Article

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

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Abstract

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.

EXTENDED REPORT

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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subsets are associated with particular organ manifestations, but in this analysis the clinical distinction seemed to be superseded by an antibody-based classification in predicting some scleroderma complications.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 $5/10^5$ and an incidence of $1/10^5$.[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 scerosis; PAH, pulmonary artery hypertension (assessed by echocardiography); SSc, sytemic 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 plausability 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 Nagelkerkes-R^2) 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.

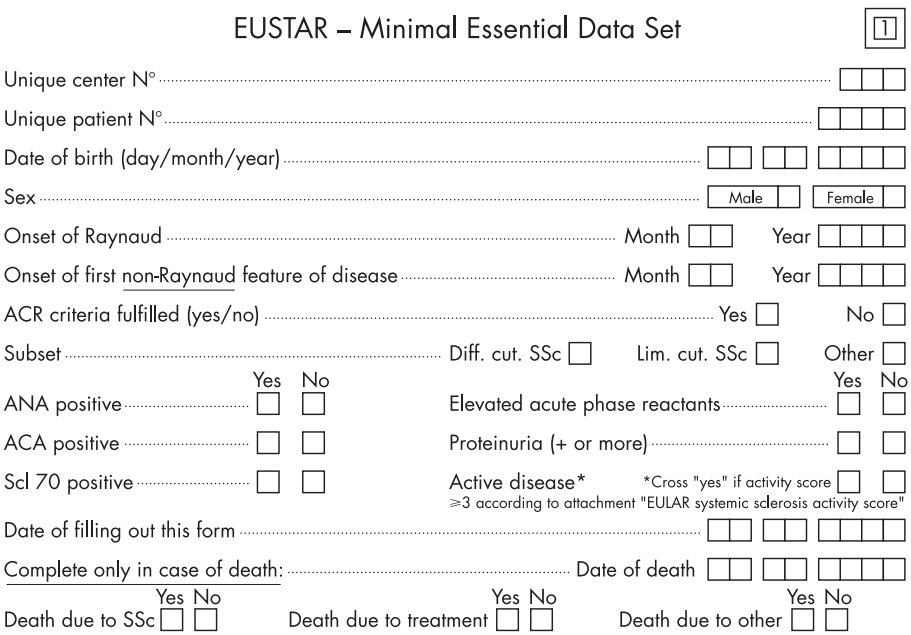
Pulmonary fibrosis was more common in dcSSc (53.4%) than in lcSSc (34.7%), whereas the frequency of pulmonary artery hypertension (PAH) diagnosed by echocardiography was similar between the two subsets (in 22.3% of patients with dcSSc and in 20.5% of patients with lcSSc). Isolated PAH (in the absence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

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

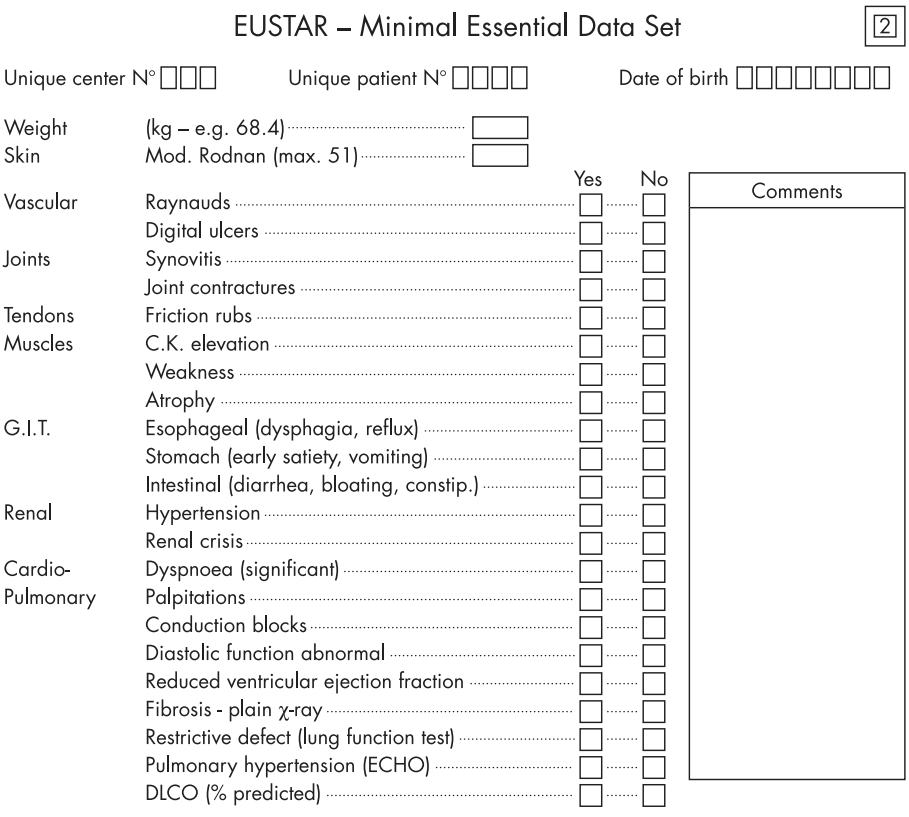
Subset Diff. cut. SSc Lim. cut. SSc Other

	Yes	No		Yes	No
ANA positive			Elevated acute phase reactants		
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
Vascular	Raynauds		
	Digital ulcers		
Joints	Synovitis		
	Joint contractures		
Tendons	Friction rubs		
Muscles	C.K. elevation		
	Weakness		
	Atrophy		
G.I.T.	Esophageal (dysphagia, reflux)		
	Stomach (early satiety, vomiting)		
	Intestinal (diarrhea, bloating, constip.)		
Renal	Hypertension		
	Renal crisis		
Cardio-Pulmonary	Dyspnoea (significant)		
	Palpitations		
	Conduction blocks		
	Diastolic function abnormal		
	Reduced ventricular ejection fraction		
	Fibrosis - plain χ-ray		
	Restrictive defect (lung function test)		
	Pulmonary hypertension (ECHO)		
	DLCO (% predicted)		

Comments

Figure 1 Items of the Minimal Essential Data Set.

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).

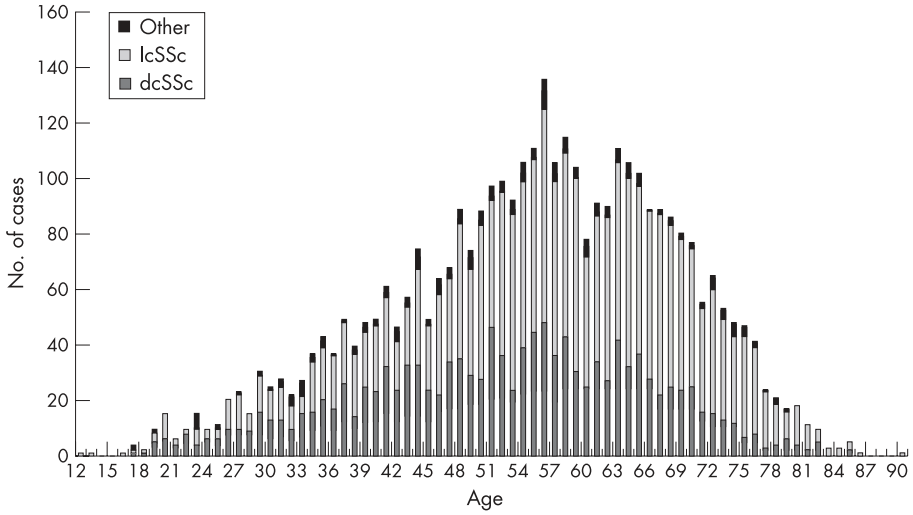


Figure 2 Age distribution of scleroderma subsets. dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic scerosis.

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 scerosis; 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 scerosis; 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 UK[6] (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.

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

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