fulfilling the new ACR/EULAR classification criteria.

Acknowledgements

We thank Nicole Schneider for data entry and data cleaning of our database.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: O.D. has/had a consultancy relationship and/or has received research funding in the area of SSc and related conditions from Actelion, Pfizer, Ergonex, BMS, Sanofi-Aventis, United BioSource, Roche/Genentech, Medac, Biovitrium, Boehringer, Novartis, 4D Science, Active Biotec, Bayer, Sinoxa, Serodapharm, EpiPharm, Biogen, Pharmacyclics, Inventiva and GSK. All other authors declare no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Barnett AJ. Scleroderma (progressive systemic sclerosis): progress and course based on a personal series of 118 cases. Med J Aust 1978;2:129–34.

2 Rodnan GP, Lipinski E, Luksick J. Skin thickness and collagen content in progressive systemic sclerosis and localized scleroderma. Arthritis Rheum 1979;22:130–40.

3 Giordano M, Valentini G, Migliaresi S, Picillo U, Vatti M. Different antibody patterns and different prognoses in patients with scleroderma with various extent of skin sclerosis. J Rheumatol 1986;13:911–6.

4 LeRoy EC, Black C, Fleischmajer R *et al*. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202–5.

5 LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573–6.

6 Nadashkevich O, Davis P, Fritzler MJ. A proposal of criteria for the classification of systemic sclerosis. Med Sci Monit 2004;10:CR615–21.

7 Maricq HR, Valter I. A working classification of scleroderma spectrum disorders: a proposal and the results of testing on a sample of patients. Clin Exp Rheumatol 2004; 22(3 Suppl 33):S5–13.

8 Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581–90.

9 Fransen J, Johnson SR, van den Hoogen F *et al*. Items for developing revised classification criteria in systemic sclerosis: results of a consensus exercise. Arthritis Care Res 2012;64:351–7.

10 Johnson SR, Fransen J, Khanna D *et al*. Validation of potential classification criteria for systemic sclerosis. Arthritis Care Res 2012;64:358–67.

11 van den Hoogen F, Khanna D, Fransen J *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2013; 72:1747–55.

12 van den Hoogen F, Khanna D, Fransen J *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2013; 65:2737–47.

13 Meier FM, Frommer KW, Dinser R *et al*. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012;71:1355–60.

14 Minier T, Guiducci S, Bellando-Randone S *et al*. Preliminary analysis of the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis 2014;73:2087–93.

15 Galie N, Hoeper MM, Humbert M *et al*. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–537.

16 Walker UA, Tyndall A, Czirjak L *et al*. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2007;66:754–63.

17 Valentini G, Marcoccia A, Cuomo G, Iudici M, Vettori S. The concept of early systemic sclerosis following 2013 ACR\EULAR criteria for the classification of systemic sclerosis. Curr Rheumatol Rev 2014;10:38–44.

18 Lepri G, Guiducci S, Bellando-Randone S *et al*. Evidence for oesophageal and anorectal involvement in very early systemic sclerosis (VEDOSS): report from a single VEDOSS/EUSTAR centre. Ann Rheum Dis 2015;74:124–8.

19 Andreasson K, Saxne T, Bergknut C, Hesselstrand R, Englund M. Prevalence and incidence of systemic sclerosis in southern Sweden: population-based data with case ascertainment using the 1980 ARA criteria and the proposed ACR-EULAR classification criteria. Ann Rheum Dis 2014;73:1788–92.

20 Koenig M, Joyal F, Fritzler MJ *et al*. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum 2008;58: 3902–12.