

Session 1: Management and Assessment of Newly Diagnosed SSc

S.1.2

NEW EULAR/ACR CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS IN CLINICAL PRACTICE

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Background. ARA/ACR classification criteria for systemic sclerosis (SSc) developed in 1980 lack sensitivity for early and mild SSc patients. Therefore, the EULAR/ACR committee developed new classification criteria for SSc with higher sensitivity. Their applicability in clinical practice and in patients with early/mild SSc remains to be shown.

Objective. To evaluate the performance of the new classification criteria for SSc in clinical practice in a cohort of patients with early and mild disease.

Methods. Consecutive patients with a clinical diagnosis of SSc were prospectively recruited and assessed according to EUSTAR and VEDOSS recommendations. Diagnosis of SSc was based on the evaluation of two experienced experts from this tertiary scleroderma center. Patients fulfilling the old criteria were classified as "established SSc", and patients not fulfilling the old criteria were classified as early/mild SSc. Next, the new EULAR/ACR criteria were applied and patients with a total score of 9 or more were classified as definite SSc patients. The score for each patient was calculated automatically from the local database using Excel. In some patients, missing values were retrieved retrospectively from the patients' records. Baseline characteristics were statistically analyzed using Graph Pad Prism and standard descriptive statistics.

Results. The final data set for the analysis consisted of 314 patients. Two patients were excluded due to missing data on items important for classification, unavailable from the patients' records. Based on fulfillment of the old ARA/ACR criteria, 162/314 (51.6%) had established and 152/314 (48.4%) had early/mild SSc. All 162 patients with established SSc fulfilled also the new EULAR/ACR classification criteria. Their median disease duration was 6 (IQR 3-13) years, there were 132 females/30 males, and 66 diffuse SSc/96 limited SSc patients. The 152 patients (135 females/17 males) with early/mild SSc had disease duration 6 (2-13) years. There was 80/152 (52.6%) patients with early/mild disease who fulfilled the new EULAR/ACR classification criteria with a median score 10 (range 9-21). Remaining 72/152 (47.4%) patients, who didn't fulfill the new EULAR/ACR criteria, had a median score 6 (2-8). Most of these patients had Raynaud's phenomenon (91.1%), pathological capillaroscopy (63.8%) and SSc-autoantibodies (51.4%).

Thus, sensitivity of the new EULAR/ACR classification criteria for the overall cohort was 242/314 (77.1%) compared to 162/314 (51.6%) for the old ACR criteria.

Conclusions. In this prospective, observational cohort with early or mild SSc patients, the new EULAR/ACR classification criteria showed increased sensitivity and classified higher number of patients as definite SSc patients than the old ACR criteria.

S.1.3

2013 CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS AN AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM COLLABORATIVE INITIATIVE

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Background. The 1980 classification criteria for systemic sclerosis (SSc) lack sensitivity in early SSc and limited cutaneous SSc. A joint ACR-EULAR committee was established to develop new classification criteria for SSc.

Methods. Using consensus methods, 23 candidate items were arranged in a multi-criteria 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: a) determining specificity and sensitivity in SSc cases and controls with scleroderma-like disorders; b) validating against the combined view of a group of experts on a set of cases with or without SSc.

Results. Skin thickening of the fingers extending proximal to the MCPs is sufficient to be classified as SSc, if that is not present, seven additive items apply with varying weights for each: skin thickening of the fingers, finger tip 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 0.91 and 0.92 for the new classification criteria and 0.75 and 0.72 for the 1980 ARA classification criteria. All selected cases were classified in accordance with consensus-based expert opinion. All cases classified as SSc by the 1980 ARA criteria were classified 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 ARA Criteria for SSc and should allow for more patients to be classified correctly as SSc.

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as; nephrogenic sclerosing fibrosis, scleroderma diabeticum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthrophy. Patients with [^]Skin thickening sparing the fingers also are not classified as having SSc.

Items	Sub-items	Weight/Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers (<i>only count the highest score</i>)	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions (<i>only count the highest score</i>)	Digital Tip Ulcers	2
	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerase I [anti-Scl 70], anti-RNA polymerase III)		3
Total score [^] :		

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. aAdd the maximum weigh (score) in each category to calculate the total score.

S.1.4

PERFORMANCE OF THE OLD 1980 ACR AND THE NEW ACR-EULAR SYSTEMIC SCLEROSIS (SSC) CLASSIFICATION CRITERIA IN PATIENTS WITH LIMITED CUTANEOUS SSC

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Objective. To analyze the fulfillment of the old ACR1980 and the new ACR-EULAR Preliminary Classification Criteria for Systemic Sclerosis (SSc) in patients with limited cutaneous disease.

Patients and methods. From 1990, all patients with clinical diagnosis of SSc were included in a database containing demographic and clinical information. Patients with limited cutaneous disease were selected. The old ACR1980 and the new ACR-EULAR criteria were applied to the group. Clinical characteristics and survival were compared between patients with or without ACR1980 criteria, using Chi-Square, t test and Cox-proportion regression analysis.

Results. From 404 patients, 283 (70%, 257f, 59±19y) had limited cutaneous disease. All but 4 had Raynaud, 51(18%) lung fibrosis, 34(12%) severe PAH, 280(99%) sclerodactily, 136(48%) scleroderma, 113(40%) ischaemic lesions, 113/219(52%) telangiectasia and 57/212(27%) calcinosis. Capillaroscopic changes were observed in 189/228(83%), ANA in 258(92%), ACA in 137(49%) and aScl70 in 46(16%). Only 184(65%) fulfilled ACR1980 criteria, whereas 260(92%) fulfilled the new ACR-EULAR criteria. Patients not fulfilling the old, but fulfilling the new criteria, presented more frequently PAH ($p=0.05$) and ACA (0.03), but less hand edema ($p=0.01$), joint contractures ($p=0.01$), calcinosis ($p=0.005$), GE reflux ($p=0.003$), lung fibrosis ($p<0.0001$), sclerodactily ($p<0.0001$), ischaemic lesions ($p<0.0001$), ANA ($p=0.008$) and aScl70 ($p<0.0001$). After 12±9 y of follow-up from SSc diagnosis, 63 (22%) patients died, 38 fulfilling and 25 not fulfilling ACR1980 criteria. Due to the greater prevalence of severe PAH in this group, age-adjusted mortality was higher in patients not fulfilling ACR1980 criteria (HR 0.4; 95%CI 0.2-0.9; $p=0.03$).

Conclusions. The new ACR-EULAR criteria for the classification of SSc have much higher sensitivity than the old ACR1980 criteria for patients with limited cutaneous involvement, and allow more patients to be classified. The new criteria would help to diagnose patients with mild limited disease, not fulfilling ACR1980 criteria, but still at risk of developing severe PAH. Since PAH prognosis improves with early diagnosis, these patients might benefit from regular PAH screening, as recommended for all SSc patients.

S.1.5

EARLY ACCRUAL OF ORGAN DAMAGE IN SCLERODERMA: RATIONALE FOR DERIVATION AND VALIDATION OF A DISEASE DAMAGE INDEX IN SYSTEMIC SCLEROSIS

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Background. Unlike some other rheumatological diseases with a relapsing-remitting course, the disease course in systemic sclerosis (SSc; 'scleroderma') is often one of progressive damage in multiple organ systems. There are no validated indices to describe and quantify organ damage in SSc.

Objective. We sought to (i) determine the frequency of organ damage in early disease using preliminary criteria and (ii) develop a protocol for the derivation and validation of a disease damage index (DI) in SSc (SSc-DI). Methods: Part (i) all patients enrolled in the Australian Scleroderma Cohort Study (ASCS) within two years of SSc disease onset were included. Preliminary criteria for organ damage, defined as permanent loss of organ function that prognosticates morbidity

and mortality, were defined by a panel of 6 Australian experts. Frequency and accrual of organ damage at 2, 3, 4 and 5 years following onset were determined. Part (ii) an international multidisciplinary panel of 16 experts prepared a protocol for the derivation and validation of an SSc-DI.

Results. Part (i) 182 patients (81% female, 54% diffuse disease) were recruited into the ASCS within 2 years of disease onset. The frequency and accrual of organ damage from years 2 to 5 are presented in Table I and Figure 1. Using preliminary criteria, damage was seen in all organ systems, but was most common in the skin/musculoskeletal (23.1%), respiratory (12.1%), gastrointestinal (GI; 7.1%) and genitourinary systems (31.4%) at 4 years. Part (ii) the protocol for deriving an SSc-DI is comprised of the following steps: (1) Item generation through systematic review of the literature; (2) Item reduction using a two-step Delphi exercise; (3) Nominal group discussion; (4) Item weighting using regression analysis of data in the ASCS database against the end-points of mortality, physical function and HRQoL. The newly-derived SSc-DI will be externally validated against the same end-points using data from the Canadian Scleroderma Research Group (CSRG) database ('retrospective validation'), and the International SYstemic sclerosis INception Cohort ('prospective validation').

Conclusion. Early accrual of organ damage in SSc forms a compelling rationale for developing a SSc-DI that may be used to systematically quantify permanent loss of organ function in this disease and may serve as an outcome measure in cohort studies and clinical trials. This SSc-DI will be derived using a combination of consensus and data-driven methodology, and externally validated to fulfill the OMERACT criteria.

Table I. Frequency of organ damage at 2 & 4 yrs.

Disease damage indicator	2 years n (%)	4 years n (%)
Skin/Musculoskeletal	21 (11%)	42 (23.1%)
Digital gangrene or amputation	3 (1.6%)	5 (2.7%)
Joint contractures	12 (6.6%)	31 (17.0%)
Muscle weakness	11 (6.0%)	19 (10.4%)
Gastro-intestinal	7 (3.8%)	13 (7.1%)
Esophageal stricture	2 (1.1%)	3 (1.6%)
Bowel dysmotility/pseudo-obstruction	1 (0.5%)	2 (1.1%)
Anal incontinence	4 (2.2%)	8 (4.4%)
Cardiovascular	8 (4.4%)	12 (6.6%)
Myocardial disease + either conduction defect or LV dysfunction	4 (2.2%)	5 (2.7%)
Respiratory	9 (4.9%)	22 (12.1%)
Pulmonary fibrosis + either FVC<70% or DLCO <50%	5 (2.7%)	15 (8.2%)
Pulmonary hypertension + RV dysfunction or dilation	2 (1.1%)	6 (3.3%)
Renal		
Renal crisis ever + eGFR <60 ml/sec	1 (0.5%)	1 (0.5%)
Genitourinary		
Erectile dysfunction (men)	6 (17.1%)	11 (31.4%)

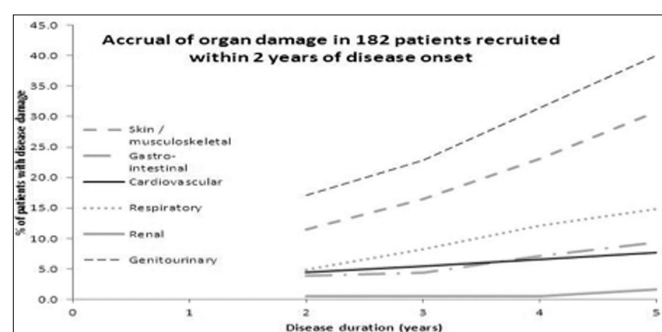


Fig. 1. Accrual of organ damage in SSc in the first 2 to 5 years of disease onset.

S.1.6

PERFORMANCE OF THE 2013 ACR/EULAR CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS IN A SINGLE CENTER SETTING

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Background. Systemic sclerosis (SSc) is often diagnosed late in its course, when there is irreversible visceral damage, which accounts for a high morbidity and mortality rate. The 1980 American Rheumatology Association (ARA) classification criteria for SSc have a low sensitivity for early disease or the limited cutaneous subset of SSc. Recently, a new set of criteria developed by the joint effort of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) has been put forward.

Objectives. To evaluate the performance of the new classification criteria for SSc in clinical practice.

Methods. All patients diagnosed with SSc by expert opinion, who have attended our clinic between 2004-2013, were included. They were assessed according to current EUSTAR recommendations. We also included a control group of patients with primary or secondary non-sclerodermic Raynaud's phenomenon, who were assessed between 2009-2011 in the process of screening for the VEDOSS project. The 1980 ARA criteria and the 2013 ACR/EULAR criteria were applied to data from the patients' first visit and sensitivity and specificity were calculated.

Results. We included 133 expert-diagnosed SSc patients, of which 6 were excluded from the analysis because classification according to the new criteria was impossible due to incomplete data. Of the remaining 127 patients (females:males = 113:14), 49 (38.6%) presented with the diffuse subset of SSc (dcSSc). A hundred and ten patients fulfilled the 1980 ARA criteria (sensitivity: 86.6%) and 122 the 2013 ACR/EULAR criteria (sensitivity: 96.1%). All patients who fulfilled the 1980 ARA also met the 2013 ACR/EULAR criteria. Twelve patients (9.4%) fulfilled only the new set of criteria (4 with dcSSc, 7 with lcSSc, 1 with incomplete CREST syndrome). Five patients (3.9%) did not meet any set of criteria. In the control group, the 2013 ACR/EULAR criteria were fulfilled by 5 (16.1%) patients (diagnosed by expert opinion with either mixed connective tissue disease (MCTD) or with undifferentiated connective tissue disease), while the 1980 ARA criteria were met by only one patient with MCTD. The specificity of the ACR/EULAR criteria was 83.9%, while that of the 1980 ARA criteria was 96.8%.

Conclusions. The 2013 ACR/EULAR criteria have a higher sensitivity compared with the 1980 ARA criteria, being able to better detect limited or early SSc. Specificity was lower, but still acceptable. Further studies with larger cohorts and control groups are needed for these results to be validated.

S.1.7

SSc INTRINSIC SUBSET CLASSIFICATION IN PATIENTS THAT DEMONSTRATE CLINICAL IMPROVEMENT DURING TREATMENT

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Background. Gene expression analysis of skin from SSc patients has been used to identify four 'intrinsic' subsets (normal-like, limited, inflammatory and fibroproliferative). We previously reported that patients with improved skin disease during mycophenolate mofetil (MMF) were classified in the inflammatory while non-improvers were classified in the normal-like or fibroproliferative intrinsic subsets. The goals of this study are to identify clinical phenotypes of patients in intrinsic subsets and evaluate intrinsic subset classification stability over time.

Materials and Methods. Patients with and without progressive skin disease and healthy individuals were enrolled. Standardized clinical assessments including serum autoantibody assessment, pulmonary function test, 2-dimensional echocardiography with tissue Doppler (interpreted by one research echosonographer) and high-resolution computed tomography (scored for lung disease by one chest radiologist) and skin biopsies were performed. mRSS was determined at baseline, 6-, 12-, 24-, and 36-months. Clinical response was defined as decreased mRSS ≥ 5 .

Results. Microarray and clinical data were analyzed for 12 SSc with baseline biopsies (Registry) and 26 SSc patients with longitudinal biopsies (Study) and 12 healthy controls. 4 out of 12 Registry patients were taking MMF (2) or methotrexate (2) at baseline. 22 of 26 Study patients started MMF at baseline. SSc patients were classified as normal-like (11), limited (2), inflammatory (18), and fibroproliferative (7) intrinsic subset. 11 of 12 healthy controls were classified as normal-like. Pts in inflammatory (100% dcSSc) and fibro-proliferative (86% dcSSc) patients had higher mRSS ($p=0.003$) and longer SSc duration ($p=0.029$) compared to other subsets. Autoantibodies were not different between groups. Fibroproliferative patients had highest LV mass [86.2g/m² (14.6), $p=0.027$] and lowest forced vital capacity % predicted [68 (14.5, $p=0.07$), while inflammatory patients had lowest tricuspid annular plane systolic excursion [1.96cm (0.37), $p=0.029$] (mean (SD)). 9 out of 26 (35%) patients with longitudinal biopsies changed intrinsic subset, and six (50% taking MMF) demonstrated ≥ 5 mRSS change. Disease duration and duration of follow-up (mean (SD)) was 53mo (35) and 27mo (10), and 75 mo (86) and 12mo (7) in patients that changed or did not change subset. Change from inflammatory to the fibroproliferative subset was most common.

Conclusions. Intrinsic subset classification of SSc patients is independent of clinical subtype. Patients in the inflammatory and fibroproliferative subsets are more likely to have heart and lung involvement. A subset of patients change from inflammatory to fibroproliferative intrinsic subset which may be due to increased disease duration, longer follow-up, treatment or combination.