Gender differences in early systemic sclerosis patients: a report from the EULAR scleroderma trials and research group (EUSTAR) database

P.E. Carreira[1], L. Carmona[2], B.E. Joven[1], E. Loza[2], J.L. Andreu[3], G. Riemekasten[4], S. Vettori[5], A. Balbir-Gurman[6], P. Airò[7], U.A. Walker[8], N. Damjanov[9], M. Matucci-Cerinic[10], L.P. Ananieva[11], S. Rednic[12], L. Czirják[13], O. Distler[14], D. Farge[15], R. Hesselstrand[16], A. Corrado[17], P. Caramaschi[18], M. Tikly[19], Y. Allanore[20], and the EUSTAR co-authors

Patricia E. Carreira, MD
Loreto Carmona, MD, PhD
Beatriz E. Joven, MD
Estibaliz Loza, MD
Jose Luis Andreu, MD, PhD
Gabriela Riemekasten, MD, PhD
Serena Vettori, MD, PhD
Alexandra Balbir-Gurman, MD, PhD
Paolo Airò, MD, PhD
Ulrich A. Walker, MD, PhD
Nemanja Damjanov, MD, PhD
Marco Matucci-Cerinic, MD, PhD
Lidia P. Ananieva, MD, PhD
Simona Rednic, MD, PhD
László Czirják, MD, PhD
Oliver Distler, MD, PhD
Dominique Farge, MD, PhD
Roger Hesselstrand, MD, PhD
Ada Corrado, MD, PhD
Paola Caramaschi, MD, PhD
Mohammed Tikly, MD, PhD
Yannick Allanore, MD, PhD
*EUSTAR co-authors**

**The list of EUSTAR co-authors is in the additional file 1.*

Please address correspondence to:
Dr Patricia E. Carreira,
Servicio de Reumatología,
Hospital Universitario 12 de Octubre,
CAA planta 5 zona D, A
vda de Córdoba s/n,
28041 Madrid, Spain.
E-mail: carreira@h12o.es

Received on April 21, 2017; accepted in revised form on March 9, 2018.

Clin Exp Rheumatol 2018; 36 (Suppl. 113): S68-S75.

Key words: systemic sclerosis, gender, cohort

For the authors' affiliations, funding and competing interests, see page S-74.

ABSTRACT

Objective. *To describe differences in clinical presentation between men and women in a large group of patients with early (<3 years' duration) systemic sclerosis (SSc) according to disease subsets.*

Methods. *A cross-sectional analysis of the prospective EULAR Scleroderma Trial and Research database (EUSTAR) was performed. Patients fulfilling preliminary ACR 1980 classification criteria for SSc, with less than 3 years from the first non-Raynaud's symptom at first entry, were selected. A group of patients with less than 3 years from the first SSc symptom, including Raynaud's phenomenon, was also analysed. SSc related variables, including antibodies, SSc subsets, disease activity and organ involvement were included. Descriptive and bivariate analyses were performed.*

Results. *A total of 1,027 patients were included, 90% Caucasian, 80% women, and 40% with diffuse cutaneous disease. In early stages of SSc, men showed more frequently than women active disease, diffuse cutaneous subset, anti-Scl-70 antibodies, elevated acute phase reactants, muscular and pulmonary involvement. Differences between men and women were confirmed in the limited, but not in the diffuse SSc subset. The results were similar when 650 patients with less than three years from the first SSc symptom, including Raynaud's phenomenon, were analysed.*

Conclusion. *In early stages of SSc, men present signs and symptoms of more severe disease. In the limited disease subset, men might appear with clinical features and organ involvement similar to those of the diffuse subgroup. In clinical practice, the identification of such differences might help to select the appropriate management for each particular patient.*

Introduction

Systemic sclerosis (SSc) is a rare disease, with an estimated prevalence of 8-30 cases per 100,000 inhabitants (1-3) and a very low annual incidence, from 1 to 2.5 new cases per 100,000 inhabitants (1, 4). SSc affects more frequently women than men, and is associated with significant morbidity, including pain, disability, depression, reduced quality of life, increased mortality, and high costs (1, 2, 5-8).

SSc is also a complex disease, presenting different clinical patterns that may influence outcomes. These differences could be present both at the onset and/or during the disease course. Thus, as in other chronic autoimmune diseases, the study of factors that might modulate disease outcome is crucial. Among these factors, gender has been described to play a key role in the incidence, severity and progression of autoimmune diseases (9). Such differences have been explained, at least in part, by genetic and hormonal factors, as well as by lifestyle patterns (10).

In SSc, male sex is associated with worse outcomes including survival (1, 2, 6, 11-14). In prevalent studies, men have been found to present more frequently diffuse cutaneous involvement, anti-Scl-70 antibodies and severe organ involvement, less frequently anti-centromere antibody (ACA), and a shorter time between the onset of Raynaud's phenomenon and first non-Raynaud's symptom of the disease (15-17). Nevertheless, the low number of men analysed in previous studies and

the clinical heterogeneity of the disease, make difficult the generalisation of these findings. Moreover, there is little information regarding to whether the effect of these factors might be already present at disease onset.

The EULAR Scleroderma Trials and Research (EUSTAR) group established a prospective multicentre SSc cohort to foster the awareness, understanding and research of SSc and its care and management throughout Europe (18). EUSTAR database provides a unique opportunity to study a large and representative number of SSc patients, facilitating the accuracy of a very well defined set of outcomes, including disease onset.

The aim of this study is to analyse in detail gender differences in clinical presentation early after disease onset, in an effort to contribute to the understanding of SSc clinical course and outcome. In clinical practice, this might also lead to improvements in the identification of cases, monitoring and decision making, in order to minimise SSc impact during the disease course.

Methods

EUSTAR database

The EUSTAR database has been previously described (18). Briefly, the database was initiated in June 2004 and documents a multinational (194 centres), prospective and open SSc cohort. Participating centres seek ethics committee approval, followed by the entry of the Minimal Essential Data set (MEDS) for all consecutive consenting patients with SSc, including data on demographics, disease onset, clinical features and disease activity. The disease is considered active, according to the SSc activity score proposed by the European Scleroderma Study Group (19), if the sum of the scores of detected items with their respective weight (modified Rodnan skin score> 14, hand or fingers oedema, skin worsening, digital ischaemia/necrosis, vascular worsening, arthritis, DLCO<80%, worsening of heart/lung disease, ESR>30, hypocomplementaemia) is ≥3 (19). Data are updated annually. For the purpose of the present study, all patients included in the EUSTAR database until June 2008 (the time of data extraction for this analysis), fulfilling the preliminary ACR 1980 classification criteria for SSc (20), and with less than 3 years from the first non-Raynaud's SSc symptom at the first EUSTAR entry, were selected. The group of patients with less than 3 years from the first SSc symptom, including Raynaud's phenomenon, was also studied. Very early subgroups, defined as disease duration of less than 12 months from the first non-Raynaud's symptom or from the first SSc symptom, including Raynaud's phenomenon, respectively, were analysed as well.

Variables

Baseline data of the first EUSTAR entry were analysed. All the variables included in the analysis have been previously defined in EUSTAR (18). From EUSTAR MEDS, only objective variables, defined and measured by validated criteria, specific measurements or imaging techniques were considered. Subjective variables such as dyspnea, palpitations or muscular weakness were not analysed. Digestive symptoms (oesophagus, stomach and gut symptoms), although subjective, were integrated into one variable (digestive involvement) and analysed. The presence of Raynaud's phenomenon and ANA positivity as dichotomised variables, were also excluded from the analyses because they were present in more than 90% of the study sample, and their presence did not influence the results.

Finally, we analysed the following variables a) socio-demographic including sex, age (at EUSTAR entry, at first non-Raynaud's symptom, at first SSc symptom, including Raynaud's); b) disease related variables: time between Raynaud's and first non-Raynaud symptom; disease duration, calculated from the onset of the first non-Raynaud's symptom and also from the first SSc symptom, including Raynaud's; SSc subsets as previously proposed (21): diffuse cutaneous systemic sclerosis (dcSSc), and limited cutaneous systemic sclerosis (lcSSc), considering the disease course from the beginning, and being mutually exclusive, that is, if a patient had ever diffuse cutaneous involvement he/she would be always considered dcSSc; positivity for anti-Scl70 and ACA antibodies; mRSS (modified Rodnan skin score); disease activity - calculated as a composite score from MEDS features according to the preliminary index for SSc, proposed by the European Scleroderma Study Group, described above and detailed elsewhere(19) - ; elevation of acute phase reactants (ESR higher than 30 mm and/or CRP over normal values); vascular involvement including ischaemic digital ulcers; joint involvement defined as the presence of synovitis, joint contractures or tendon friction rubs; muscle involvement defined as CK (creatine kinase) elevation; digestive involvement as previously defined; lung involvement including fibrosis (diagnosed by x-ray or thoracic computed tomography), lung restrictive defect, defined as Forced Vital Capacity (FVC) below 80%, and DLCO (diffusion capacity of the lung for carbon monoxide, % of predicted) level; cardiac involvement, including the presence of conduction blocks in EKG, diastolic dysfunction, or left ventricular ejection fraction <55% in cardiac echocardiography; elevated sPAP (estimated systolic pulmonary artery pressure), defined as an estimated sPAP higher than 40 mmHg in Doppler echocardiography; and renal crisis.

Statistical analysis

Quantitative variables were described by means ± standard deviations (SD) and qualitative variables with frequencies and percentages. For comparisons between men and women, Pearson chi-square test for qualitative variables, and the two-sample *t*-test were used. Bonferroni adjustment for multiple comparisons lead to a *p*-value <0.002 considered statistically significant. Analyses were performed using Stata 12 statistical software (Stata Corporation, College Station,TX).

Results

The study sample comprised 1,027 patients (early group), almost 90% Caucasian, with mean disease duration, from the first non-Raynaud symptom, of 18 months, 80% were women, and 40% presented dcSSc. A subgroup of

Table I. Baseline characteristics and bivariate associations between sex and clinical and demographic characteristics in early (less than 3 years from the first non-Raynaud symptom) and very early (less than 1 year from the first non-Raynaud symptom) groups.

Variable	Very early disease (≤1 year) n=461			Early disease (≤ 3 years)§ n=1027		
	Men (n=100)	Women (n=361)	*p*-value*	Men (n=200)	Women (n=827)	*p*-value*
	Quantitative variables, mean±SD (n)					
Age (yr)						
• At 1st non-Raynaud's symptom	50.9±13.7 (100)	49.6±14.7 (361)	0.414	50.0±14.9 (200)	50.4±14.5 (827)	0.730
• At 1st SSc symptom	48.3±1.4 (100)	46.4±0.8 (361)	0.271	47.5±1.0 (200)	46.9±0.5 (827)	0.603
• At 1st EUSTAR entry	52.1±13.6 (100)	50.8±14.7 (361)	0.458	51.6±14.9 (200)	52.2±14.6 (827)	0.589
Disease duration (m)†	11.9±0,7 (100)	11.8±0.9 (413)	0.695	18.0±6.2 (200)	18.6±6.2 (827)	0.198
Raynaud – non-Raynaud (m)	31.2±66 (100)	38.4±84 (361)	0.390	28.8±68.4 (200)	40.8±86.4 (827)	0.031
mRSS	14.8±9.6 (99)	10.5±9.4 (352)	0.0001	16.0±10.5 (199)	10.8±9.8 (816)	<0.0001
DLCO (% of predicted)	62.8±23.8 (78)	73.3±18.8 (255)	0.0005	66.2±22.3 (155)	72.3±20.0 (585)	0.001
	Qualitative variables, n; percentage (n)					
Active disease	61; 66% (92)	143; 42% (344)	**<0.0001**	112; 59% (190)	307; 38% (802)	**<0.0001**
Antibodies						
Scl-70	57; 57% (99)	109; 31% (353)	**<0.0001**	104; 53% (196)	256; 31% (811)	**<0.0001**
ACA	11; 11% (96)	110; 32% (340)	**<0.0001**	18; 9% (189)	263; 33% (789)	**<0.0001**
SSc subsets						
• dcSSc	59; 60.2% (98)	120; 33.6% (357)	**<0.0001**	120; 61% (197)	286; 35% (818)	**<0.0001**
• lcSSc	34; 34.7% (98)	202; 56.6% (357)	**<0.0001**	68; 34% (197)	463; 57% (818)	**<0.0001**
Elevated acute phase reactants	60; 61% (98)	121; 34% (351)	**<0.0001**	109; 56% (195)	259; 32% (808)	**<0.0001**
Digital ischaemic ulcers	40; 40% (99)	98; 27% (360)	0.011	73; 37% (199)	233; 28% (825)	0.020
Synovitis	21; 21% (99)	85; 24% (360)	0.616	46; 23% (199)	161; 19% (826)	0.253
Joint contractures (any joint)	35; 36% (98)	95; 26% (359)	0.072	75; 38% (198)	220;27% (825)	**0.002**
Tendon friction rubs	23; 24% (96)	49; 14% (357)	0.015	46; 23% (196)	110; 13% (820)	**<0.0001**
CK elevation	25; 26% (97)	47; 13% (351)	0.003	55; 26% (195)	92; 11% (807)	**<0.0001**
Digestive tract involvement‡	64; 65% (99)	236; 66% (359)	0.840	135; 69% (135)	561; 68% (824)	0.947
sPAP> 40 mm Hg on Doppler-echocardiography	25; 26% (97)	57; 16% (348)	0.035	40; 20% (196)	129; 16% (804)	0.144
Pulmonary fibrosis	43; 45% (96)	95; 27% (353)	0.001	86; 44% (194)	232; 29% (810)	**<0.0001**
FVC<80% of predicted	40; 41% (98)	70; 20% (347)	**<0.0001**	77; 39% (196)	208; 26% (803)	**<0.0001**
Cardiac conduction blocks	16; 16% (98)	26; 7% (348)	0.008	89; 9% (196)	60; 7% (806)	**0.001**
LV diastolic dysfunction	22; 23% (97)	48; 14% (348)	0.034	35; 18% (196)	116; 14% (805)	0.227
LV ejection fraction<55%	5; 5% (98)	14; 4% (346)	0.648	10; 5% (197)	34; 4% (799)	0.616
Renal crisis	6; 6% (98)	11; 3% (360)	0.155	8; 4% (198)	26; 3% (826)	0.529

Yr: year; m: month; mRSS: modified Rodnan skin score; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; CK: creatin kinase; sPAP: estimated systolic pulmonary artery pressure; FVC: forced vital capacity; LV: left ventricle; SD: standard deviation.
§Early group (≤3 years) includes the patients from the very early group (≤1 year). *Bonferroni adjustment was used for multiple comparisons. A *p*-value <0.002 was considered statistically significant. †Disease duration was calculated on the basis of the onset of the first SSc symptom, including Raynaud's phenomenon. ‡Digestive tract involvement includes oesophagus, stomach and gut symptoms.

461 patients with disease duration of less than 12 months (very early group) was also analysed. In the very early subgroup, 78% were women and 34% presented dcSSc. Patient's characteristics and bivariate associations between sex and clinical and demographic characteristics of the early and very early groups, are presented in Table I.

In the early group, men, compared to women, presented higher mRSS score (16 *vs*. 11), and more frequently dcSSc subset (61% *vs*. 35%), anti-Scl70 antibodies (53% *vs*. 31%), active disease (59% *vs*. 38%), elevated acute phase reactants (56% *vs*. 32%), CK elevation (26% *vs*. 11%), tendon friction rubs (23% *vs*. 13%), pulmonary fibrosis (44% *vs*. 29%), FVC<80% (39% *vs*. 26%) and cardiac conduction blocks (9% *vs*. 7%). On the other hand, women presented lcSSc and ACA positivity more frequently than men. In the very early group, the results were similar: men, compared to women, presented higher mRSS, more aScl70 and less ACA, more active disease and acute phase reactant elevation, and more frequent organ involvement, specifically FVC<80%.

In the analysis stratified by SSc subsets, as shown in Table II, in the early group there were no significant differences related to sex in demographic and clinical characteristics in the dcSSc subset, except for more elevated acute phase response, and a trend towards more aScl70 and CK elevation. However, in the lcSSc subset, men had higher mRSS (8 *vs*. 6), more frequently elevated acute phase reactants (45% *vs*. 25%) and cardiac conduction blocks (18% *vs*. 5%), and less ACA (21% *vs*. 51%) than women. Although no other differences showed statistical significance within the lcSSc subset, we found a marked trend towards more frequent active disease, joint contractures, CK elevation, FVC<80% and pulmonary fibrosis in men compared to women.

Table II. Bivariate associations between sex and clinical and demographic characteristics, according to disease subset, in patients with disease duration of less than 3 years from the first non-Raynaud symptom.

Variable	dcSSc n=406 (43%)§			lcSSc n=531 (57%)§		
	Men (n=120)	Women (n=286)	*p*-value*	Men (n=68)	Women (n=463)	*p*-value*
	Quantitative variables: mean±SD (N)					
Age (yr)						
• At 1st non-Raynaud symptom	48.0±13.8 (120)	48.6±14.8 (286)	0.711	53.8±15.6 (68)	51.9±14.0 (463)	0.293
• At 1stSSc symptom	46.3±1.2 (120)	46.9±0.9 (286)	0.711	50.1±2.0 (68)	47.1±0.7 (463)	0.125
• At 1st EUSTAR entry	49.7±13.8 (120)	50.5±14.8 (286)	0.620	55.4±15.6 (77)	53.8±14.1 (463)	0.384
Disease duration (m)†	18.1±6.3 (120)	18.8±6.1 (286)	0.322	17.8±6.2 (68)	18.6±6.2 (463)	0.369
Raynaud – non-Raynaud (m)	19.2±55.2 (120)	18±60 (286)	0.905	43.2±85.2 (68)	57.6±99.6 (463)	0.297
mRSS	21.2±9.9 (120)	20.2±9.4 (280)	0.336	8.2±4.5 (68)	6.2±5.1 (459)	**0.002**
DLCO (% of predicted)	65.5±20.9 (89)	66.2±20.6 (184)	0.775	67.4±25.1 (57)	74.9±18.5 (315)	0.036
	Qualitative variables: n; percentage (N)					
Active disease	84; 73% (115)	188; 67% (280)	0.250	23; 36% (63)	105; 23% (448)	0.025
Antibodies						
• Scl-70	78; 67% (116)	141; 51% (278)	0.003	22; 32% (68)	97; 21% (455)	0.043
• ACA	3;3% (112)	14; 5% (263)	0.260	14; 21% (66)	228 ; 51% (450)	**<0.0001**
Elevated acute phase reactants	73; 62% (117)	125; 45% (275)	0.002	30; 45% (66)	114; 25% (457)	**<0.0001**
Digital Ischaemiculcers	47; 39% (120)	95; 33% (286)	0.251	22; 32% (68)	125; 27% (461)	0.368
Synovitis	29; 24% (120)	65; 24% (286)	0.754	15; 22% (68)	78; 17% (462)	0.295
Joint contractures (any joint)	52; 44% (119)	131; 46% (286)	0.698	19; 28% (68)	79; 17% (513)	0.032
Tendon friction rubs	39; 33% (118)	74; 26% (283)	0.161	6; 9% (68)	27; 6% (459)	0.350
CK elevation	34; 29% (116)	46; 17% (274)	0.005	12; 18% (68)	32; 7% (457)	0.003
Digestive tract involvement‡	78; 65% (120)	218; 76% (286)	0.020	51; 75% (68)	301; 65% (460)	0.118
sPAP> 40 mm Hg on Doppler-echocardiography	32; 23% (137)	63; 19% (332)	0.283	11; 16% (67)	71; 16% (451)	0.888
Pulmonary fibrosis	59; 50% (117)	116; 41% (279)	0.106	24; 35% (68)	100; 22% (457)	0.015
FVC<80% of predicted	49; 42% (117)	107; 39% (275)	0.582	23; 34% (68)	89; 20% (454)	0.008
Cardiac conduction blocks	17; 14% (117)	28; 10% (280)	0.194	14; 18% (68)	25;5% (452)	**<0.0001**
LV diastolic dysfunction	23; 19% (119)	47; 17% (279)	0.552	10; 15% (67)	59; 13% (451)	0.679
LV ejection fraction<55%	7; 6% (119)	11; 4% (274)	0.416	3; 4% (68)	18; 4% (451)	0.870
Renal crisis	6; 5% (120)	19; 7% (285)	0.525	2; 3% (68)	6; 1% (463)	0.298

dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; yr: year; m: month; mRSS: modified Rodnan skin score; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; CK: creatin kinase; sPAP: estimated systolic pulmonary artery pressure; FVC: forced vital capacity; LV: left ventricle; SD: standard deviation.

§From 1,027 patients in the early group, only 937 had information regarding disease subset. *Bonferroni adjustment was used for multiple comparisons. A *p*-value <0.002 was considered statistically significant. †Disease duration was calculated on the basis of the onset of the first non-Raynaud's symptom. ‡Digestive tract involvement includes oesophagus, stomach and gut symptoms.

From the total sample, 650 patients had a disease duration of less than 3 years from the first SSc symptom, including Raynaud's phenomenon (77%women, mean disease duration 17±10 months). The results of the analysis of this group, including the very early subgroup, with less than one year from the first SSc symptom, including Raynaud (204 patients, 74% women, mean disease duration 7±5 months) were very similar to the results found in the whole sample (Table III). In the analysis stratified by SSc subsets (Table IV), in the dcSSc group, men presented more frequently anti-Scl70 and elevated acute phase reactants than women. There were not statistical differences between men and women in the lcSSc subgroup, but there was a trend towards a higher mRSS, more active disease and elevated acute phase reactants, CK elevation, FVC>80% of predicted and cardiac conduction blocks in men compared to women.

Discussion

Although male sex has been associated with worse disease outcomes in SSc, to our knowledge, no studies have properly examined sex differences in clinical expression at early stages of the disease.

In the initial reports of the EUSTAR cohort, the only sex differences identified were basically that men, compared to women, were younger at disease onset, presented a shorter time between the onset of Raynaud's phenomenon and the first non-Raynaud's symptom and had less ACA positivity than women (18, 23). In a recent study analysing the effect of sex on disease phenotype and outcome in the EUSTAR cohort, including more than 9,000 patients, male sex was associated with more severe disease at baseline, showing more dcSSc subset, digital ulcers, and pre-capillary pulmonary hypertension and was also predictive of new development of pre-capillary pulmonary hypertension and heart dysfunction (22). However, in this study, patients mean disease duration was 8.5 years from the first non-Raynaud symptom, a prevalent cohort, where most patients had already developed the full clinical picture.

Our study shows that men present a more severe disease than women from very early stages of the disease. Men

Table III. Bivariate associations between sex and clinical and demographic characteristics, according to disease duration at first EUSTAR entry, from thefirst SSc symptom, including Raynaud's phenomenon.

Variable	Very early disease (≤1 year) n=204			Early disease (≤ 3 years)[§] n=650		
	Men (n=53)	Women (n=151)	*p*-value*	Men (n=149)	Women (n=501)	*p*-value*
	Quantitative variables, mean±SD (n)					
Age (yr)						
• At 1st non-Raynaud's event	50.5±15.3 (53)	50.0±13.9 (151)	0.830	49.0±15.0 (149)	49.5±14.5 (501)	0.726
• At 1st Raynaud event	50.5±15.2 (53)	50.1±13.9 (151)	0.855	48.8±15.0 (149)	49.2±14.6 (501)	0.764
• At 1st EUSTAR entry	51.7±15.3 (53)	51.2±13.8 (151)	0.832	50.6±15.0 (149)	51.2±14.6 (501)	0.706
Disease duration (m)[†]	5.88±5.88 (53)	6.6±4.68 (151)	0.416	16.9±10.3 (149)	18.0±9.6 (501)	0.226
Raynaud – non-Raynaud (m)	-0.6±6.0 (53)	-1.7±6.0 (151)	0.328	3.0±7.1 (149)	3.5±8.6 (501)	0.507
mRSS	18.4±10.1 (53)	13.0±10.1 (151)	0.0008	17.0±10.5 (149)	12.7±10.3 (502)	**<0.0001**
DLCO (% of predicted)	63.6±23.3 (41)	70.7±18.2 (96)	0.058	66.9±21.0 (117)	71.5±19.2 (332)	0.033
	Qualitative variables, n; percentage (n)					
Active disease	35; 74% (47)	77; 53% (144)	0.011	89; 63% (142)	212; 44% (483)	**<0.0001**
Antibodies						
• Scl-70	36; 70% (51)	42; 29% (147)	**<0.0001**	78; 54% (145)	176; 36% (489)	**<0.0001**
• ACA	2; 4% (51)	25; 18% (141)	0.015	10; 7% (141)	105; 22% (471)	**<0.0001**
SSc subsets						
• dcSSc	39; 73.6% (53)	75; 50.0% (150)	0.003	97; 66% (147)	220; 44% (495)	**<0.0001**
• lcSSc	13; 24.5% (53)	59; 39.3% (150)	0.053	44; 30% (147)	237; 49% (495)	**<0.0001**
Elevated acute phase reactants	34; 65% (52)	53; 36% (146)	**<0.0001**	82; 56% (146)	165; 34% (487)	**<0.0001**
Digital ischaemic ulcers	19; 36% (53)	39; 26% (151)	0.164	54; 36% (149)	125; 25% (500)	0.007
Synovitis	14; 26% (53)	40; 26% (151)	0.992	33; 22% (149)	96; 19% (500)	0.429
Joint contractures (any joint)	20; 38% (53)	51; 34% (151)	0.602	58; 39% (148)	156; 31% (500)	0.069
Tendon friction rubs	15; 29% (52)	28; 18% (151)	0.117	36; 24% (147)	79; 16% (497)	0.017
CK elevation	15; 29% (52)	24; 16% (146)	0.053	42; 29% (145)	67; 14% (491)	**<0.0001**
Digestive tract involvement[‡]	37;70% (53)	99; 66% (151)	0.572	102; 68% (149)	333; 67% (500)	0.672
sPAP> 40 mm Hg on Doppler-echocardiography	9; 17% (52)	29; 20% (144)	0.658	25; 17% (147)	79; 16% (485)	0.837
Pulmonary fibrosis	21; 40% (52)	46; 31% (147)	0.233	60; 41% (146)	155; 31% (489)	0.028
FVC<80% of predicted	16; 31% (52)	35; 24% (144)	0.363	60; 41% (147)	130; 27% (487)	**0.001**
Cardiac conduction blocks	11; 21% (52)	12; 8% (144)	0.014	19; 13% (146)	37; 8% (486)	0.044
LV diastolic dysfunction	19; 21% (52)	19; 13% (143)	0.178	27; 18% (146)	75; 15% (487)	0.340
LV ejection fraction<55%	4; 8% (52)	5; 3% (142)	0.221	8; 5% (147)	19; 4% (480)	0.438
Renal crisis	2; 4% (53)	4; 3% (150)	0.683	7; 5% (149)	18; 4% (500)	0.541

SSc: systemic sclerosis; yr: year; mRSS: modified Rodnan skin score; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; CK: creatin kinase; sPAP: estimated systolic pulmonary artery pressure; FVC: forced vital capacity; LV: left ventricle; SD: standard deviation.

[§]Early group (≤ 3 years) includes the patients from the very early group (≤1 year). *Bonferroni adjustment was used for multiple comparisons. A *p*-value <0.002 was considered statistically significant. [†]Disease duration was calculated on the basis of the onset of the first SSc symptom, including Raynaud's phenomenon. [‡]Digestive tract involvement includes oesophagus, stomach and gut symptoms.

showed more frequently active disease, dcSSc subset, anti-Scl-70 antibodies, elevated acute phase reactants, muscular and pulmonary involvement. The most interesting finding of the present study is that men with early lcSSc present a clinical picture suggestive of a more severe disease than women, with increased organ involvement, similar to that observed in dcSSc patients. In contrast, men and women with early dcSSc presented similar disease severity. Although less evident and not statistically significant, probably due to the lower number of patients in this subgroup, even in patients with very early disease (less than one year from the first non-Raynaud symptom), sex differences were still apparent (Table I). It is possible that at least some of these early lcSSc patients have not developed yet the full disease expression at the moment of EUSTAR entry, and could become dcSSc soon after inclusion. In this regard, our results would suggest that some men with early lcSSc, but showing some features of dcSSc, should be managed as dcSSc patients with very close clinical monitoring, in order to detect as early as possible any kind of organ involvement. Another explanation to our findings could be, as it has been suggested, that men with less severe and indolent disease course might not demand medical care for milder features, whereas women may consult more often for non-specific symptoms (15). This may account, at least in part, for the high rate of severe cases in the group of men with limited disease subset. It is known that mRSS may decline spontaneously even in patients with very early disease (25), so it would be possible that some of the lcSSc patients could have a dcSSc whose skin disease has regressed to an lcSSc distribution at EUSTAR enrolment. However, this seems not to be the cause, because in EUSTAR, by definition, patients with dcSSc involvement at any time during

Table IV. Bivariate associations between sex and clinical and demographic characteristics, according to disease subset, in patients with disease duration of less than 3 years from the first SSc symptom, including Raynaud's phenomenon.

Variable	dcSSc (N=317)§			lcSSc (N=281)§		
	Men (n=97)	Women (n=220)	*p*-value*	Men (n=44)	Women (n=237)	*p*-value*
	Quantitative variables, mean±SD (n)					
Age (yr)						
• At 1st non-Raynaud's event	47.5±13.8 (97)	48.3±14.6 (220)	0.613	53.7±16.1 (44)	50.7±14.3 (237)	0.206
• At 1st Raynaud event	47.2±13.8 (97)	48.1±14.7 (220)	0.610	53.4±16.2 (44)	50.3±14.3 (237)	0.195
• At 1st EUSTAR entry	49.1±13.8 (97)	50.1±14.6 (220)	0.566	55.4±16.0 (44)	52.4±14.4 (237)	0.319
Disease duration (m)†	16.8±10.8 (97)	16.8±9.6 (220)	0.706	18.0±10.8 (44)	19.2±9.6 (237)	0.312
Raynaud – non-Raynaud (m)	2.4±6.96 (97)	2.04±8.16 (220)	0.753	4.08±7.56 (44)	4.92±9.12 (237)	0.543
mRSS	21.2±10.0 (97)	20.7±9.1 (219)	0.653	8.9±4.9 (44)	6.6±5.5 (237)	0.010
DLCO (% of predicted)	66.9±20.1 (76)	67.0±20.2 (144)	0.975	67.3±23.8 (35)	74.5±17.4 (155)	0.102
	Qualitative variables, n; percentage (n)					
Active disease	66; 71% (93)	146; 68% (215)	0.594	19;46% (41)	56; 25% (26)	0.005
Antibodies						
• Scl-70	63; 68% (93)	104; 49% (214)	**0.002**	13;30% (44)	63; 27% (231)	0.757
• ACA	2; 2% (90)	6; 3% (201)	0.713	8;18% (44)	91; 40% (227)	0.006
Elevated acute phase reactants	59; 63% (94)	92; 43% (212)	**0.002**	18;41% (44)	62; 27% (232)	0.060
Digital ischaemic ulcers	35; 36% (97)	63; 29% (220)	0.186	16; 36% (44)	54;23% (236)	0.058
Synovitis	22; 23% (97)	50; 21% (220)	0.993	9; 20% (44)	39; 16% (236)	0.526
Joint contractures (any joint)	42; 44% (96)	102; 46% (220)	0.635	12; 27% (44)	47; 20% (236)	0.272
Tendon friction rubs	31; 33% (95)	60; 27% (218)	0.360	4; 9% (44)	13; 5% (235)	0.365
CK elevation	29; 31% (93)	36; 17% (214)	0.005	9; 20% (44)	21; 9% (234)	0.024
Digestive tract involvement‡	64; 66% (97)	166; 75% (220)	0.081	33; 75% (44)	144; 61% (236)	0.077
sPAP> 40 mm Hg on Doppler-echocardiography	18; 19% (96)	38; 17% (218)	0.779	7; 16% (44)	39; 17% (229)	0.856
Pulmonary fibrosis	44; 46% (95)	87; 40% (216)	0.321	14; 32% (44)	56; 24% (232)	0.283
FVC<80% of predicted	38; 40% (95)	76; 36% (213)	0.468	18; 41% (44)	49; 21% (233)	0.005
Cardiac conduction blocks	11; 12% (94)	21; 10% (216)	0.598	8; 18% (44)	12; 5% (229)	0.003
LV diastolic dysfunction	19; 20% (96)	37; 17% (214)	0.597	6; 14% (43)	31; 13% (231)	0.925
LV ejection fraction<55%	5; 5% (96)	9; 4% (212)	0.707	3; 7% (44)	5; 2% (227)	0.098
Renal crisis	6; 6% (97)	15; 7% (219)	0.827	1; 2% (44)	2; 1% (237)	0.397

SSc: systemic sclerosis**;** dcSSC: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; yr: year; m: months; mRSS: modified Rodnan skin score; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; CK: creatinkinase; sPAP: stimated systolic pulmonary artery pressure; FVC: forced vital capacity; LV: left ventricle; SD: standard deviation.

§From 650 patients in the group, only 598 had information regarding disease subset. *Bonferroni adjustment was used for multiple comparisons. A *p*-value <0.002 was considered statistically significant. †Disease duration was calculated on the basis of the onset of the first SSc symptom, including Raynaud's phenomenon. ‡Digestive tract involvement includes esophagus, stomach and gut symptoms.

disease course have to be considered always dcSSc. Nevertheless, to discard this possibility we analysed the group of patients with less than 3 years from the first SSc symptom, including Raynaud's phenomenon, with very similar results both in the early, very early and lcSSc subgroups, although with less statistical power, probably due to the smaller number of patients analysed.

The main strength of the present study is the large number of patients included in the early EUSTAR database. This allowed us to assess sex differences even across population subgroups as those with very early disease or the SSc subsets. Therefore, we are confident that the study sample is representative and our results robust and reliable.

Our study has also some limitations. First, while nowadays there is external monitoring done for a selection of patients, at the time of the data export for the present study, external monitoring was not part of the EUSTAR procedures. Then, although it is supposed that in each participating centre, all patients with SSc are incorporated into the EUSTAR database, there could be a bias towards the inclusion of more severe cases. If this is true, this should be both for men and women, then no affecting the results. Second, since the new 2013 ACR/EULAR classification criteria for SSc (24) were not available in this early database, only patients fulfilling the 1980 ACR criteria for the classification of SSc (20) were selected, and it is well known that these exclude up to 20% of lcSSc patients, and there could be patients not fulfilling SSc ACR 1980 classification criteria with severe visceral involvement (25, 26). Nevertheless, these cases are scarce (27). Third, serum autoantibodies have been performed in a large number of laboratories, without standardisation. However, only ACA and anti-Scl70 antibodies are analysed in our study, and both antibodies have shown good agreement between different methods (indirect immunofluorescence and multiplex) (28). Other limitation could be the lack of data regarding to smoking status in our patients. Finally, most EUSTAR patients come from European countries and the vast majority is therefore Caucasian. As a result, our findings should be carefully extrapolated to other ethnic groups (28).

In conclusion, our results show that there is a different clinical pattern according to sex in patients with early onset SSc. Men, compared to women, presented data of more severe disease from very early stages of the disease, and these differences are much more evident in patients with early lcSSc. Our findings suggest that men with early SSc, even those with the lcSSc subset, should be carefully monitored, in order to detect visceral involvement even in the absence of other clinical symptoms. This will help to select the best therapeutic strategy for every SSc patient

Acknowledgements
The authors and all EUSTAR centres are grateful for the support of the European League Against Rheumatism until 2013. We also would like to thank all EUSTAR collaborators who are listed in the online additional file 1, the patients who gave their consent to participate in EUSTAR, and the support from the Instituto de Salud Carlos III (Spanish Ministry of Economy and Competitiveness) and Merck Sharp and Dome.

Affiliations
[1]Servicio de Reumatología, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Spain; [2]Instituto de Salud Musculoesquelética, Madrid, Spain; [3]Servicio de Reumatología, Hospital Universitario Puerta de Hierro, Madrid, Spain; [4]Department of Rheumatology, University of Lübeck, Germany; [5]U.O.C. di Reumatologia, Dipartimento di Internistica Clinica e Sperimentale "F. Magrassi-A-Lanzara", Seconda Università degli Studi di Napoli, Italy; [6]B. Shine Rheumatology Unit, Rambam Health Care Campus and Rappaport Faculty of Medicine-Technion, Haifa, Israel; [7]UO Reumatologia e Immunologia Clinica, Spedali Civili, Brescia, Italy; [8]Rheumatologische Universitätsklinik, Felix Platter Spital, Basel, Switzerland; [9]University of Belgrade School of Medicine, Institute of Rheumatology Belgrade, Serbia; [10]Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Florence, Italy; [11]Institute of Rheumatology, Russian Academy of Medical Science, Moscow, Russia; [12]Clinica Reumatologie, University of Medicine & Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania; [13]Department of Immunology and Rheumatology, Faculty of Medicine, University of Pécs, Hungary; [14]Department of Rheumatology, University Hospital Zürich, Switzerland; [15]Department of Internal Medicine, Hopital Saint-Louis, Paris, France; [16]Department of Rheumatology, Lund University Hospital, Sweden; [17]U.O. Reumatologia-Università degli Studi di Foggia, Ospedale "Col. D'Avanzo", Foggia, Italy; [18]Rheumatology Unit, AOUI, Verona, Italy; [19]Rheumatology Unit, Department of Medicine Chris Hani Baragwanath, Hospital and University of the Witwatersrand, Johannesburg, South Africa; [20]Rheumatology A Department, Cochin Hospital, APHP, Paris Descartes University, Paris, France.

Funding
EUSTAR was supported by the European League Against Rheumatism until 2013.This work was partially supported by FIS grant 11/01506 from the Instituto de Salud Carlos III, Spain (Spanish Ministry of Economy and Competitiveness), and from an unrestricted grant from Merck Sharp and Dome to the Instituto de Investigación del Hospital 12 de Octubre, Madrid (2014 0062).

Competing interests
O. Distler had consultancy relationship and/or has received research funding from Actelion, AnaMar, Bayer, Boehringer Ingelheim, Catenion, CSL Behring, ChemomAb, Roche, GSK, Inventiva, Italfarmaco, Lilly, Medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Sanofi and UCB in the area of potential treatments of scleroderma and its complications. In addition, Prof. Distler has a patent mir-29 for the treatment of systemic sclerosis licensed. S. Vettori has received speaking fees from Pfizer, Abbvie, Bristol-Myers Squibb, consultant fee from Thermofischer and Educational support from Pfizer, Roche; E. Loza and L. Carmona have received research funding from Abbvie, MSD, Pfizer, Roche, Novartis, BMS, UCB. J.L. Andreu has received funding to attend courses and congresses from Pfizer, Abbvie, Gebro, Menarini, speaking fee from Abbvie, GSK, Roche, UCB, and consultant fee from UCB and GSK. M. Matucci-Cerinic has received speaker bureau and research grants from BMS and Pfizer, and consultancy and research grant from Eli Lilly. All the other authors have declared no competing interests.

References

1. MAYES MD, LACEY JV, JR, BEEBE-DIMMER J *et al*.: Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003; 48: 2246-55.
2. ARIAS-NUNEZ MC, LLORCA J, VAZQUEZ-RODRIGUEZ TR *et al*.: Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. *Medicine* (Baltimore) 2008; 87: 272-80.
3. VONK MC, BROERS B, HEIJDRA YF *et al*.: Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. *Ann Rheum Dis* 2009; 68: 961-5.
4. BARNES J, MAYES MD: Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol* 2012; 24: 165-70.
5. KOMOCSI A, VOROBCSUK A, FALUDI R *et al*.: The impact of cardiopulmonary manifestations on the mortality of SSc: a systematic review and meta-analysis of observational studies. *Rheumatology* (Oxford) 2012; 51: 1027-36.
6. SIMEON CP, ARMADANS L, FONOLLOSA V *et al*.: Mortality and prognostic factors in Spanish patients with systemic sclerosis. *Rheumatology* (Oxford) 2003; 42: 71-5.
7. NGUYEN C, RANQUE B, BAUBET T *et al*.: Clinical, functional and health-related quality of life correlates of clinically significant symptoms of anxiety and depression in patients with systemic sclerosis: a cross-sectional survey. *PLoS One* 2014; 9: e90484.
8. LEROY EC, BLACK C, FLEISCHMAJER R *et al*.: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
9. GLEICHER N, BARAD DH: Gender as risk factor for autoimmune diseases. *J Autoimmun* 2007; 28: 1-6.
10. SIMEON CP, CASTRO-GUARDIOLA A, FONOLLOSA V *et al*.: Systemic sclerosis in men: clinical and immunological differences. *Br J Rheumatol* 1996; 35: 910-1.
11. JOVEN BE, ALMODOVAR R, CARMONA L, CARREIRA PE: Survival, causes of death, and risk factors associated with mortality in Spanish systemic sclerosis patients: results from a single university hospital. *Semin Arthritis Rheum* 2010; 39: 285-93.
12. HESSELSTRAND R, SCHEJA A, AKESSON A: Mortality and causes of death in a Swedish series of systemic sclerosis patients. *Ann Rheum Dis* 1998; 57: 682-6.

13. HOFFMANN-VOLD AM, MOLBERG O, MIDTVEDT O, GAREN T, GRAN JT: Survival and causes of death in an unselected and complete cohort of Norwegian patients with systemic sclerosis. *J Rheumatol* 2013; 40: 1127-33.
14. CZIRJAK L, KUMANOVICS G, VARJU C *et al*.: Survival and causes of death in 366 Hungarian patients with systemic sclerosis. *Ann Rheum Dis* 2008; 67: 59-63.
15. HUDSON M, THOMBS B, BARON M: Time to diagnosis in systemic sclerosis: is sex a factor? *Arthritis Rheum* 2009; 61: 274-8.
16. AL-DHAHER FF, POPE JE, OUIMET JM: Determinants of morbidity and mortality of systemic sclerosis in Canada. *Semin Arthritis Rheum* 2010; 39: 269-77.
17. ALLANORE Y, MEUNE C, VONK MC *et al*.: Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. *Ann Rheum Dis* 2010; 69: 218-21.
18. WALKER UA, TYNDALL A, CZIRJAK L *et al*.: Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis* 2007; 66: 754-63.
19. VALENTINI G, BENCIVELLI W, BOMBARDIERI S *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.
20. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23: 581-90.
21. HUDSON M, THOMBS BD, STEELE R *et al*.: Health-related quality of life in systemic sclerosis: a systematic review. *Arthritis Rheum* 2009; 61: 1112-20.
22. ELHAI M, AVOUAC J, WALKER UA *et al*.: A gender gap in primary and secondary heart dysfunctions in systemic sclerosis: a EUSTAR prospective study. *Ann Rheum Dis* 2016; 75: 163-9.
23. MEIER FM, FROMMER KW, DINSER R *et al*.: Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. *Ann Rheum Dis* 2012; 71: 1355-60.
24. VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al*.: 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72: 1747-55.
25. KARIMIFAR M, HASHEMI H, KAZIZADEH A: A case of sine scleroderma with parenchymal lung disease. *Adv Biomed Res* 2014; 3: 39.
26. MARANGONI RG, ROCHA LF, DEL RIO AP, YOSHINARI NH, MARQUES-NETO JF, SAMPAIO-BARROS PD: Systemic sclerosis sine scleroderma: distinct features in a large Brazilian cohort. *Rheumatology* (Oxford) 2013; 52: 1520-4.
27. SIMEON-AZNAR CP, FONOLLOSA-PLA V, TOLOSA-VILELLA C *et al*.: Registry of the Spanish network for systemic sclerosis: clinical pattern according to cutaneous subsets and immunological status. *Semin Arthritis Rheum* 2012; 41: 789-800.
28. SILVER RM, BOGATKEVICH G, TOURKINA E, NIETERT PJ, HOFFMAN S: Racial differences between blacks and whites with systemic sclerosis. *Curr Opin Rheumatol* 2012; 24: 642-8.