



Article scientifique

Article

2007

Published version

Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database

Walker, U; Tyndall, A; Czirják, L; Denton, C; Farge-Bancel, D; Kowal-Bielecka, O; Müller-Ladner, U; Bocelli-Tyndall, C; Matucci-Cerinic, M

Collaborators: Ribi, Camillo; Chizzolini, Carlo

How to cite

WALKER, U et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. In: Annals of the rheumatic diseases, 2007, vol. 66, n° 6, p. 754–763. doi: 10.1136/ard.2006.062901

This publication URL: <https://archive-ouverte.unige.ch/unige:73762>

Publication DOI: [10.1136/ard.2006.062901](https://doi.org/10.1136/ard.2006.062901)

EXTENDED REPORT

Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database

U A Walker, A Tyndall, I Czirják, C Denton, D Farge-Bancel, O Kowal-Bielecka, U Müller-Ladner, C Bocelli-Tyndall, M Matucci-Cerinic, EUSTAR Co-authors*

Ann Rheum Dis 2007;**66**:754–763. doi: 10.1136/ard.2006.062901

See end of article for authors' affiliations

Correspondence to:
U A Walker, Department of Rheumatology, Basle University, Felix Platter Spital, Burgfelderstrasse 101, Basel 4012, Switzerland;
ulrich.walker@fps-basel.ch

Accepted 21 December 2006
Published Online First
1 February 2007

Background: Systemic sclerosis (SSc) is a multisystem autoimmune disease, which is classified into a diffuse cutaneous (dcSSc) and a limited cutaneous (lcSSc) subset according to the skin involvement. In order to better understand the vascular, immunological and fibrotic processes of SSc and to guide its treatment, the EULAR Scleroderma Trials And Research (EUSTAR) group was formed in June 2004.

Aims and methods: EUSTAR collects prospectively the Minimal Essential Data Set (MEDS) on all sequential patients fulfilling the American College of Rheumatology diagnostic criteria in participating centres. We aimed to characterise demographic, clinical and laboratory characteristics of disease presentation in SSc and analysed EUSTAR baseline visits.

Results: In April 2006, a total of 3656 patients (1349 with dcSSc and 2101 with lcSSc) were enrolled in 102 centres and 30 countries. 1330 individuals had autoantibodies against Scl70 and 1106 against anticentromere antibodies. 87% of patients were women. On multivariate analysis, scleroderma subsets (dcSSc vs lcSSc), antibody status and age at onset of Raynaud's phenomenon, but not gender, were found to be independently associated with the prevalence of organ manifestations. Autoantibody status in this analysis was more closely associated with clinical manifestations than were SSc subsets.

Conclusion: dcSSc and lcSSc subsets are associated with particular organ manifestations, but in this analysis the clinical distinction seemed to be superseded by an antibody-based classification in predicting some scleroderma complications. The EUSTAR MEDS database facilitates the analysis of clinical patterns in SSc, and contributes to the standardised assessment and monitoring of SSc internationally.

Systemic sclerosis (SSc) is a multisystem disease with prevalence rate of around 5/10⁵ and an incidence of 1/10⁵.¹ Higher rates are reported in the US, Australia and Eastern Europe, and lower rates in Northern Europe and Japan.^{2–7} SSc may be rapidly fatal in its severe form, but may also have a prolonged course, with patients being compromised only by distal vasospasm, sclerodactyly and dysphagia.^{8–11} Predicting outcome early in the course of the disease is critical in deciding on the appropriate treatment, but is not yet sufficiently reliable in many patients. The diagnosis is generally established with high specificity, according to the criteria of the American College of Rheumatology (ACR, formerly called American Rheumatism Association).¹² Early SSc can be further divided into diffuse cutaneous (dcSSc) and limited cutaneous (lcSSc), with a part of those manifestations previously called CREST (calcinosis raynaud phenomenon esophageal dysmotility sclerodactyly and telangiectasia) syndrome.¹³ Other forms are characterised by features of scleroderma combined with features of a second connective tissue disease.¹⁴

SSc subsets are also associated with the presence of autoantibodies: dcSSc has been associated with Scl70 autoantibodies (also called topoisomerase I autoantibodies), whereas anticentromere autoantibodies (ACA) are typically detected in lcSSc. However, autoantibody profiles do not completely predict disease presentation. For example, a Japanese study showed that 31% of patients with SSc with Scl70 antibodies had lcSSc.¹⁵ Conversely, 18% of patients with lcSSc were positive for Scl70 antibodies in a US report.¹⁶ Autoantibodies may even disappear during the course of the disease, which then predicted a more favourable outcome.¹⁷

Genetic factors also seem to have an influence on SSc, as the disease occurs more frequently within families than in the general population.¹⁸ A relatively high concordance rate between monozygotic twins for antinuclear antibodies also supports the influence of genetic factors on autoantibody production, although the low overall concordance between monozygotic twins demonstrates the importance of environmental factors.¹⁹

The low incidence of SSc and the clinical variability result in difficulties in understanding the pathogenesis and evolution of the disease, and in selecting appropriate patients for clinical trials.^{20–22}

In order “to foster the awareness, understanding and research of scleroderma and its care and management throughout Europe”, the EULAR Scleroderma Trials And Research (EUSTAR) group (www.eustar.org) was inaugurated, and, under the auspices of the EULAR Standing Committee on International Clinical Studies Including Therapeutic Trials, has established a prospective multicentre scleroderma cohort.

In this paper, we report the cross-sectional prevalence of clinical and laboratory characteristics in SSc, and present a multivariate analysis in order to gain insight into factors that are associated with particular organ manifestations and therefore possibly also with the disease process. By focusing on age at onset of Raynaud's phenomenon, gender and autoantibodies, we also examined

Abbreviations: ACA, anticentromere autoantibody; ACR, American College of Rheumatology; CK, creatine kinase; dcSSc, diffuse cutaneous systemic sclerosis; EUSTAR, EULAR Scleroderma Trials And Research; lcSSc, limited cutaneous systemic sclerosis; PAH, pulmonary artery hypertension (assessed by echocardiography); SSc, systemic sclerosis

whether the dichotomy into limited and diffuse subsets is the best way to capture the disease and its organ manifestations, or whether other variables may be more appropriate.

PATIENTS AND METHODS

The EUSTAR database

The EUSTAR database was inaugurated in June 2004 and documents a multinational, prospective and open scleroderma cohort. Participating centres seek ethics committee approval, followed by the entry of the Minimal Essential Data set (MEDS) for all consecutive consenting patients most of whom fulfil the ACR classification criteria for SSc.¹² Scleroderma subsets are classified as “diffuse SSc” if skin thickening extends proximal to the elbows and knees or includes the trunk. The SSc subset is classified as “limited SSc” if skin thickening is confined to the elbows and knees, or the face.¹³ Patients who fulfil the ACR criteria for scleroderma but who had simultaneous overlap syndromes with typical features of one or more of other connective tissue diseases (mixed connective tissue disease, systemic lupus erythematosus, Sjögren’s syndrome, dermatomyositis, polymyositis or rheumatoid arthritis), are classified as “other”. Cases of localised scleroderma (morphea and linear disease) are not included. The MEDS (fig 1) was constructed in consensus by the EUSTAR members, and covers demographic aspects, disease duration, organ involvement and laboratory data. Disease activity was calculated as a composite score from MEDS features according to the preliminary index for SSc as a whole, proposed by the European Scleroderma Study Group and detailed elsewhere.²³ Annual follow-up examinations are carried out. The centres were coached several times on how to fill out the forms. Coaching sessions included ACR classification of SSc, and definitions of the subgroups and the activity score. Standardised teaching sessions included the documentation of the modified Rodnan skin score at the bedside, following two “teach the teachers” sessions held in 2004 and 2005. Pseudonymised paper entry forms are faxed or mailed to the EUSTAR registry in Florence, Italy. Data monitoring includes suspect double entries, missing data and plausibility checks. The definitions of the MEDS parameters and video coaching material are also available on the EUSTAR website (<http://www.eustar.org>).

Data analysis

SSc presentations were analysed cross-sectionally for differences in demographic and clinical features. For each patient, only the baseline data from the first visit were used. The dataset was analysed using the SPSS V.13.0 statistical package. Group means and percentages within dichotomised groups were compared by *t* test.

Significant differences in disease presentation on univariate comparisons were then retested by forward multivariate logistic regression. The following variables were entered in the model: presence or absence of dcSSc, lcSSc, antinuclear antibodies, ACA, Scl70 autoantibodies and gender. Further variables included early versus late onset of first Raynaud’s phenomenon (dichotomised at the mean onset of Raynaud’s phenomenon among all patients), and the time interval between the first Raynaud’s phenomenon and first non-Raynaud’s event (dichotomised at the mean interval among all patients). Variables with quantitatively minor explanatory power (contributing <0.01 to the overall Nagelkerke-R²) were removed from the model even if their effect on the model was statistically significant.

RESULTS

As of April 2006, a total of 3656 patients had been enrolled from 102 participating centres in 24 European and 6 non-European countries. There were very little missing data (table 1), apart

from parameters relating to the onset of Raynaud’s phenomenon, onset of first non-Raynaud’s event and diffusing capacity of the lung for carbon monoxide, as these three parameters were included only after the first year of data collection. A total of 1349 (36.9%) patients had dcSSc, 2101 (57.5%) patients had lcSSc and 206 (5.6%) had scleroderma in combination with another connective tissue disease (table 1). Compared with patients with lcSSc, patients with dcSSc were on average 5.1 years younger. In all SSc subsets, the age of patients was normally distributed (fig 2).

Disease manifestations

Patients with dcSSc and lcSSc had an identical mean age of onset (42.9 years) of Raynaud’s phenomenon. However, the age at onset of first non-Raynaud’s manifestation differed between dcSSc and lcSSc, being 44.8 (SD 14.2) years on average in the former and 47.9 (SD 13.4) years in the latter (*p*<0.001). Consequently, there was a significantly longer lag period between the onset of Raynaud’s phenomenon and the next non-Raynaud’s clinical feature of disease in the lcSSc (mean (SD) 4.8 (8.5) years), as opposed to the dcSSc (mean (SD) 1.9 (5.4) years). In total, 148 (4.0%) patients fulfilled the ACR criteria for scleroderma but had no Raynaud’s phenomenon.

The mean skin score (modified Rodnan’s skin score) was higher (19.0 (SD 10.0)) in dcSSc than in lcSSc (8.1 (SD 5.3)) or in other scleroderma presentations (6.4 (SD 6.6)), as expected. Overlapping skin scores between dcSSc and lcSSc emphasise that the numerical value of the score is not just determined not only by distribution but also by the severity of skin involvement.

Disease activity was scored as “active” in 49.8% of dcSSc, 21.5% of lcSSc and 28.2% of “other”. Acute-phase reactants were more frequently elevated in dcSSc (table 1).

Musculoskeletal manifestations (joint contractures, tendon friction rubs, muscle weakness, muscle atrophy and raised creatine kinase (CK)) were almost twice as common in dcSSc as in lcSSc. Joint contractures were reported most commonly. A substantial number of patients had muscle weakness and atrophy, but only a few had simultaneous CK elevation.

Gastrointestinal involvement was most common in the oesophagus, but, with the exception of a slightly more predominant gastric involvement in the dcSSc (26.6% in dcSSc vs 22.8% in lcSSc), was observed in similar frequencies among the scleroderma subsets.

Pulmonary fibrosis was more common in dcSSc (53.4%) than in lcSSc (34.7%), whereas the frequency of pulmonary artery hypertension (PAH) diagnosed by echocardiography was similar between the two subsets (in 22.3% of patients with dcSSc and in 20.5% of patients with lcSSc). Isolated PAH (in the absence of lung fibrosis) was found in 26% of patients with dcSSc with PAH and in 45% of patients with lcSSc with PAH.

Objective cardiac complications (conduction block, diastolic dysfunction and left ventricular ejection failure) were reported with a similar frequency among scleroderma subsets. Subjective manifestations (palpitations) were slightly more common in dcSSc, than in lcSSc (27.3% vs 22.6%). Reduced left ventricular ejection fraction was associated with PAH in only 3.2% of patients with dcSSc. This prevalence was similar in patients with lcSSc (2.8%, *p* = 0.52).

Renal complications (hypertensive renal crisis and proteinuria) were more frequent in the dcSSc subset.

Differences in disease presentation according to gender

Among all scleroderma patients, 87% were women; the women-to-men ratio was 6:1. Women were slightly older than men (mean (SD) age 55.5 (13.6) vs 53.9 (13.3) years; *p* = 0.02).

EUSTAR – Minimal Essential Data Set

1

Figure 1 Items of the Minimal Essential Data Set.

Unique center N°

Unique patient N°

Date of birth (day/month/year)

Sex Male Female

Onset of Raynaud Month Year

Onset of first non-Raynaud feature of disease Month Year

ACR criteria fulfilled (yes/no) Yes ☐ No ☐

Subset Diff. cut. SSc ☐ Lim. cut. SSc ☐ Other ☐

ANA positive Yes ☐ No ☐ Elevated acute phase reactants Yes ☐ No ☐

ACA positive ☐ ☐ Proteinuria (+ or more) ☐ ☐

Scl 70 positive ☐ ☐ Active disease* ☐ ☐

*Cross "yes" if activity score ≥ 3 according to attachment "EULAR systemic sclerosis activity score"

Date of filling out this form

Complete only in case of death: Date of death

Death due to SSc ☐ ☐ Yes No Death due to treatment ☐ ☐ Yes No Death due to other ☐ ☐ Yes No

EUSTAR – Minimal Essential Data Set

2

Unique center N° Unique patient N° Date of birth

Weight (kg – e.g. 68.4)

Skin Mod. Rodnan (max. 51)

		Yes	No	Comments	
Vascular	Raynauds	<input type="checkbox"/>	<input type="checkbox"/>		
	Digital ulcers	<input type="checkbox"/>	<input type="checkbox"/>		
Joints	Synovitis	<input type="checkbox"/>	<input type="checkbox"/>		
	Joint contractures	<input type="checkbox"/>	<input type="checkbox"/>		
Tendons	Friction rubs	<input type="checkbox"/>	<input type="checkbox"/>		
	Muscles	C.K. elevation	<input type="checkbox"/>	<input type="checkbox"/>	
Muscles	Weakness	<input type="checkbox"/>	<input type="checkbox"/>		
	Atrophy	<input type="checkbox"/>	<input type="checkbox"/>		
	G.I.T.	Esophageal (dysphagia, reflux)	<input type="checkbox"/>	<input type="checkbox"/>	
		Stomach (early satiety, vomiting)	<input type="checkbox"/>	<input type="checkbox"/>	
Intestinal (diarrhea, bloating, constip.)		<input type="checkbox"/>	<input type="checkbox"/>		
Renal	Hypertension	<input type="checkbox"/>	<input type="checkbox"/>		
	Renal crisis	<input type="checkbox"/>	<input type="checkbox"/>		
Cardio-	Dyspnoea (significant)	<input type="checkbox"/>	<input type="checkbox"/>		
	Pulmonary	Palpitations	<input type="checkbox"/>	<input type="checkbox"/>	
Conduction blocks		<input type="checkbox"/>	<input type="checkbox"/>		
Diastolic function abnormal		<input type="checkbox"/>	<input type="checkbox"/>		
Reduced ventricular ejection fraction		<input type="checkbox"/>	<input type="checkbox"/>		
Fibrosis - plain x-ray		<input type="checkbox"/>	<input type="checkbox"/>		
Restrictive defect (lung function test)		<input type="checkbox"/>	<input type="checkbox"/>		
Pulmonary hypertension (ECHO)		<input type="checkbox"/>	<input type="checkbox"/>		
DLCO (% predicted)		<input type="checkbox"/>	<input type="checkbox"/>		

Women had an earlier onset of Raynaud's phenomenon than men (mean (SD) age 42.2(14.5) vs 46.4 (14.3) years; $p < 0.001$). Similarly, the onset of non-Raynaud's manifestations was reported at a slightly younger age in women than in men (46.4 (13.8) vs 47.9 (13.8) years; $p = 0.04$).

Within the dcSSc subset, 1094 patients were women and 254 patients were men (women:men ratio 4:1). Within the lcSSc subset, 1910 patients were women and 180 patients were men (women:men ratio 11:1). Men were more commonly affected

by dcSSc than by lcSSc ($p < 0.001$). The mean age of patients did not differ between sexes when compared among individual SSc subsets (table 2). Women, however had an earlier onset of Raynaud's phenomenon in both SSc (by a mean of 4.3 years earlier) and lcSSc (by a mean of 4.6 years earlier) compared with men. In absolute numbers, ACA were rarely positive in men. Among the lcSSc subset, women had more frequently ACA and men more frequently Scl-70 autoantibodies (table 2).

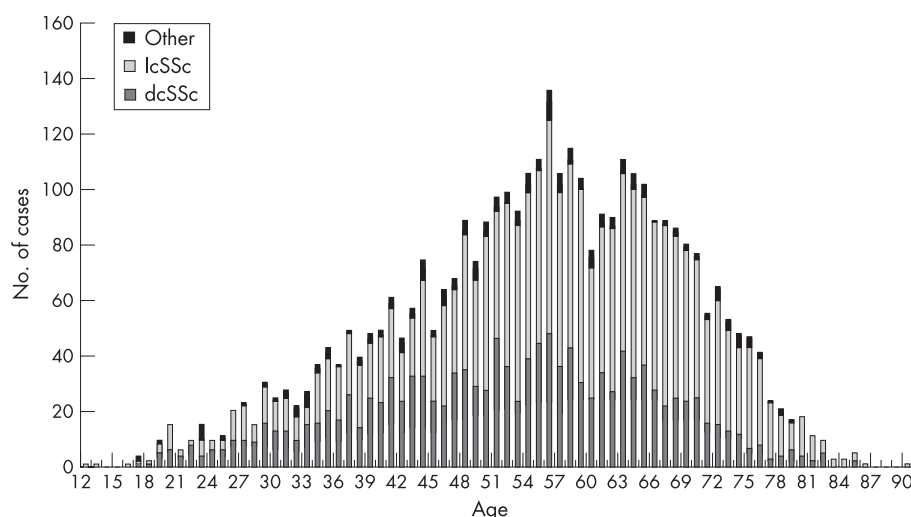


Figure 2 Age distribution of scleroderma subsets. dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis.

Table 1 Prevalence of disease presentation among clinical scleroderma subsets

	dcSSc	lcSSc	p (dcSSc vs lcSSc)	Other	Missing data (%)
ACR criteria fulfilled	100%	100%	NA	100%	0
Number of patients	1349 (36.9%)	2101 (57.5%)	<0.001	206 (5.6%)	0
Women	81.1%	90.9%	<0.001	86.9%	0.4
Age (years), mean (SD)	52.3 (13.7)	57.4 (13.1)	<0.001	52.7 (13.9)	0.4
Age at RO (years), mean (SD)	42.9 (14.7)	42.9 (14.5)	0.98	40.6 (14.3)	11.2
Age at first non-RO (years), mean (SD)	44.8 (14.2)	47.9 (13.4)	<0.001	43.8 (14.0)	10.4
Disease duration* (years), mean (SD)	7.4 (6.9)	9.6 (8.1)	<0.001	9.0 (7.5)	10.7
Time between RO and first non-RO (years), mean (SD)	1.9 (5.4)	4.8 (8.5)	<0.001	3.2 (7.3)	12.2
ANA positive	92.1%	91.3%	0.19	89.3%	0.8
Scl70 positive	60.8%	23.4%	<0.001	26.1%	3.4
ACA positive	6.0%	46.7%	<0.001	21.4%	4.4
mRSS, mean (SD)	19.0 (10.0)	8.1 (5.3)	<0.001	6.4 (6.6)	3.0
Active disease	49.8%	21.5%	<0.001	28.2%	3.5
Elevated acute phase reactants	41.8%	24.6%	<0.001	34.5%	1.8
Raynaud's phenomenon	96.1%	95.9%	0.58	92.7%	0.1
Digital ulcers	42.7%	32.9%	<0.001	22.3%	0.3
Synovitis	20.8%	13.7%	<0.001	21.4%	0.4
Joint contractures (any joint)	47.1%	24.4%	<0.001	29.1%	0.6
Tendon friction rubs	22.1%	7.4%	<0.001	8.3%	0.9
Muscle weakness	37.1%	22.8%	<0.001	36.4%	0.4
Muscle atrophy	21.1%	10.8%	<0.001	20.9%	1.1
CK elevation	11.3%	4.4%	<0.001	12.1%	2.8
Oesophagus	68.2%	66.8%	0.38	68.0%	0.3
Stomach	26.6%	22.8%	0.04	21.8%	0.7
Intestine	22.5%	21.7%	0.68	19.4%	0.7
Pulmonary fibrosis	53.4%	34.7%	<0.001	44.2%	2.2
Lung restrictive defect	49.3%	26.7%	<0.001	32.0%	2.4
% of predicted DLCO, mean (SD)	64.0 (20.7)	71.8 (21.0)	<0.001	71.6 (19.5)	62.5
PAH	22.3%	20.5%	0.32	18.9%	2.5
PAH without fibrosis	5.9%	9.2%	<0.001	5.8%	2.5
PAH with fibrosis	15.8%	11.0%	<0.001	12.6%	3.9
Dyspnoea	44.9%	34.0%	<0.001	37.4%	0.2
Palpitations	27.3%	22.6%	0.003	31.6%	0.5
Conduction block	12.7%	10.4%	0.12	9.7%	1.9
Diastolic dysfunction	16.6%	15.4%	0.42	15.0%	2.3
LVEF	7.2%	5.0%	0.59	2.4%	3.2
Hypertension	19.3%	18.6%	0.46	15.5%	0.3
Hypertensive renal crisis	4.2%	1.1%	<0.001	1.9%	0.4
Proteinuria	9.2%	3.7%	<0.001	10.2%	1.5

ACA, anticentromere autoantibody; ACR, American College of Rheumatology; ANA, antinuclear antibodies; CK, creatine kinase; DLCO, diffusion capacity of the lung for carbon monoxide; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan Skin Score; NA, not applicable; PAH, pulmonary artery hypertension (assessed by echocardiography); RO, onset of Raynaud's phenomenon.

* Disease duration was calculated on the basis of the onset of the first non-Raynaud's feature.

Table 2 Gender-specific variations among SSc subsets

	dcSSc			lcSSc		
	Men	Women	p (♂ vs ♀)	Men	Women	p (♂ vs ♀)
Number of patients	254	1094	NA	180	1910	NA
Age (years), mean (SD)	52.7 (12.6)	52.3 (14.0)	0.66	56.2 (13.2)	57.5 (13.0)	0.21
Age at RO (years), mean (SD)	46.4 (13.4)	42.1 (14.9)	<0.001	47.1 (14.9)	42.5 (14.4)	<0.001
Age at first non-RO (years), mean (SD)	47.6 (13.1)	44.1 (14.3)	0.001	49.0 (14.1)	47.8 (13.3)	0.26
Disease duration, years mean (SD)	5.1 (5.0)	7.9 (7.2)	<0.001	6.7 (5.7)	9.8 (8.2)	<0.001
Time between RO and first non-RO (years), mean (SD)	1.4 (4.7)	2.0 (5.6)	0.10	2.0 (5.2)	5.1 (8.7)	<0.001
ANA positive	93.7%	93.0%	0.71	92.7%	91.8%	0.67
Scl-70 positive	62.7%	60.4%	0.51	31.3%	22.8%	0.02
ACA positive	4.3%	7.0%	0.08	26.3%	50.3%	<0.001

ACA, anticentromere autoantibody; ANA, antinuclear antibodies; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; SSc, Systemic sclerosis; RO, onset of Raynaud's phenomenon; ♂, male; ♀, female.

Differences in disease presentation according to age at disease onset

In order to analyse the possible differences in organ manifestations according to the patient's age at disease onset (defined as the first onset of Raynaud's phenomenon), we categorised patients according to their mean age at the onset of Raynaud's phenomenon into two groups: one below and the other above the mean. The former group of "early" onset had an average age of 42.8 years and the latter group of "late" onset of Raynaud's phenomenon had an average age of 60.9 years (table 3). Although the groups exhibiting early and late onset of Raynaud's manifestation had no or only slight differences in their autoantibody profile within the individual SSc subsets (table 3), they differed in the prevalence of clinical manifestations. In both subsets, people with an earlier onset of Raynaud's phenomenon had digital ulcers more often than those with a late onset. However, patients with an early onset of Raynaud's phenomenon had significantly less pulmonary fibrosis, pulmonary hypertension, diastolic dysfunction and arterial hypertension (table 3).

Differences in disease presentation according to autoantibodies

Patients positive for ACA mostly (88.7%) had lcSSc (table 4), whereas only 60% of those carrying Scl70 autoantibodies had dcSSc; 36.1% of Scl70-positive patients were classified as lcSSc. Patients with ACA were slightly older than those with anti-Scl70 autoantibodies. Although there was no significant difference in the mean age at onset of Raynaud's phenomenon within people carrying the two different autoantibodies (42.2 years in anti-Scl70 autoantibody positive individuals vs 43.3 years in ACA positive patients), those with ACA had a significantly longer lag period (mean (SD) 6.5 (10.0) years) until the onset of first non-Raynaud's manifestations compared with those with anti-Scl70 autoantibodies (mean (SD) 2.4 (5.6) years).

Autoantibody associations with particular clinical complications are shown in table 4. The presence of autoantibodies (Scl70 and ACA on the one hand) distinguished the frequency of clinical manifestations very similarly to the distinction of dcSSc and lcSSc subsets on the other hand (table 1). However,

Table 3 Prevalence of disease presentation according to the onset of Raynaud's phenomenon

	dcSSc			lcSSc		
	Early Raynaud	Late Raynaud	p (early vs late)	Early Raynaud	Late Raynaud	p (early vs late)
Number of patients	553	594	NA	914	1003	NA
Age (years), mean (SD)	42.8 (11.9)	60.9 (8.5)	<0.001	49.9 (12.9)	64.1 (8.6)	<0.001
Women	84.6%	77.9%	0.004	93.1%	89.4%	0.004
ANA positive	93.8%	93.4%	0.76	92.5%	91.6%	0.46
Scl70 positive	63.2%	60.0%	0.26	25.5%	21.5%	0.04
ACA positive	5.5%	6.6%	0.45	46.5%	49.6%	0.18
mRSS (years), mean (SD)	18.7 (9.4)	19.5 (10.4)	0.18	8.1 (5.2)	8.0 (5.2)	0.66
Active disease	43.8%	52.7%	0.005	18.1%	21.9%	0.05
Elevated acute-phase reactants	37.3%	44.3%	0.02	21.8%	26.3%	0.03
Digital ulcers	50.8%	35.2%	<0.001	38.8%	27.9%	<0.001
Muscle weakness	32.7%	39.2%	0.02	21.0%	22.5%	0.43
Pulmonary fibrosis	47.4%	59.4%	<0.001	31.8%	37.2%	0.02
Lung restrictive defect	47.9%	50.3%	0.26	24.1%	29.2%	0.009
PAH	17.7%	26.3%	<0.001	16.8%	23.4%	<0.001
Dyspnoea	37.8%	52.2%	<0.001	31.3%	37.0%	0.008
Palpitations	23.5%	30.3%	0.006	20.6%	23.6%	0.07
Conduction block	11.4%	13.5%	0.18	9.0%	12.2%	0.01
Diastolic dysfunction	11.9%	20.7%	<0.001	12.2%	18.6%	<0.001
Hypertension	11.6%	23.9%	<0.001	12.9%	22.0%	<0.001

ACA, anticentromere autoantibody; ANA, antinuclear antibodies; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; mRSS, modified Rodnan Skin Score; NA, not applicable; PAH, pulmonary artery hypertension (assessed by echocardiography). Manifestations with statistically similar prevalence between early and late onset are not shown.

Table 4 Prevalence of disease presentation according to autoantibody serology

	ANA positive	Scl70 positive	ACA positive	p (Scl70 vs ACA)
Number of patients	3346	1330	1106	<0.001
Presenting as dcSSc	37.1%	60.0%	7.3%	<0.001
Presenting as lcSSc	57.4%	36.1%	88.7%	<0.001
Presenting as "other"	5.5%	3.9%	4.0%	0.88
Women	87.3%	83.7%	94.4%	<0.001
Age (years), mean (SD)	55.1 (13.6)	52.6 (13.7)	59.6 (11.8)	<0.001
Age at RO (years), mean (SD)	42.7 (14.6)	42.2 (14.4)	43.4 (14.7)	0.28
Age at first non-RO (years), mean (SD)	46.4 (13.8)	44.5 (14.0)	50.0 (12.6)	<0.001
Time between RO and non-RO (years), mean (SD)	3.7 (7.6)	2.4 (5.6)	6.5 (10.0)	<0.001
mRSS (years), mean (SD)	12.0 (9.1)	15.1 (9.9)	8.2 (5.9)	<0.001
Active disease	32.7%	45.2%	18.9%	<0.001
Elevated acute-phase reactants	31.9%	42.6%	20.7%	<0.001
Raynaud's phenomenon	96.3%	97.4%	96.7%	0.45
Digital ulcers	36.7%	44.8%	31.2%	<0.001
Synovitis	16.7%	21.4%	11.9%	<0.001
Joint contractures (any joint)	33.7%	44.5%	17.6%	<0.001
Tendon friction rubs	13.1%	18.9%	6.0%	<0.001
Muscle weakness	28.4%	32.2%	22.7%	<0.001
Muscle atrophy	14.6%	16.1%	9.5%	<0.001
CK elevation	7.6%	8.7%	2.9%	<0.001
Oesophagus	67.9%	68.0%	70.7%	0.18
Stomach	24.5%	24.1%	26.9%	0.11
Intestine	22.5%	20.7%	25.1%	0.01
Pulmonary fibrosis	42.6%	60.2%	21.3%	<0.001
Lung restrictive defect	35.8%	50.3%	17.4%	<0.001
% of predicted DLCO (years), mean (SD)	68.9 (21.6)	65.1 (20.9)	75.0 (20.9)	<0.001
PAH	21.1%	23.2%	22.0%	0.36
PAH without fibrosis	8.0%	5.0%	13.0%	<0.001
PAH with fibrosis	12.7%	17.2%	8.0%	<0.001
Dyspnoea	38.6%	44.5%	29.4%	<0.001
Palpitations	24.8%	27.2%	23.2%	0.01
Conduction block	11.2%	13.6%	9.1%	<0.001
Diastolic dysfunction	15.7%	17.7%	12.7%	0.001
Reduced LVEF	5.7%	5.9%	5.2%	0.29
Hypertension	18.5%	14.4%	20.0%	<0.001
Hypertensive renal crisis	2.3%	2.0%	1.3%	0.15
Proteinuria	6.0%	7.8%	2.7%	<0.001

ACA, anticentromere autoantibody; ANA, antinuclear antibodies; CK, creatine kinase; DLCO, diffusion capacity of the lung for carbon monoxide; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; LVEF, left ventricular ejection fraction; PAH, pulmonary artery hypertension (assessed by echocardiography); RO, onset of Raynaud's phenomenon.

there were some differences. Most notably, Scl70 positivity, unlike diffuse skin involvement, was associated with significant differences in the prevalence of intestinal symptoms, myocardial conduction block, diastolic dysfunction and renal hypertension. On the other hand, a positive history of gastric complications and hypertensive renal crisis was associated with skin involvement, but not with autoantibody status.

Multivariate analysis of disease determinants

The multivariate analysis confirmed the results of most univariate comparisons (table 5). The ranking of the variables according to their overall explanatory effect on the model shows that, for some disease manifestations, the contributory effect of antibody status exceeds that of the clinical dichotomy into lcSSc and dcSSc. For many other disease manifestations, antibody status also contributed as an independent variable. In accord with the univariate analysis, late onset of Raynaud's phenomenon was negatively associated with digital ulcers and positively associated with pulmonary fibrosis, PAH and renal hypertension. On multivariate analysis, gender was only significantly associated with a few disease manifestations—for example, association of raised CK with male gender. However, gender was removed from all models because it did not have a quantitatively pronounced explanatory effect, as it contributed <0.01 to the overall Nagelkerkes' R^2 in the model.

DISCUSSION

In this large EUSTAR cohort of predominantly Caucasian patients with scleroderma, 57% of individuals were classified as

lcSSc and 36.9% as dcSSc. Other investigators also found that limited disease was more common than diffuse disease among prevalent cases (65.1% vs 34.9%).⁷

Women were six times more frequent than men in our cohort. This sex ratio is between the numbers reported in smaller cohorts for the UK⁶ (women:men ratio 3:1) and Japan (women:men ratio 14:1), and similar to those from Iceland (8:1).³⁻⁵ Differences may be partly explained by the proportion of lcSSc within the cohorts, because our data suggest that the women:men ratio may be higher in lcSSc than in dcSSc. In the UK study, however, the women:men ratio was lower in the lcSSc subset (3.2:1) than in the dcSSc subset (4.6:1).⁶ In lcSSc, we found a higher prevalence of Scl70 autoantibodies and a lower prevalence of ACA among men than in women, whereas in dcSSc there were no differences in autoantibodies between sexes. Other investigators also suggest that ACA are less common among men.⁷

In previous studies, the mean age at diagnosis was not different between sexes.⁷ In our cohort, patients with dcSSc experienced the first non-Raynaud's feature of their disease at a slightly younger age than patients with lcSSc. Previous incidence calculations suggested that the difference in prevalence between diffuse and limited disease was not attributable to the survival advantage of patients with limited disease.⁷

Our analysis found no differences between the two SSc subsets with regard to the age at onset of Raynaud's phenomenon, but in patients with diffuse disease, the first non-Raynaud's manifestation developed sooner than in those with limited disease. These findings fit well with the observation that

Table 5 Independent predictors of disease presentation

	1	2	3
mRSS above mean	DcSSc		
Active disease	DcSSc	ACA negative	
Elevated acute-phase reactants	Not lcSSc	Scl70 positive	
Digital ulcers	Scl70 positive	Early RO	
Synovitis	ACA negative		
Joint contractures (any joint)	DcSSc	ACA negative	
Tendon friction rubs	DcSSc	ACA negative	
Muscle weakness	Not lcSSc		
Muscle atrophy	Not lcSSc		
CK elevation	Not lcSSc	ACA negative	
Oesophagus	None		
Stomach	None		
Intestine	None		
Pulmonary fibrosis	Scl70 positive	ACA negative	Late RO
Lung restrictive defect	DcSSc	Scl70 positive	ACA negative
DLCO above mean	ACA positive		
PAH	Late RO		
PAH without fibrosis	ACA		
PAH with fibrosis	Scl70-positive	ACA-negative	
Dyspnoea	ACA negative	Late RO	
Palpitations	None		
Conduction block	None		
Diastolic dysfunction	Late RO		
LVEF	None		
Hypertension	Scl70 negative	Late RO	
Hypertensive renal crisis	DcSSc	Scl70 negative	
Proteinuria	Not lcSSc		

ACA, anticentromere autoantibody; CK, creatine kinase; DLCO, diffusion capacity of the lung for carbon monoxide; dcSSc, diffuse cutaneous systemic sclerosis; late and early RO, age at onset of Raynaud's phenomenon above and below the mean age of all patients; lcSSc, limited cutaneous systemic sclerosis; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan Skin Score; PAH, pulmonary artery hypertension (assessed by echocardiography).

The variables are calculated by multivariate logistic regression and ranked in columns 1, 2 and 3 according to the magnitude of their explanatory effect ("1" being the strongest predictor). Variables discarded from the model are not listed. Details are described in patients and methods section.

ACA positivity was associated with longer duration of Raynaud's phenomenon before the diagnosis of SSc was made.²⁴ The onset of disease, whether based on first Raynaud's phenomenon or on first non-Raynaud's event, was earlier in women. Furthermore, an early onset of disease was associated with a reduced prevalence of the more severe complications of scleroderma, such as lung fibrosis and PAH, in our cohort. This is in accordance with the observation that being a woman positively affects survival.⁷ The gender-specific differences of the disease features indicate a modifying influence of sex hormones or reproduction. They could also point to gender-specific environmental exposure.

In the multivariate analysis, however, gender was not associated with disease manifestations. This suggests that any effect of gender may be better explained by other variables such as age of onset of Raynaud's phenomenon and/or autoantibody status.

In both SSc subsets, individuals with an early onset of Raynaud's phenomenon had digital ulcers more commonly than those with a late onset, whereas an onset of Raynaud's phenomenon later in life was associated with a higher prevalence of more severe disease manifestations such as pulmonary fibrosis and PAH. The independent contribution of the time of onset of Raynaud's phenomenon to the prevalence of the above-mentioned complications despite a similar prevalence of autoantibodies was confirmed in the multivariate analysis, and is in accord with the finding of others that older age at diagnosis negatively affects survival.⁷ It should be noted, however, that the time of onset of Raynaud's phenomenon does not discriminate between the two disease subsets. The first non-Raynaud's feature does follow the onset of Raynaud's phenomenon more rapidly in dcSSc than in lcSSc; the relatively

small difference however may not be helpful in the assessment of an individual patient.

Scl70 autoantibodies are associated with the more severe diffuse form of SSc, but 36.1% of patients were classified as lcSSc. Another study found that 31% of patients with SSc with this autoantibody had limited disease.¹⁵ Conversely, 23.4% of patients with lcSSc in our cohort and 18% in other investigations were positive for anti-Scl70,¹⁶ and serum levels of anti-Scl70 autoantibody levels also appear to be correlated with disease activity in some studies.²⁵ Disappearance of anti-Scl70 autoantibodies has been noted in patients with a more favourable outcome.¹⁷ The multivariate analysis shows that autoantibody status contributes to 15 of the organ complications, whereas the clinical SSc subtype serves as an explanatory variable to 11 of the organ complications. This could imply that autoantibody status is more closely related to organ involvement than SSc subsets in the LeRoy classification.

Of note, the MEDS does not capture the status of anti-RNA-polymerase antibodies which are associated with dcSSc and renal involvement.²⁶ The presence of anti-RNA-polymerase antibodies may explain the finding that hypertensive renal crisis was not more frequent in individuals carrying anti-Scl-70 autoantibodies (table 4), but on the other hand was associated with the absence of Scl70 autoantibodies (table 5), despite the link between renal complications and dcSSc (table 1).

Our analysis nevertheless confirms the importance of dcSSc and lcSSc scleroderma subdivision in their association with particular organ manifestations. The age at onset of Raynaud's phenomenon may also contribute in the assessment of the likelihood of some organ complications. Clearly, both clinical and laboratory parameters must be combined and evaluated longitudinally in the prognostication of SSc. The EUSTAR

MEDS database contributes to the critical assessment of the current diagnostic and prognostic dogma. The long-term prospective data on this large and still growing number of patients will continue to facilitate the analysis of clinical patterns in SSc and allow rapid evaluation of new diagnostic tests and therapeutic strategies. Large-scale co-operation is a necessary and powerful tool in the study of a rare disease like SSc.

ACKNOWLEDGEMENTS

EUSTAR is supported by a research grant from EULAR, and is under the auspices of the Standing Committee for International Studies Including Clinical Trials (ESCISIT). We thank M Enters (Statsolutions, Freiburg, Germany) for statistical assistance.

Authors' affiliations

U A Walker, A Tyndall, C Bocelli-Tyndall, Department of Rheumatology, Basle University, Felix Platter Spital, Basel, Switzerland

L Cziráj, University of Pécs, Department of Immunology and Rheumatology, Pécs, Hungary

C Denton, Centre for Rheumatology, Royal Free and University College London Medical School, London, UK

D Farge-Bancel, Department of Internal Medicine, Hospital Saint Louis, Paris, France

O Kowal-Bielecka, Department of Rheumatology, Medical University of Białystok, Białystok, Poland

U Müller-Ladner, Department of Rheumatology Kerckhoff Klinik, Bad Nauheim, Germany

M Matucci-Cerinic, Department of Internal Medicine, Section of Rheumatology, University of Florence, Italy

Competing interests: None declared.

*Names and addresses of the remaining co-authors of the paper are listed in the appendix

REFERENCES

- Alamanos Y, Tsifetaki N, Voulgari PV, Siozos C, Tsamandouraki K, Alexiou GA, et al. Epidemiology of systemic sclerosis in northwest Greece 1981 to 2002. *Semin Arthritis Rheum* 2005;**34**:714–20.
- Roberts-Thomson PJ, Jones M, Hakendorf P, Kencana Dharmapatri AA, Walker JG, MacFarlane JG, et al. Scleroderma in South Australia: epidemiological observations of possible pathogenic significance. *Intern Med J* 2001;**31**:220–9.
- Tamaki T, Mori S, Takehara K. Epidemiological study of patients with systemic sclerosis in Tokyo. *Arch Dermatol Res* 1991;**283**:366–71.
- Czirjak L, Kiss CG, Lovei C, Suto G, Varju C, Fuzesi Z, et al. Survey of Raynaud's phenomenon and systemic sclerosis based on a representative study of 10 000 south-Transdanubian Hungarian inhabitants. *Clin Exp Rheumatol* 2005;**23**:801–8.
- Geirsson AJ, Steinsson K, Guthmundsson S, Sigurthsson V. Systemic sclerosis in Iceland. A nationwide epidemiological study. *Ann Rheum Dis* 1994;**53**:502–5.
- Silman A, Jannini S, Symmons D, Bacon P. An epidemiological study of scleroderma in the West Midlands. *Br J Rheumatol* 1988;**27**:286–90.
- Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003;**48**:2246–55.
- Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. *Arthritis Rheum* 1999;**42**:2660–5.
- Cox SR, Walker JG, Coleman M, Rischmueller M, Proudman S, Smith MD, et al. Isolated pulmonary hypertension in scleroderma. *Intern Med J* 2005;**35**:28–33.
- Mayes MD. Race, scleroderma, and survival: why is there a difference? *J Rheumatol* 2005;**32**:1873–4.
- Iannidis JP, Vlachoyiannopoulos PG, Haidich AB, Medsger TA Jr, Lucas M, Michet CJ, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med* 2005;**118**:2–10.
- Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma) *Arthritis Rheum* 1980;**23**:581–90.
- LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*, 1988;**15**:202–5.
- Wallheim FA. Classification of systemic sclerosis. Visions and reality. *Rheumatology* 2005;**44**:1212–16.
- Kuwana M, Kaburaki J, Okano Y, Tojo T, Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. *Arthritis Rheum* 1994;**37**:75–83.
- Steen VD, Powell DL, Medsger TA Jr. Clinical correlation and prognosis based on serum autoantibodies in patients with systemic sclerosis. *Arthritis Rheum* 1988;**31**:196–203.
- Kuwana M, Kaburaki J, Mimori T, Kawakami Y, Tojo T. Longitudinal analysis of autoantibody response to topoisomerase I in systemic sclerosis. *Arthritis Rheum* 2000;**43**:1074–84.
- Arnett FC, Cho M, Chatterjee S, Aguilar MB, Reveille JD, Mayes MD. Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts. *Arthritis Rheum* 2001;**44**:1359–62.
- Feghali-Bostwick C, Medsger TA Jr, Wright TM. Analysis of systemic sclerosis in twins reveals low concordance for disease and high concordance for the presence of antinuclear antibodies. *Arthritis Rheum* 2003;**48**:1956–63.
- Lin AT, Clements PJ, Furst DE. Update on disease-modifying antirheumatic drugs in the treatment of systemic sclerosis. *Rheum Dis Clin North Am* 2003;**29**:409–26.
- van Laar JM, Farge D, Tyndall A. Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial: hope on the horizon for patients with severe systemic sclerosis. *Ann Rheum Dis* 2005;**64**:1515.
- Hachulla E, Coghlan JG. A new era in the management of pulmonary arterial hypertension related to scleroderma: endothelin receptor antagonism. *Ann Rheum Dis* 2004;**63**:1009–1014.
- Valentini G, Bencivelli W, Bombardieri S, D'Angelo S, Della RA, Silman AJ, et al. European Scleroderma Study Group to define disease activity criteria for systemic sclerosis. III. Assessment of the construct validity of the preliminary activity criteria. *Ann Rheum Dis* 2003;**62**:901–3.
- Cutolo M, Pizzorni C, Tuccio M, Burrioni A, Craviotto C, Basso M, et al. Nailfold videocapillaroscopic patterns and serum autoantibodies in systemic sclerosis. *Rheumatology* 2004;**43**:719–26.
- Sato S, Hamaguchi Y, Hasegawa M, Takehara K. Clinical significance of anti-topoisomerase I antibody levels determined by ELISA in systemic sclerosis. *Rheumatology* 2001;**40**:1135–40.
- Bunn CC, Denton CP, Shi-Wen X, Knight C, Black CM. Anti-RNA polymerases and other autoantibody specificities in systemic sclerosis. *Br J Rheumatol* 1998;**37**:15–20.

APPENDIX

CO-AUTHOR LIST

Gabriela Riemekasten¹, Claudia Brückner¹, Paolo Airo², Mirko Scarsi², Raffaella Scorza³, Lorenzo Beretta³, Franco Cozzi⁴, Francesco Tiso⁴, MC Vonk⁵, FHJ van den Hoogen⁵, Fredrick M Wigley⁶, Laura Hummers⁶, Tatjana Nevskaya⁷, Lidia Ananieva⁷, Irene Miniati⁸, Nicoletta Tartaglia⁹, Claudia Lomater⁹, Alexandra Balbir-Gurman¹⁰, Yolanda Braun-Moscovici¹⁰, Lisa Maria Bambara¹¹, Paola Caramaschi¹¹, Gabriele Valentini¹², Luigia Ruocco¹², Thomas Krieg¹³, Nicolas Hunzelmann¹³, Cecília Varjú¹⁴, Patricia E Carreira¹⁵, Beatriz Joven¹⁵, Florenzo Iannone¹⁶, Giovanni Lapadula¹⁶, André Kahan¹⁷, Yannick Allanore¹⁷, Armando Gabrielli¹⁸, Michele Imperatore¹⁸, Agneta Scheja¹⁹, Frank Wollheim¹⁹, Nemanja Damjanov²⁰, Predrag Ostojic²⁰, Petra Saar²¹, Ingo H. Tarner²¹, Ina Kötter²², Stefano Bombardieri²³, Laura Bazzichi²³, Nicoletta Del Papa²⁴, Denise P Comina²⁴, Andrea Lo Monaco²⁵, Renato La Corte²⁵, Eric Hachulla²⁶, David Launay²⁶, Oliver Distler²⁷, Adrian Ciurea²⁷, Stanislaw Sierakowski²⁸, Holly Mitchell²⁹, Richard M Silver²⁹, Dorota Krasowska³⁰, Malgorzata Michalska-Jakubus³⁰, Mohammed Tikly³¹, Nazrana Abou³¹, Margitta Worm³², Pascal Klaus³², Jozef Rovinsky³³, Olga Lukáčová³³, Blaz Rozman³⁴, Alenka Sipek³⁴, Paulo Clemente-Coelho³⁵, Yehuda Shoenfeld³⁶, Pnina Langewitch³⁶, Da Silva José A P³⁷, Salvador MJ³⁷, Annegret Kuhn³⁸, Gunilla Erdmann³⁸, Radim Bečvář³⁹, Elke Friedl⁴⁰, Winfried Granger⁴⁰, Valeria Riccieri⁴¹, Roberto Caporali⁴², Carlomaurizio Montecucco⁴², P Vlachoyiannopoulos⁴³, Meike Distler⁴⁴, Kristian Reich⁴⁴, Maria Majdan⁴⁵, Ewa Wielosz⁴⁵, Simona Rednic⁴⁶, Jacob M van Laar⁴⁷, Stefan Heitmann⁴⁸, Andreas Bruckner⁴⁸, Andrea Himsel⁴⁹, Julia Riemann⁴⁹, Rotraud Meyringer⁵⁰, Adelheid Müller⁵⁰, Duska Martinovic⁵¹, Mislav Radic⁵¹, Michael Sticherling⁵², Zoltan Szekancz⁵³, Gabriella Szűcs⁵³, Roberto Giacomelli⁵⁴, Alessandra Marrelli⁵⁴, Bojana Stamenkovic⁵⁵, Aleksandra Stankovic⁵⁵, Martin Aringer⁵⁶, Josef S Smolen⁵⁶, Eugene J Kucharz⁵⁷, Anna T Kotulska⁵⁷, Stefania Jablonska⁵⁸, Maria Blaszczak⁵⁸, Jae-Bum Jun⁵⁹, Carmel Mallia⁶⁰, Bernard Coleiro⁶⁰, Vera Ortiz Santamaria⁶¹, Ralf Hinrichs⁶², Henrik Nielsen⁶³, Roberta Cossutta⁶⁴, Ruxandra Ionescu⁶⁵, Daniela

Opris⁶⁵, Kerstin Steinbrink⁶⁶, Boris Grundt⁶⁶, Gianluigi Bajocchi⁶⁷, Štork Jiří⁶⁸, Paloma García de la Peña Lefebvre⁶⁹, Antonio C Zea Mendoza⁶⁹, Camillo Ribi⁷⁰, Carlo Chizzolini⁷⁰, Margaret Wisłowska⁷¹, Srdan Novak⁷², Francesco Indiveri⁷³, Søren Jacobsen⁷⁴, Per Brown Frandsen⁷⁴, I Zimmermann Gorska⁷⁵, Jan Tore Gran⁷⁶, Øyvind Midtvedt⁷⁶, Filipa Oliveira Ramos⁷⁷, Ljubinka Damjanovska Rajcevska⁷⁸, Georgi Bozinovski⁷⁸, Dieter Schöffel⁷⁹, Cord Sunderkötter⁸⁰, Markus Böhm⁸⁰, Jadranka Morović-Vergles⁸¹, Melanie-Ivana Čulo⁸¹, Maurizio Cutolo⁸², Alberto Sulli⁸², Chris T Derk⁸³, Sergio A Jimenez⁸³, Panagiota Siakka⁸⁴, Klaus Søndergaard⁸⁵, Kristian Stengaard-Pedersen⁸⁵, Jean Cabane⁸⁶, TIEV Kiet Phong⁸⁶, Carina Mihai⁸⁷, Roxana Sfrent-Cornateanu⁸⁷, Michael Jendro⁸⁸, Piia Tuvik⁸⁹, Marco Antivale⁹⁰, Giovanna Randisi⁹⁰, Matthias Seidel⁹¹, Ricarda Clarenbach⁹¹, Ismail Simsek⁹², Ayhan Dinc⁹², Murat Inanc⁹³, Monica Sinziana Capraru⁹⁴, Dorin Capraru⁹⁴, Inmaculada Bañegil⁹⁵, Jutta Richter⁹⁶, Saad Alhasani⁹⁷, Ivan Földvari⁹⁸, Sandra Pinto⁹⁹, Filipe Brandão⁹⁹, Antonio Juan Mas¹⁰⁰

1. Department of Rheumatology-Charité University Hospital, Berlin, Germany

2. Servizio di Reumatologia Allergologia e Immunologia Clinica Spedali Civili di Brescia, Brescia, Italy

3. UO Immunologia Clinica-Centro di Riferimento per le Malattie Autoimmuni Sistemiche, Milano, Italy

4. Division of Rheumatology, Department of Medical and Surgical Sciences, University of Padova, Padova, Italy

5. Radboud University Medical Centre, Nijmegen, The Netherlands

6. Johns Hopkins University Division of Rheumatology, Baltimore, Maryland, USA

7. Institute of Rheumatology, Russian Academy of Medical Science, Moscow, Russia

8. Department of Medicine, Division of Rheumatology, University of Florence, Florence, Italy

9. Ospedale Mauriziano Centro di Reumatologia, Torino, Italy

10. Rambam Medical Center, Haifa, Israel

11. Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Verona, Verona, Italy

12. Dipartimento Medicina Clinica e Sperimentale II Policlinico UO Reumatologia, Napoli, Italy

13. Universitätsklinik Köln, Köln, Germany

14. Department of Immunology and Rheumatology, Faculty of Medicine, University of Pécs, Pécs, Hungary

15. Hospital Universitario 12 de Octubre, Servicio de Reumatología, Madrid, Spain

16. UO Reumatologia Università degli studi di Bari, Bari, Italy

17. Paris Cochin Hospital, Groupe Hospitalier Cochin, Paris, France

18. Istituto di Clinica Medica Generale, Ematologia ed Immunologia Clinica Università di Ancona, Ancona, Italy

19. Department of Rheumatology, University Hospital Lund, Lund, Sweden

20. Institute of Rheumatology, Belgrade, Serbia

21. Kerckhoff-Klinik Bad Nauheim Universität Giessen, Bad-Nauheim, Germany

22. Medizinische Klinik und Poliklinik Internal Medicine, Rheumatology, Tübingen, Germany

23. Department of Internal Medicine, Rheumatology Unit, University of Pisa, Pisa, Italy

24. Day Hospital Rheumatology, "Gaetano Pini", Milano, Italy

25. Department of Clinical and Experimental Medicine, Section of Rheumatology, University of Ferrara, Ferrara, Italy

26. Department of Internal Medicine, Hôpital Claude Huriez, Lille, France

27. Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland

28. Department of Rheumatology and Internal Diseases, Medical University of Białystok, Białystok, Poland

29. Division of Rheumatology & Immunology, Charleston, South Carolina, USA

30. Department of Dermatology, Medical University of Lublin, Lublin, Poland

31. Rheumatology Unit Hospital and University of the Witwatersrand, Johannesburg, South Africa

32. Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany

33. Institute of Rheumatic Diseases, Piešťany, Slovak Republic

34. Division of Internal Medicine, Department of Rheumatology, University of Ljubljana, Ljubljana, Slovenia

35. Instituto português de Reumatologia, Lisbon, Portugal

36. Center for Autoimmune Diseases, Department of Medicine B, Sakler Tel-Aviv University, Tel Aviv, Israel

37. Reumatologia, Hospitais da Universidade, Coimbra, Portugal

38. Department of Dermatology, University of Düsseldorf, Düsseldorf, Germany

39. Institute of Rheumatology, 1st Medical School, Charles University of Prague, Prague, Czech Republic

40. Medizinische Universitätsklinik – Abteilung für Rheumatologie, University of Graz, Graz, Austria

41. Divisione di Reumatologia – Università "La Sapienza" Roma, Italy

42. Unità Operativa e Cattedra di Reumatologia, Policlinico S. Matteo, Pavia, Italy

43. Department of Pathophysiology Medical School, National University of Athens, Athens, Greece

44. Department of Dermatology, Georg-August-University of Göttingen, Göttingen, Germany

45. Department of Rheumatology and Connective Tissue Diseases, University of Lublin, Lublin, Poland

46. Clinica Reumatologie – Medicală II University of Medicine & Pharmacy, Cluj-Napoca, Romania

47. Department of Rheumatology University Medical Center of Leiden, Leiden, The Netherlands

48. Department of Rheumatology Marienhospital, Stuttgart, Germany

49. Klinikum der Johan Wolfgang Goethe – Universität Medizinische Klinik III, Rheumatologische Ambulanz, Frankfurt am Main, Germany

50. Department of Internal Medicine-I, University of Regensburg, Regensburg, Germany

51. Rheumatology Department of Internal Clinic Clinical Hospital of Split, Split, Croatia

52. Klinik für Dermatologie, Venerologie und Allergologie University of Leipzig, Leipzig, Germany

53. Rheumatology Division University of Debrecen, Debrecen, Hungary

54. Dipartimento di Medicina Interna e Sanità Pubblica, Insegnamento di Reumatologia University of L'Aquila, Aquila, Italy

55. Institute for prevention, treatment and rehabilitation rheumatic and cardiovascular disease Niska Banja, Serbia

56. Department of Rheumatology, Internal Medicine III, University of Vienna, Vienna, Austria

57. Department of Internal Medicine and Rheumatology, Medical University of Silesia, Katowice, Poland

58. Department of Dermatology, University of Warsaw, Warsaw, Poland

59. Hanyang University, Seoul, Korea

60. St Luke's Hospital, Guardamangia, Balzan, Malta

61. Rheumatology Granollers General Hospital, Granollers (Barcelona), Spain
62. Klinik für Dermatologie und Allergologie University of Ulm, Ulm, Germany
63. Department of Rheumatology and Endocrinology, Herlev, Denmark
64. Rheumatology Unit, Humanitas Clinical Institute, Rozzano Milano, Italy
65. Department of Rheumatology-St Maria Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
66. Department of Dermatology, University of Mainz, Mainz, Germany
67. Arcispedale Santa Maria Nuova UO di Reumatologia, Pad Spallanzani, Reggio Emilia, Italy
68. Department of Dermatology the 1st Faculty of Medicine, Charles University, Prague, Czech Republic
69. Servicio de Reumatología, Hospital Ramon Y Cajal, Madrid, Spain
70. Immunology and Allergy, University Hospital of Genève, Genève, Switzerland
71. Department of Rheumatology, Warsaw, Poland
72. Department of Rheumatology and Clinical Immunology, KBC, Rijeka, Croatia
73. Clinica di medicina interna ad orientamento immunologico Università di Genova, Genova, Italy
74. Department of Rheumatology Rigshospitalet, Copenhagen, Denmark
75. Department of Rheumatology and Rehabilitation, University of Poznan, Poznan, Poland
76. Department of Rheumatology, Rikshospitalet, Oslo, Norway
77. Department of Rheumatology, Hospital Santa Maria, Lisbon, Portugal
78. Rheumatology Clinic, Clinical Center Skopje, FYR Macedonia
79. Department of Rheumatology Westpfalz-KliniKum, Kusel, Germany
80. Department of Dermatology, University of Münster, Münster, Germany
81. Division of Clinical Immunology and Rheumatology, Dubrava University Hospital of Zagreb, Zagreb, Croatia
82. Research Laboratory and Division of Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy
83. Thomas Jefferson University of Philadelphia, Philadelphia, PA, USA
84. Department of Rheumatology, Thessaloniki, Greece
85. Department of Rheumatology, University Hospital of Aarhus, Aarhus, Denmark
86. Service de Médecine Interne 2° Hopital Saint Antoine, Paris, France
87. Clinic of Internal Medicine and Rheumatology, Dr I Cantacuzino Hospital, Bucharest, Romania
88. Rheumatologische Ambulanz, Medizinische Klinik I, Universitätsklinikum Saarlandes, Homburg, Germany
89. North-Estonian Regional Hospital, Tallin, Estonia
90. Unità Operativa di Reumatologia, Azienda Ospedaliera-Polo Universitario, Ospedale L Sacco, Milano, Italy
91. Department of Rheumatology, Medizinische Universitäts-Poliklinik, Bonn, Germany
92. Division of Rheumatology, Gulhane Military Medical Academy, Ankara, Turkey
93. Department of Internal Medicine, Division of Rheumatology, Medical Faculty of Istanbul, Turkey
94. Department of Rheumatology, "Professor Dr D Gerota" Emergency Hospital, Bucharest, Romania
95. Consulta Reumatologia, Hospital de Mendaro, Mendaro, Spain
96. Department of Rheumatology Heinrich-Heine University of Düsseldorf, Düsseldorf, Germany
97. Rheumatology and Rehabilitation Department of Mosul, Mosul, Iraq
98. Pediatric Rheumatology Clinic, Hamburg, Germany
99. Hospital São João Serviço de Reumatologia, Porto, Portugal
100. Hospital son Llätzer, Palma de Mallorca, Spain



Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database

U A Walker, A Tyndall, L Czirják, C Denton, D Farge-Bancel, O Kowal-Bielecka, U Müller-Ladner, C Bocelli-Tyndall and M Matucci-Cerinic

Ann Rheum Dis 2007 66: 754-763 originally published online January 18, 2007
doi: 10.1136/ard.2006.062901

Updated information and services can be found at:
<http://ard.bmj.com/content/66/6/754>

	<i>These include:</i>
References	This article cites 26 articles, 10 of which you can access for free at: http://ard.bmj.com/content/66/6/754#BIBL
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Immunology \(including allergy\)](#) (4381)
[Connective tissue disease](#) (3682)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>