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SPECIAL ARTICLE

2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League
Against Rheumatism Collaborative Initiative

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an external data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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Objective. The 1980 American College of Rheumatology (ACR) classification criteria for systemic sclerosis (SSc) lack sensitivity for early SSc and limited cutaneous SSc. The present work, by a joint committee of the ACR and the European League Against Rheumatism (EULAR), was undertaken for the purpose of developing new classification criteria for SSc.

Methods. Using consensus methods, 23 candidate items were arranged in a multicriteria additive point system with a threshold to classify cases as SSc. The classification system was reduced by clustering items and simplifying weights. The system was tested by 1) determining specificity and sensitivity in SSc cases and controls with scleroderma-like disorders, and 2) validating against the combined view of a group of experts on a set of cases with or without SSc.

Results. It was determined that skin thickening of the fingers extending proximal to the metacarpophalangeal joints is sufficient for the patient to be classified as having SSc; if that is not present, 7 additive items apply, with varying weights for each: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon, and SSc-related autoantibodies. Sensitivity and specificity in the validation sample were, respectively, 0.91 and 0.92 for the new classification criteria and 0.75 and 0.72 for the 1980 ACR classification criteria. All selected cases were classified in accordance with consensus-based expert opinion. All cases classified as SSc accord-

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ing to the 1980 ACR criteria were classified as SSc with the new criteria, and several additional cases were now considered to be SSc.

Conclusion. The ACR/EULAR classification criteria for SSc performed better than the 1980 ACR criteria for SSc and should allow for more patients to be classified correctly as having the disease.

Introduction

Systemic sclerosis (SSc; scleroderma) is a heterogeneous disease whose pathogenesis is characterized by 3 hallmarks: small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction leading to increased deposition of extracellular matrix (1). The clinical manifestations and the prognosis of SSc vary, with the majority of patients having skin thickening and variable involvement of internal organs. Subsets of SSc can be discerned, i.e., limited cutaneous SSc, diffuse cutaneous SSc, and SSc without skin involvement (1).

In the absence of a diagnostic test proving the absence or presence of SSc, several sets of classification criteria have been developed (2–6). The purpose of classification criteria is to enroll, in research studies, patients who in fact have the disease as determined using a uniform definition (7). Classification criteria are not synonymous with diagnostic criteria but will almost always mirror the list of criteria that are used for diagnosis (7). However, classification criteria generally are more standardized and less inclusive than physician diagnosis.

The current standard classification criteria for SSc are the 1980 preliminary criteria for the classification of systemic sclerosis (scleroderma), developed by the American College of Rheumatology (ACR) (2–4,8). These classification criteria were developed using patients with longstanding SSc. As a consequence, patients with early SSc and ~20% of patients with limited cutaneous disease do not meet the criteria and are excluded from clinical studies (1,9,10). Since the development of the 1980 criteria, knowledge regarding SSc-related autoantibodies has improved (11–13). In addition, characteristic nailfold capillary changes have been found to be associated with SSc, and nailfold capillaroscopy is widely accepted as a diagnostic tool (10,14–17). In 1988, LeRoy et al proposed new criteria that included clinical features, autoantibodies, and capillaroscopy results, highlighting the differences between the 2 main SSc subsets (11). In 2001, LeRoy and Medsger proposed to revise the classification criteria to include “early” SSc, using nailfold capillary pattern and SSc-related

autoantibodies (6). It also has been demonstrated that the addition of nailfold capillary abnormalities and telangiectasias to the ACR SSc criteria improves their sensitivity (9,18).

Because of the insufficient sensitivity of the 1980 criteria and advances in knowledge about SSc, the ACR and the European League Against Rheumatism (EULAR) established a committee to provide a joint proposal for new classification criteria for SSc. The aims were to develop criteria that 1) encompass a broader spectrum of SSc including patients whose disease is in the early stage as well as those in the late stage; 2) include vascular, immunologic, and fibrotic manifestations; 3) are feasible to use in daily clinical practice; and 4) are in accordance with criteria used for diagnosis of SSc in clinical practice (7). These criteria are intended to be used by rheumatologists, researchers, national and international drug agencies, pharmaceutical companies, or any others involved in studies of SSc. Our objective was to develop a set of criteria that would enable identification of individuals with SSc for inclusion in clinical studies, being more sensitive and specific than previous criteria.

Methods

Overview. The development and testing of the classification system for SSc was based on both data and expert clinical judgment. First, candidate items for the classification criteria were generated using consensus methods and evaluated using existing databases (19,20). Second, multicriteria decision analysis was used to reduce the number of candidate criteria and assign preliminary weights (21). The classification system was repeatedly tested and adapted using prospectively collected SSc cases and non-SSc controls, and compared against expert clinical judgment. Third, the classification criteria were tested in a validation cohort and tested against preexisting criteria sets.

Item generation and reduction. One hundred sixty-eight candidate criteria were identified through 2 Delphi exercises. A 3-round Delphi exercise and a face-to-face consensus meeting using nominal group technique facilitated reduction of the 168 items to 23 (19). Using a random sample of existing databases (SSc [n = 783] and control patients with diseases similar to SSc [n = 1,071], all based on physician diagnosis), the candidate criteria were found to have good discriminative validity (20).

Item reduction and weighting. *Draft classification system.* A face-to-face meeting of 4 European and 4 North American SSc experts was held to further reduce items and assign preliminary weights using multicriteria decision analysis. The number of experts was limited in advance to 8, and they were invited based on geographic representation, knowledge from a scientific and a practical diagnostic viewpoint, and availability. At the meeting, the experts determined by consensus to which cases the criteria should be and should not be

applied, and which items are sufficient to allow classification of a patient as having SSc (sufficient criteria). They then participated in a multicriteria decision analysis to further reduce the 23 items and assign preliminary weights (21). The experts were presented hypothetical pairs of cases with 2 of the 23 items at a time (e.g., Raynaud's phenomenon positive *and* abnormal nailfold capillaries absent versus Raynaud's phenomenon negative *and* abnormal nailfold capillaries present, all other manifestations being considered equal) and they were asked to individually vote electronically on which case of the pair was more likely to be SSc. The result of the votes was immediately presented. If there was no complete agreement among the experts, considerations were discussed and a second round of voting was conducted. As a result of the repeated choices between 2 alternative cases, items were ranked, and weights for the items were derived using 1000Minds decision-making software (21). Additional details about the methods are available in ref. 22.

Initial threshold identification. The committee prepared summaries of 45 SSc cases, with a concentration of cases that were difficult to classify. These were presented to 22 SSc experts who classified the cases as definite SSc or not. The draft classification system derived from the multicriteria decision analysis was applied to the 45 cases, resulting in a score for each case. The ranking of cases by the SSc experts and the ranking of cases based on the scores provided with the draft scoring system were examined. Higher scores in the scoring system were expected to relate to a higher probability that the experts would classify the case as SSc. Using these results, an initial threshold score for SSc was identified.

Reduction and testing of iterative changes. In the next step, the committee reduced the number of items, simplified the weights, and modified the threshold score. First, data on the candidate items were prospectively collected at 13 SSc centers in North America and 10 in Europe, using standardized case record forms. Data from 368 consecutive patients with SSc (diagnosis based on physician opinion) were collected, of whom half were to have had SSc for a maximum of 2 years (based on the time from the first non-Raynaud's symptom) in order to include early SSc. Data from 237 consecutive control patients with a scleroderma-like disorder (eosinophilic fasciitis [also called Shulman's disease or diffuse fasciitis with eosinophilia], scleromyxedema, systemic lupus erythematosus, dermatomyositis, polymyositis, primary Raynaud's phenomenon, mixed connective tissue disease, undifferentiated connective tissue disease, generalized morphea, nephrogenic systemic sclerosis, and diabetic cheiroarthropathy) were also collected. From these 605 patients a random sample of 100 SSc cases and 100 controls (50% from North America and 50% from Europe) was selected to form the derivation sample. The remaining 268 cases and 137 controls formed the validation sample. Institutional research ethics board approval was obtained for the collection of patient data.

The committee then met and made iterative changes to the draft system, which they continually applied in real time to the derivation cohort derived as described above. Using the derivation cohort, the scoring system was simplified by removing items that occurred with low frequency or were redundant, by aggregating similar items and then transforming the weights to obtain single digits. The preliminary score threshold was adjusted to account for the weight simplification. The impact of all proposed changes was evaluated by assessing changes

to sensitivity and specificity of the criteria in the derivation cohort. The reference standard to test the sensitivity and specificity was the diagnosis by the SSc expert who submitted the case(s) and control(s).

At the same time, the changes in the classification system were also tested in 38 difficult-to-classify cases. Consequently, weights of some items were adjusted to align the scoring system with the reference standard formed by the opinions of the SSc experts as to which cases were to be classified as having SSc.

Validation. The final classification system was independently tested using the validation sample of SSc cases and controls. Sensitivity and specificity were calculated for the 1980 ACR preliminary classification criteria for SSc (3), the classification criteria proposed by LeRoy and Medsger in 2001 (6), and the newly developed classification criteria. Exact binomial confidence limits were calculated for sensitivity and specificity. The ACR criteria and LeRoy/Medsger criteria were compared with the new criteria using 2×2 tables with McNemar's chi-square test and continuity correction. The criteria sets were also tested separately using only the subgroup of patients with a disease duration of ≤ 3 years. Further, the classification system was validated against the expert consensus on the set of 38 selected cases.

Results

Draft classification system. The experts concluded that "skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints" was sufficient to classify a subject as having SSc. Further, patients with "skin thickening sparing the fingers" are classified as not having SSc. It was agreed that the criteria should be applied to any patient considered for inclusion in an SSc study, without further specifications. Items with relatively low weights were deleted, and items considered to be from a similar domain were clustered (e.g., fingertip lesions encompasses ulcers and pitting scars; lung involvement encompasses interstitial lung disease and pulmonary hypertension). Using conjoint analysis, the number of items was reduced from 23 to 14 and all items were assigned weights. The 14 resulting items (with weights) were as follows: bilateral skin thickening of the fingers (sclerodactyly) (weighted 14 if distal to a proximal interphalangeal joint only, 22 if whole finger), puffy fingers (weighted 5), fingertip lesions (weighted 16 if pitting scars or 9 if digital ulcers), finger flexion contractures (weighted 16), telangiectasia (weighted 10), abnormal nailfold capillaries (weighted 10), calcinosis (weighted 12), Raynaud's phenomenon (weighted 13), tendon or bursal friction rubs (weighted 21), interstitial lung disease/pulmonary fibrosis (weighted 14), pulmonary arterial hypertension (weighted 12), scleroderma renal crisis (weighted 11), esophageal dilation (weighted 7), and SSc-related auto-antibodies (weighted 15 if anticentromere antibody pres-

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (<i>sufficient criterion</i>)	–	9
Skin thickening of the fingers (<i>only count the higher score</i>)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (<i>only count the higher score</i>)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease (<i>maximum score is 2</i>)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) (<i>maximum score is 3</i>)	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥ 9 are classified as having definite SSc.

Table 2. Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits—a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of “Velcro” crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase color change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
SSc-related autoantibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti-topoisomerase I antibody (also known as anti-Scl-70 antibody), or anti-RNA polymerase III antibody. Positive according to local laboratory standards.

Table 3. Characteristics of the derivation sample and the validation sample*

Item	Derivation sample			Validation sample		
	SSc (n = 100)	Scleroderma- like disorder (n = 100)	P	SSc (n = 268)	Scleroderma- like disorder (n = 137)	P
Age, mean ± SD years	55 ± 13	51 ± 15	0.05	54 ± 13	52 ± 15	0.17
Female	86 (86)	79 (79)	0.25	221 (83)	101 (75)	0.08
Region						
North America	50	50	–	191 (68)	91 (32)	–
Europe	50	50	–	77 (63)	46 (37)	0.32
Time since onset of Raynaud's phenomenon, median (IQR) years	13 (7–18)	12 (4–18)	0.42	9 (5–18)	10 (4–22)	0.40
Time since first non-Raynaud's symptom, median (IQR) years	10 (4–13)	9 (2–14)	0.58	7 (3–12)	7 (3–15)	0.89
Time since diagnosis, median (IQR) years	8 (3–12)	6 (1–9)	0.10	5 (2–11)	4 (1–7)	0.016
Scleroderma-like disorders						
Systemic lupus erythematosus	–	28 (28)	–	–	32 (23)	–
Polymyositis/dermatomyositis	–	23 (23)	–	–	21 (15)	–
Primary Raynaud's phenomenon	–	19 (19)	–	–	7 (5)	–
Mixed connective tissue disease	–	9 (9)	–	–	14 (10)	–
Undifferentiated connective tissue disease	–	8 (8)	–	–	17 (12)	–
Eosinophilic fasciitis	–	6 (6)	–	–	16 (12)	–
Nephrogenic sclerosing fibrosis	–	3 (3)	–	–	3 (2)	–
Generalized morphea	–	5 (5)	–	–	8 (6)	–
Scleromyxedema	–	1 (1)	–	–	3 (2)	–
Graft-versus-host disease	–	3 (3)	–	–	3 (2)	–
Other diagnoses	–	8 (8)	–	–	13 (9)	–
Manifestations†						
Raynaud's phenomenon	91 (91)	49 (49)	<0.0001	257 (96)	63 (46)	<0.0001
Autoantibodies	68 (68)	7 (7)	<0.0001	137 (51)	15 (11)	<0.0001
Anticentromere antibody	33 (33)	5 (5)	<0.0001	41 (15)	8 (6)	0.0057
Anti-topoisomerase-I	34 (34)	1 (1)	<0.0001	69 (26)	7 (5)	<0.0001
Anti-RNA polymerase III	2 (2)	1 (1)	1.0	27 (10)	0	<0.0001
Puffy fingers	61 (61)	17 (17)	<0.0001	169 (63)	24 (18)	<0.0001
Abnormal nailfold capillaries	54 (54)	24 (24)	<0.0001	146 (54)	51 (37)	0.0010
Dilated vessels	37 (37)	28 (28)	0.08	124 (46)	34 (25)	0.0080
Avascular areas	21 (21)	11 (11)	0.08	86 (32)	9 (7)	<0.0001
Hemorrhages	12 (12)	9 (9)	0.64	63 (24)	8 (6)	<0.0001
Digital tip ulcers	53 (53)	8 (8)	<0.0001	108 (40)	12 (9)	<0.0001
Pitting scars	53 (53)	5 (5)	<0.0001	105 (39)	5 (4)	<0.0001
PAH or ILD	48 (48)	14 (14)	<0.0001	138 (52)	14 (10)	<0.0001
PAH	44 (44)	10 (10)	<0.0001	20 (7)	2 (1)	0.012
ILD	12 (12)	4 (4)	0.037	131 (49)	12 (9)	<0.0001
Telangiectasia	35 (35)	10 (10)	<0.0001	68 (25)	13 (9)	0.0002
Skin thickening of fingers proximal to MCP joints	26 (26)	1 (1)	<0.0001	105 (39)	6 (4)	<0.0001
Skin thickening of fingers distal to MCP joints	5 (5)	38 (38)	<0.0001	178 (66)	24 (18)	<0.0001

* Data were prospectively collected on 605 consecutive patients with systemic sclerosis (SSc) or a scleroderma-like disorder (see Methods); half of the SSc patients at each site were to have early SSc. A random sample of 100 SSc cases and 100 controls, 50% from North America and 50% from Europe, was selected to form the derivation sample, and the remaining patients formed the validation sample. Except where indicated otherwise, values are the number (%). IQR = interquartile range; PAH = pulmonary arterial hypertension; ILD = interstitial lung disease; MCP = metacarpophalangeal.

† Listed in order of frequency of occurrence in the SSc derivation sample.

ent, anticentromere pattern seen on antinuclear antibody testing, or anti-topoisomerase I [also called anti-Scl-70] or anti-RNA polymerase III present).

Initial threshold identification. Comparison of the case ranking from the scoring system and by the experts revealed that most of the experts ($\geq 75\%$) considered the cases with a score of >55 (except for 1 case)

to be SSc. Similarly, most experts ($\geq 88\%$) considered cases with a score of <40 not to be SSc. With scores between 40 and 55 there was more diversity of opinion. Thus, it was concluded that the initial threshold would be a score of ≥ 56 .

Reduction and testing of iterative changes. The 14 items in the scoring system were reduced to 9 while

Table 4. Sensitivity and specificity of the 2013 SSc classification criteria and previous SSc classification criteria, overall and in early SSc*

	Derivation sample (n = 200)		Validation sample (n = 405)		Validation sample, disease duration ≤3 years (n = 100)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1980 ACR SSc criteria	0.80 (0.72–0.87)	0.77 (0.68–0.84)	0.75 (0.70–0.80)	0.72 (0.64–0.79)	0.75 (0.70–0.80)	0.72 (0.63–0.79)
2001 LeRoy/Medsger SSc criteria	0.76 (0.68–0.84)	0.69 (0.68–0.84)	0.75 (0.70–0.80)	0.78 (0.70–0.85)	0.80 (0.69–0.88)	0.76 (0.53–0.92)
2013 ACR/EULAR SSc criteria	0.95 (0.90–0.98)	0.93 (0.86–0.97)	0.91 (0.87–0.94)	0.92 (0.86–0.96)	0.91 (0.83–0.96)	0.90 (0.70–0.99)

* SSc = systemic sclerosis; 95% CI = 95% confidence interval; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.

maintaining sensitivity and specificity in the derivation sample. The items deleted were finger flexion contractures, calcinosis, tendon or bursal friction rubs, renal crisis, and esophageal dilation. Puffy fingers and sclerodactyly were combined into one item, and pulmonary arterial hypertension and interstitial lung disease were also combined into one item, resulting in 7 items for the scoring system. In the derivation sample, with reduction of the 14 items to 7, the sensitivity and specificity were 0.93 and 0.94, respectively. Weights were simplified by dividing each weight by 5 and rounding to the nearest integer. The threshold for this simplified scoring system was determined to be 9. The resulting sensitivity and specificity were 0.97 and 0.88, respectively.

Weights were further adjusted to align the scoring system with the experts' opinions (SSc or not SSc) on each of the 38 difficult-to-classify cases. To improve the specificity of the classification criteria, an exclusionary criterion was added: patients with a diagnosis that better explains their manifestations should not be classified as having SSc. These revisions resulted in the correct classification of all patient profiles judged to have SSc by the majority of experts.

The SSc classification criteria. The new classification criteria are presented in Table 1. The table shows the 1 criterion that, if present, is sufficient for classification as SSc, the 2 exclusionary criteria, and the 7 items with a combined threshold above which cases are classified as SSc. The classification criteria may be applied to patients who may have SSc and are being considered for inclusion in an SSc study. As noted above, they are *not to be applied* to patients who have a scleroderma-like disorder that better explains their manifestations; and patients with “*skin thickening sparing the fingers*” are not classified as having SSc.

If a patient has skin thickening of the fingers of both hands that extends proximal to the metacarpo-

phalangeal joints, the classification system assigns 9 points for this one item alone, which is sufficient to classify the patient as having SSc with no further application of the point system needed. Otherwise, the point system is applied by adding the scores for manifestations that are “positive.” The items are skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nail-fold capillaries, pulmonary arterial hypertension and/or interstitial lung disease, Raynaud's phenomenon, and SSc-related autoantibodies. Two items, skin thickening of the fingers and fingertip lesions, include 2 different possible manifestations. If a patient has both manifestations, the score for the category is the higher score of the 2 manifestations. For example, in the item skin thickening of the fingers, if a patient has both manifestations, i.e., puffy fingers (weighted 2) and sclerodactyly (weighted 4), the total score for the item would be 4. The maximum possible score is 19, and patients with a score of ≥9 are classified as having SSc. The definitions of the items used in the criteria are provided in Table 2.

Validation. Table 3 shows the characteristics of the validation sample (268 patients with SSc, 137 controls). The sensitivity and specificity of the new SSc classification criteria were compared with those of the 1980 ACR classification criteria and the classification criteria proposed by LeRoy and Medsger, and the results are shown in Table 4. The sensitivity and specificity of the new SSc criteria were, respectively, 0.91 and 0.92 in the validation sample. The new criteria performed better than the 2 earlier classification schemes in terms of sensitivity and specificity ($P = 0.01$ versus the 1980 ACR criteria, $P = 0.004$ versus the LeRoy/Medsger criteria). The area under the receiver operating characteristic curve of the classification system tested against presence of SSc in the validation sample was 0.81 (95% confidence interval 0.77–0.85). The performance of the new criteria in patients with disease of ≤3 years' duration

Table 5. Expert consensus versus classification systems for selected case profiles*

No.	Skin thickening of the fingers	Fingertips	Telangiectasia	Abnormal nailfold capillaries	Puffy fingers	Raynaud's phenomenon	ILD/pulmonary fibrosis	PAH	SSc-related autoantibodies	Classified as SSc	Score	1980 ACR criteria fulfilled	No. of experts agreeing (n = 16)
1	Whole finger	Pitting scars	-	Yes	Yes	Yes	-	Yes	Yes	Yes	17	Yes	16
2	Whole finger	Pitting scars	-	-	Yes	Yes	Yes	-	Yes	Yes	15	Yes	16
3	Whole finger	Pitting scars	-	-	Yes	Yes	-	-	Yes	Yes	13	Yes	16
4	Whole finger	Pitting scars	Yes	Yes	-	Yes	-	-	-	Yes	12	Yes	15
5	Whole finger	-	-	Yes	Yes	Yes	-	-	Yes	Yes	12	No	15
6	Whole finger	-	-	Yes	-	Yes	-	-	-	Yes	11	No	10
7	-	Pitting scars	-	-	Yes	Yes	Yes	-	-	Yes	10	?	NA
8	-	Ulcers	-	-	-	Yes	Yes	-	Yes	Yes	10	No	14
9	-	-	-	Yes	-	Yes	Yes	-	Yes	Yes	10	No	NA
10	-	-	-	Yes	Yes	Yes	-	-	Yes	Yes	10	No	NA
11	-	Ulcers	-	-	Yes	Yes	-	-	Yes	Yes	10	No	NA
12	-	-	-	Yes	Yes	Yes	-	-	Yes	Yes	10	No	NA
13	Whole finger	-	-	-	Yes	Yes	-	-	Yes	Yes	10	No	15
14	Whole finger	-	-	-	-	Yes	-	-	Yes	Yes	10	No	NA
15	Whole finger	-	-	Yes	-	Yes	-	-	-	Yes	9	No	NA
16	Whole finger	-	Yes	-	Yes	Yes	-	-	-	Yes	9	No	NA
17	Whole finger	Ulcers	-	-	Yes	Yes	-	-	-	Yes	9	No	NA
18	Whole finger	-	-	Yes	-	Yes	-	-	-	Yes	9	No	NA
19	Whole finger	-	-	Yes	Yes	Yes	-	-	-	Yes	9	No	9
20	Whole finger	-	-	Yes	-	Yes	-	-	-	Yes	9	No	NA
21	-	Pitting scars	-	-	-	Yes	Yes	-	-	No	8	?	NA
22	-	-	-	-	Yes	Yes	-	-	Yes	No	8	No	NA
23	-	Pitting scars	-	Yes	-	Yes	-	-	-	No	8	No	4
24	-	Pitting scars	Yes	-	-	Yes	-	-	-	No	8	No	2
25	-	-	-	Yes	-	Yes	-	-	Yes	No	8	No	NA
26	-	-	-	-	Yes	Yes	Yes	-	-	No	7	No	NA
27	-	-	-	Yes	Yes	Yes	-	-	-	No	7	No	NA
28	Distal to PIP joints	-	-	Yes	Yes	Yes	-	-	-	No	7	No	5
29	-	-	-	Yes	-	Yes	Yes	-	-	No	7	No	NA
30	Whole finger	-	-	-	-	Yes	-	-	-	No	7	No	NA
31	Whole finger	-	Yes	-	Yes	-	-	-	-	No	6	No	NA
32	Distal to PIP joints	-	-	-	-	Yes	-	-	Yes	No	6	No	8
33	-	-	-	-	-	Yes	-	-	Yes	No	6	No	0
34	-	-	-	-	-	-	Yes	-	Yes	No	5	No	NA
35	-	-	-	-	-	Yes	-	Yes	-	No	5	No	0
36	-	-	-	Yes	-	Yes	-	-	-	No	5	No	1
37	-	-	-	Yes	-	-	-	-	Yes	No	5	No	0
38	-	-	-	Yes	-	-	-	-	-	No	2	No	0

* Profiles of 38 cases with likely systemic sclerosis (SSc) or an SSc-like disorder, with presence or absence of the manifestations in the newly developed American College of Rheumatology (ACR)/European League Against Rheumatism SSc classification criteria, are shown. The cases are listed in order of the points awarded using the classification system (Score column) and are classified as SSc if the score is ≥ 9 . For 18 of the cases, the number of experts agreeing that the case had SSc is shown. None of the cases had skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (the single criteria that, if present, immediately classifies the individual as having SSc). Whole finger is sclerodactyly of the entire finger but not proximal to the metacarpophalangeal joints. ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; ? = inconclusive; NA = not applicable (experts were not asked); PIP = proximal interphalangeal.

was similar to the performance in the group overall (Table 4).

The classification system was additionally tested against expert opinion (n = 16 experts), using the set of 38 selected cases (Table 5). All of the cases scoring ≥ 9 were considered SSc, whereas cases scoring < 9 were regarded as not being SSc or were controversial. With the proposed system all of these cases were classified in accordance with consensus-based expert opinion. All cases that were classified as SSc with the 1980 ACR criteria were also classified as SSc with the new criteria, as were several cases not classified as SSc with the 1980 ACR criteria.

Discussion

A classification system for systemic sclerosis is needed to ensure that all patients categorized as having SSc for inclusion in studies do indeed have the disease, based on specific defined characteristics. The major reason to revise the 1980 ACR criteria was that those criteria lacked adequate sensitivity, especially in patients with early SSc or with limited cutaneous SSc (9,10,18). The proposed classification criteria are superior and exhibit greater sensitivity and specificity compared to the 1980 criteria and the classification criteria proposed

by LeRoy and Medsger. All profiles of patients who were considered to have SSc by a majority of experts were indeed classified as SSc with the new classification system, and the new system is more inclusive and also performs well in patients with early disease (≤ 3 years since diagnosis).

The newly developed classification system includes disease manifestations of the 3 hallmarks of SSc: fibrosis of the skin and/or internal organs, production of certain autoantibodies, and vasculopathy. The 4 items comprising the 1980 ACR classification criteria (scleroderma proximal to the metacarpophalangeal joints, sclerodactyly, digital pitting scars [not pulp loss], and bilateral basilar pulmonary fibrosis) (3) are also included, as are the items in the criteria proposed in 2001 by LeRoy and Medsger (Raynaud's phenomenon, autoantibodies, nailfold capillaroscopy abnormalities, skin fibrosis) (6).

The new criteria include 1 criterion that alone is sufficient for classification as SSc: skin thickening of the fingers extending proximal to the metacarpophalangeal joints, which is similar to the 1980 criteria. If the single sufficient criterion is not fulfilled, the point system is applied and patients with a score of ≥ 9 are classified as having SSc. All items in the classification criteria represent measurements that are performed in routine clinical practice. The criteria are meant for inclusion of SSc patients in studies, not for SSc diagnosis. Although the list of items in the classification criteria mimics the list of items one usually uses for diagnosis, in practice the diagnosis of SSc may also be informed by items not included in the classification criteria, such as tendon friction rubs, calcinosis, and dysphagia. Consequently, patients *classified* as having SSc are a subset of patients being *diagnosed* as having SSc, with diagnosis being more sensitive. Ideally, there would be no difference between diagnosis and classification criteria.

As intended, the new classification system incorporates the considerable advances made in the diagnosis of SSc. It includes the concept of specific serum autoantibodies such as anti-topoisomerase I, anticentromere, and anti-RNA polymerase III (15,23). There is the possibility that testing for additional SSc autoantibodies, such as anti-Th/To, anti-U3 RNP, and others, may become more widely available. The criteria also acknowledge the value of magnified nailfold visualization in the diagnosis of SSc (14,15). Although capillaroscopy can be performed with highly specialized equipment such as videocapillaroscopy cameras, simple in-office ophthalmoscopes or dermatoscopes suffice for distinguishing between normal and abnormal nailfold

capillaries (24,25). Capillaroscopy is now widely used, and considering the value of magnified nailfold visualization in the diagnosis and management of SSc, these new criteria may encourage acquisition of this skill by physicians caring for SSc patients. Likewise, criteria for pulmonary artery hypertension have changed over the years. The ACR/EULAR committee recognizes this, and the diagnosis of pulmonary artery hypertension should be based on the most recent accepted criteria from right-sided heart catheterization.

Several items that are useful for recognizing SSc in clinical practice, such as calcinosis, flexion contractures of the fingers, tendon or bursal friction rubs, renal crisis, esophageal dilatation, and dysphagia are not included in the criteria. These were considered but did not substantially improve sensitivity or specificity. For example, renal crisis is a strong indicator of SSc, but its low frequency of occurrence makes it less useful for the purpose of classification (20). The committee considered a non-point-based additive system (8), such as the ACR systemic lupus erythematosus criteria (26) or the 1980 ACR SSc criteria. We concluded, however, that assigning weights yielded superior results for SSc classification. Indeed, the weights were simplified to single-digit numbers to make the system easy to use even in the absence of a computing device. Similar weighted systems have been used for other rheumatic diseases (27). The committee also decided not to include "probable" or "possible" SSc in the classification.

Examples of profiles not captured by the 1980 ACR criteria that fulfilled the new classification criteria are combinations of skin thickening of the whole finger, SSc-related autoantibodies, and pulmonary arterial hypertension and/or Raynaud's phenomenon. A patient with Raynaud's phenomenon, autoantibodies, and abnormal nailfold capillaries is not classified as having SSc, although such a patient may develop SSc over subsequent years (6,15).

Patients may have disease manifestations similar to those of SSc that are better explained by another well-defined disorder, such as nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, porphyria, lichen sclerosis, graft-versus-host disease, or diabetic cheiroarthropathy. We decided it was not necessary to develop criteria that differentiated SSc specifically from these conditions. Patients with some of these diseases were included in the validation cohort of patients with SSc-like disorders, and it is possible that specificity may have been slightly higher had they been excluded.

In developing the revised SSc classification crite-

ria, we followed the recommendations and guidelines of the ACR and EULAR, which included 1) collaboration between clinical experts and clinical epidemiologists in criteria development, 2) evaluation of the psychometric properties of each candidate criterion, and 3) description of the test sample (origin of the patients and control subjects) (7,28). Ideally, phases of criteria development should have a balance between expert opinion and data-driven methods; yet, there should be avoidance of circularity of reasoning (a bias that can occur when the same experts developing the criteria are the ones contributing cases and comparison patients) (29). We included different experts at different steps in the development of the SSc criteria, to avoid circularity.

Testing and validating a classification system for SSc is difficult because there is no gold standard for defining a particular case as SSc; that is, there is no incontrovertible test or criterion. We relied on expert opinion for our gold standard, which is similar to the process used in the development of other criteria (8).

In the absence of a gold standard, we developed and tested the proposed classification system against two standards of expert opinion: 1) the opinion of the clinician who selected cases for the North American and European derivation and validation cohorts, and 2) the combined opinion of a group of clinical experts in SSc. Both standards have strengths and weaknesses. Each individual clinician who selected cases had access to information that could have included aspects not captured by the forms, which were restricted to 23 particular manifestations. Data were obtained from several sites in Europe and North America, so this should improve generalizability and reduce selection bias. However, it is possible that other expert clinicians may have had a different opinion about particular cases. The consensus opinion of a group of experts who had the opportunity to discuss controversial cases strengthens the combined expert opinion. However, the group may not have been aware of some relevant information not included in the available data. It is also difficult for a group of experts to consider hundreds of cases in depth; however, this was managed by having the group consider in depth only those cases, or combinations of items, that appeared to be controversial. In this way, the expert group was able to form a consensus over the whole range of cases in the database. A key strength of the present work is the use of both standards for testing and validation of the proposed system.

The approach we used has other strengths and limitations as well. The methodology was state of the art, with validation by data and by expert opinion at every

step. Various methods used in the development process have already been described (19,20). The criteria have face validity, because the items are routinely assessed in daily clinical practice and also were included in other important SSc classification criteria sets. The criteria allow for new developments in e.g., autoantibody testing availability and/or new identification of scleroderma-associated autoantibodies, or assessment of nailfold capillaries. Formal conjoint analysis to derive the weights associated with items improved the sensitivity and specificity of the items, as was found also in the development of the recent ACR/EULAR criteria for the classification of rheumatoid arthritis (30).

The criteria have not been validated in ethnic groups that are not common in North America and Europe. This will require further studies. Regarding clinical use, the number of items and weights may not be easy to remember, but wide availability and (electronic) applications can be developed. The SSc classification criteria steering committee and the expert consultants agreed that the criteria could allow for classification of patients with another rheumatic disease as also having SSc (e.g., having both systemic lupus erythematosus and SSc, or rheumatoid arthritis and SSc, etc.). Although this is a possible limitation, it permits individual researchers to decide whether to include subjects who fulfill criteria for more than one rheumatic disease in any particular study.

Conclusions

The ACR/EULAR classification criteria for SSc perform better than 1980 ACR preliminary criteria in terms of both sensitivity and specificity. They are relatively simple to apply to individual subjects. These criteria may be endorsed as inclusion criteria for SSc studies. Validation in other populations is encouraged.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Van den Hoogen and Pope had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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