NEW CLASSIFICATION CRITERIA: why, rules and presentation of new criteria

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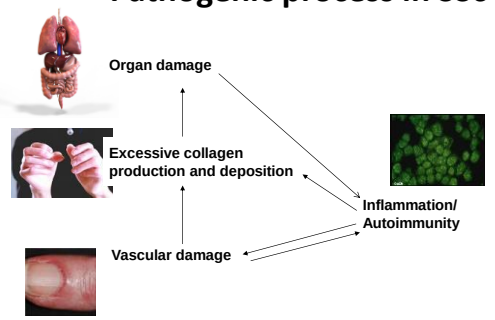
DISCLOSURES

None

Systemic Sclerosis

- **Rare disease:** **prevalence 1 in 10.000**
- **Clinical symptoms:** **heterogeneous**
  non specific ↔ more specific
- **Main symptom:** **thickened skin**

Pathogenic process in SSc



Diagnosis & Classification

- **No single diagnostic test for systemic sclerosis**
- **Recognition of SSc as a syndrome-type disease**
  - **Easy if fully developed**
  - **Difficult if early in disease process**
- **<u>Diagnosis</u> for treating and preventing an illness, and educating the patient**
- **<u>Classification</u> for inclusion in studies → classification criteria**

Disease classification criteria

- **Help to distinguish patients with the disease from those without the disease**
- **With the purpose of including patients with a similar clinical entity for clinical (observational, experimental) studies.**
- **Help to ensure that the same disease entity is consistently studied**

ACR, Arthritis Care Res. 2006;55(3)348-352

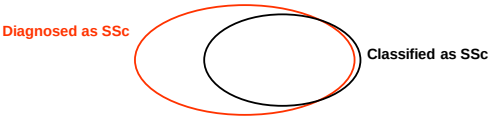
Disease classification criteria

- Help to distinguish patients with the disease from those without the disease
- With the purpose of including patients with a similar clinical entity for clinical (observational, experimental) studies.
- Help to ensure that the same disease entity is consistently studied
- **Are generally not described as diagnostic criteria**
- **Will almost always mirror the list of criteria that one uses for diagnosis**

ACR, Arthritis Care Res. 2006;55(3)348-352

Disease classification criteria

- **Conclusions from clinical studies using classification criteria should apply to patients with the diagnosis**



Ideally: classification and diagnostic criteria should be the same

1980 ACR Preliminary criteria for the classification of SSc

Major criterium: **- proximal scleroderma**

Minor criteria: **- pulmonary fibrosis on chest X-ray**
- sclerodactyly
- digital ulcers or pitting scars

The major criterion *or* 2 of the minors = 'systemic sclerosis'

Developed in patients with definite and mostly diffuse SSc

Arthritis Rheum. 1980;23(5):581-90

What are the limitations of ACR classification criteria for SSc?

1. **They don't always classify *early* SSc**
2. **They don't classify some of those with *limited* cutaneous SSc**
3. **They don't include *antibodies* that are common in SSc such as anti-centromere**
4. **They don't include *nailfold changes* that could help differentiate SSc from primary Raynaud's phenomenon**

Early SSc classification criteria

lSSc	**Raynaud's obj**	
	+ any one	*SSc-type nailfold capillary pattern*
		SSc-selective autoantibodies
	or	
	Raynaud's subj	
	+ both	*SSc-type nailfold capillary pattern*
		SSc-selective autoantibodies
lcSSc	Criteria for lSSc +	Distal cutaneous changes
dcSSc	Criteria for lSSc +	Proximal cutaneous changes

Leroy and Medsger J Rheumatol 2001;28:1573-1576.

ACR – EULAR task force

ACR		EULAR
Janet Pope	**(co-convenors)**	**Frank van den Hoogen**
Dinesh Khanna		**Jaap Fransen**
Sindhu Johnson		**Alan Tyndall**
Murray Baron		**Marco Matucci-Cerenic**

Goal of the Project

To develop SSc classification criteria

- **jointly by ACR and EULAR**
- **to enable identification of individuals with SSc for inclusion in clinical studies,**
- **being more sensitive and specific than previous criteria**

Prerequisites

1) **Classify SSc patients in early and in late stage of disease**
2) **Include vascular, immunologic and fibrotic manifestations of SSc**
3) **Feasible to use in clinical practice**
4) **In accordance with the way diagnosis is made in clinical practice**

Procedures

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 55, No. 3, June 15, 2006, pp 348–352
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EDITORIAL

Development of Classification and Response Criteria for Rheumatic Diseases

CLASSIFICATION AND RESPONSE CRITERIA SUBCOMMITTEE OF THE AMERICAN COLLEGE OF RHEUMATOLOGY COMMITTEE ON QUALITY MEASURES

EULAR REPORT

Ann Rheum Dis 2004;63:1172–1176. doi: 10.1136/ard.2004.023697

EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees

Methods overview

1) **Item collection**
2) **Item reduction, ranking and 'assembling'**
3) **Criteria validation**

Combination of expert opinion and data-driven methodology

- **Renewed Delphi exercise, using data from two recent Delphi exercises by EUSTAR and SCTC**
- **Data-driven data reduction methods**
- **Classification of 'paper' patients by experts**
- **Testing of criteria using expert opinion with Conjoint analysis**
- **Testing of criteria in datasets with SSc patients and 'controls'**

North American (17) and European (18) experts

Tom Medsger
Jim Seibold
Dan Furst
Phil Clements
Dave Collier
Mary Ellen Csuka
Peter Merkel
Virginia Steen
Lorinda Chung
Vivian Hsu
Sergio Jimenez
Bashar Kahaleh
Maureen Mayes
Richard Silver
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Gabriele Valentini
Laszlo Czirjak
Madelon Vonk
Murat Inanc
Otylia Kowal-Bielecka
Patricia Carreira
Ulf Mueller-Ladner
Ulrich Walker
Yannick Allanore
Oliver Distler
Armando Gabrielli
Jaap van Laar
Serena Guiducci
Ariane Herrick
Stanislaw Sierakowski

Item collection: Delphi

Two Delphi exercises were used

- **SCTC**
- **EUSTAR**

Revealed 168 items (!)

Web-based Delphi rounds to reveal appropriate items

Item reduction: Delphi and Nominal Group Technique

	Item	Appropriateness score		Item	Appropriateness score
1.	Presence of scleroderma	9	13.	Calcinosis	7
2.	Positive antI-topo I	9	14.	Telangiectasia	6
3.	Positive anticentromere	9	15.	Puffy fingers	6
4.	Positive anti-RNA polymerase III	9	16.	Pulm. Art. hypertension	6
5.	Abnormal nailfold pattern	8	17.	Positive ANA	5
6.	Fingertip ulcers / scars	8	18.	Contractures fingers	5
7.	Renal crisis	7	19.	Positive anti-Pm-Scl	5
8.	Raynaud's phenomenon	7	20.	Reduced FVC	5
9.	Interstitial lung disease/fibrosis	7	21.	Reduced DL_{CO}	4
10.	Tendon or bursal friction rubs	7	22.	Gastro-intestinal reflux	4
11.	Fingertip pulp loss/acreosteolysis	7	23.	Dysphagia	4
12.	Esophageal dilatation (X-ray/CT)	7			

Fransen J, Johnson SR, van den Hoogen F, et al. Arthritis Care Res 2012;64:351–7.

Item reduction: Decision analysis

- The overall ranking and weighting of the items is arrived at using a **1000Minds** Algorithm.
- Decision makers are asked series of simple questions involving ***tradeoffs between 2 items at a time***… (The number of questions asked is as small as possible.)

Which patient ('left' or 'right') is more likely to have Systemic Sclerosis, (given they are identical in all other aspects)

Left		Right
Raynaud's positive Nailfolds negative	OR	Raynaud's negative Nailfolds positive
This one	They're equal	This one

Assembling: first results

Items	Subitems	Score
1. Skin thickening fingers (*count only one*)	distal to pip only	14
	whole finger, distal to MCP	22
2. Finger tip lesions (*count only one*)	digital tip ulcers	9
	pitting scars	16
	evidence of acroosteolysis	21
3. Finger flexion contractures		16
4. Telangiectasia		10
5. Abnormal nailfold pattern		10
6. Puffy fingers		5
7. Calcinosis		12
8. Raynaud's phenomenon		13
9. Tendon or bursal friction rubs		21
10. Interst. lung disease or pulm. fibrosis		14
11. Pulmonary arterial hypertension		11
12. Renal crisis		11
13. Esopageal dilatation		7
14. Scleroderma related autoantibodies		15

Assembling and validation

The 14 items were tested in:

- **Paper cases**
- **Derivation cohort: prospectively collected data of**
  - **100 SSc patients**
  - **100 SSc-like controls**
- **Minor adaptions**

Classification system tested in:

- **Validation cohort: prospectively collected data of**
  - **268 SSc patients**
  - **137 SSc-like controls**

ACR - EULAR SSc classification criteria

Item	Sub-items	Weight/score
Skin thickening of the fingers of both hands extending proximal to MCP joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the MCP joints, proximal to the PIP joints	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcer	2
	Fingertip pitting scar	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lungdisease	-	2
Raynaud's phenomenon	-	3
SSc-related auto-antibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III)	-	3
Add to maximum weight in each category to calculate the total score **Patients having a total score of 9 or more are being classified as having definitive systemic sclerosis**		

ACR-EULAR SSc classification criteria

1. **Applicable** to any patient considered for inclusion in a SSc study

2. **Not applicable** to:

   - Patients having a ***systemic sclerosis-like disorder better explaining*** their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy.

   - Patients with '***Skin thickening sparing the fingers'***

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 reasons such as inflammatory dactylitis.
Finger tip ulcers or pitting scars	Ulcers or scars distal to or at the PIP 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	Telangiectasia(e) in a scleroderma like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or large matt-like telangiectasia(e). Telangiectasiae are visible macular dilated superficial blood vessels; which collapse upon pressure and fill slowly when pressure is released; distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with SSc	Enlarged capillaries and/or capillary loss with or without peri-capillary hemorrhages at the nailfold and may be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis on HRCT or chest radiograph, most pronounced in the basilar portions of the lungs, or presence of 'Velcro' crackles on auscultation not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self report or reported by a physician with at least a two-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.
Scleroderma specific antibodies	Anti-centromere antibody or centromere pattern on antinuclear antibody (ANA) testing; anti-topoisomerase I antibody (also known as anti-Scl70 antibody); or anti-RNA polymerase III antibody. Positive according to local laboratory standards.

Performance: in SSc cases and controls

	Validation sample (N=405)	
	Sensitivity (95% CI)	Specificity (95% CI)
1980 ACR SSc Criteria	0.75 (0.70, 0.80)	0.72 (0.64, 0.79)
2001 LeRoy and Medsger criteria	0.75 (0.70, 0.80)	0.78 (0.70, 0.85)
2013 ACR-EULAR SSc Criteria	**0.91** (0.87, 0.94)	**0.92** (0.86, 0.96)

Performance: in SSc cases and controls

	Validation sample (N=405)		Validation sample ≤ 3 years disease duration (N=100)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1980 ACR SSc Criteria	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 and Medsger criteria	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	0.91 (0.87, 0.94)	0.92 (0.86, 0.96)	**0.91** (0.83, 0.96)	**0.90** (0.70, 0.99)

Conclusions

The ACR-EULAR classification criteria for SSc:

- **Perform better than the 1980 ACR criteria**
  - **Include more patients with early SSc**
  - **Good sensitivity and specificity**
- **Are relatively simple to apply to individual subjects**
- **Are ACR-EULAR endorsed for inclusion of patients with 'definite' SSc in studies**

Validation in other cohorts is encouraged

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