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EXTENDED REPORT

A gender gap in primary and secondary heart dysfunctions in systemic sclerosis: a EUSTAR prospective study

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ABSTRACT

Objectives In agreement with other autoimmune diseases, systemic sclerosis (SSc) is associated with a strong sex bias. However, unlike lupus, the effects of sex on disease phenotype and prognosis are poorly known. Therefore, we aimed to determine sex effects on outcomes.

Method We performed a prospective observational study using the latest 2013 data extract from the EULAR scleroderma trials and research (EUSTAR) cohort. We looked at (i) sex influence on disease characteristics at baseline and (ii) then focused on patients with at least 2 years of follow-up to estimate the effects of sex on disease progression and survival.

Results 9182 patients with SSc were available (1321 men) for the baseline analyses. In multivariate analysis, male sex was independently associated with a higher risk of diffuse cutaneous subtype (OR: 1.68, (1.45 to 1.94); p<0.001), a higher frequency of digital ulcers (OR: 1.28 (1.11 to 1.47); p<0.001) and pulmonary hypertension (OR: 3.01 (1.47 to 6.20); p<0.003). In the longitudinal analysis (n=4499), after a mean follow-up of 4.9 (±2.7) years, male sex was predictive of new onset of pulmonary hypertension (HR: 2.66 (1.32 to 5.36); p=0.006) and heart failure (HR: 2.22 (1.06 to 4.63); p=0.035). 908 deaths were recorded, male sex predicted deaths of all origins (HR: 1.48 (1.19 to 1.84); p<0.001), but did not significantly account for SSc-related deaths.

Conclusions Although more common in women, SSc appears as strikingly more severe in men. Our results obtained through the largest worldwide database demonstrate a higher risk of severe cardiovascular involvement in men. These results raise the point of including sex in the management and the decision-making process.

INTRODUCTION

Autoimmune diseases include more than 70 different disorders, affecting over 5% of the population of the Western countries. They are a well-known cause of morbidity and mortality.[1] One of the major shared features among most autoimmune diseases is the predominance of women, with >80% of affected individuals being women.[1] Even though the female predisposition has been known for a long time, the mechanisms by which sex influences disease expression remain unknown. A better understanding of such effects could help towards a better stratification of the factors leading to a wide range of clinical manifestations, particularly identifying cases more likely to progress or to present severe damages and to develop novel targeted therapies and ultimately personalised medicine.[1–3]

Systemic sclerosis (SSc) is a complex multiorgan disease affecting the immune system, the microvascular system and the connective tissue.[4 5] In agreement with other autoimmune diseases, SSc is associated with a strong sex bias.[6] The various available worldwide cohorts usually report a female predominance with between four and nine affected women for one man.[7–11] However, data about the effects of sex on disease characteristics and outcomes are scarce. The very few published data were mainly obtained in non-European patients (North American or Japanese) and revealed conflicting results regarding the impact of sex on disease severity and survival.[12–17] So far, large epidemiological studies are missing, particularly in European populations. Two independent studies, each based on about 1000 European patients, suggested that male gender could be a risk factor for mortality,[8 18] but data were provided on distinct disease manifestations. In another autoimmune disease, systemic lupus erythematosus (SLE), large prospective data have well documented that male patients have more often a severe disease and greater organ progression than female patients.[19–22] Whether a similar effect occurs in SSc remains unknown. Therefore, we aimed (i) to clarify the impact of sex on SSc phenotype: time of occurrence, autoantibodies and organ involvements and (ii) to investigate the impact of sex on disease outcomes including severe damages and mortality, in a large European population. This is now made possible by the implementation of the systematic longitudinal follow-up of patients with SSc included in the EULAR scleroderma trials and research (EUSTAR) registry. Based on annual visits, on a prospective

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manner, this large database provides a powerful tool to investigate prognostic factors.

METHODS

All data for patients registered in the EUSTAR database as of November 2013 were exported.

In all, 9182 patients, fulfilling the 2013 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) criteria for SSc, were available for baseline analyses. We analysed the baseline and follow-up visit data using the predefined annual data collection protocol. We also looked at difference in sex bias according to age at disease onset by dividing the cohort in decades (disease onset <30 years, between 30 and 40, 40–50, 50–60 and >60 years).

Impact of sex on phenotype at baseline

We looked at sex influence on age at disease onset, disease subtype and disease phenotype at baseline. We also compared nailfold capillaroscopic patterns (ie, early, active and late pattern) between men and women.[23]

Impact of sex on disease outcomes

For the patients with follow-up, we focused on those having at least 2 years of follow-up after baseline to estimate the predictive value of sex on disease outcomes including mortality and disease progression. For mortality, analysis was based on the whole cohort (n=9182). Causes of death were separated in SSc related and SSc unrelated.

For disease progression, we focused on severe organ involvement (new digital ulcers (DU)), new onset of pre-capillary pulmonary hypertension (PH) on right heart catheterisation, new onset of reduction of the left ventricular ejection fraction (LVEF) to below 50% as assessed by echocardiography, new occurrence of scleroderma renal crisis (SRC), new onset or worsening of pulmonary fibrosis on X-rays and/or high-resolution CT (HRCT) *and* deterioration of lung volume (≥10% of forced vital capacity (FVC) during follow-up).

Statistical analysis

A multivariate stepwise logistic regression analysis was performed with calculation of OR estimates and 95% CIs. We applied Bonferroni correction for multiple comparisons (adjusted probability value=0.003) at baseline.

Predictors of disease progression were evaluated by univariate and multivariate Cox proportional hazards models and summarised as HRs and 95% CI. A p value <0.05 was considered statistically significant in the multivariate Cox models.

Further details are provided in online supplementary materials.

RESULTS

The study began at entry to EUSTAR database. In all, 1321/9182 (14.4%) patients with SSc were men and 4756/5260 (90.4%) were white patients. The sex ratio was six women affected for one man. There were 3359/9149 (36.7%) diffuse cutaneous forms. In diffuse cutaneous forms, the sex ratio women/men was 4:1, whereas it was 9:1 in limited cutaneous subtypes. Sex bias was similar whatever age at disease onset, with a sex ratio women/men respectively equal to 8:1 before 30 years, 6:1 between 30 and 60 years and 5:1 after 60 years (figure 1).

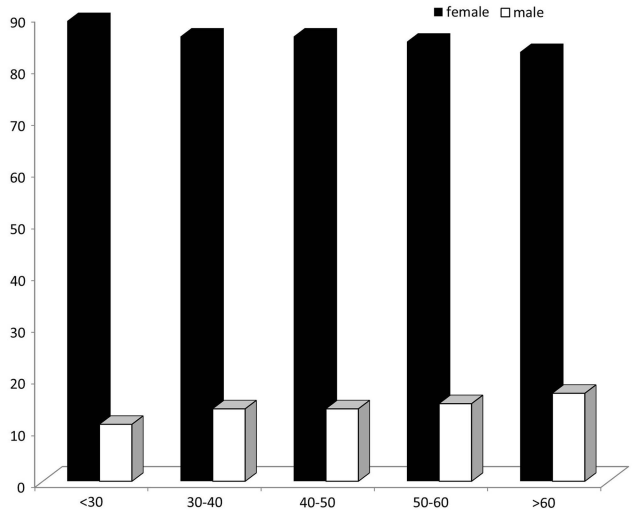

Figure 1 Sex bias according to age at disease onset. In abscissa, there are different ages at disease onset, whereas in ordinate, we can find incidence of disease in per cent. The percentage of women was 89 in the group with disease onset below 30 years, 86 in both 30–40 years and 40–50 years, 85 in the group with disease onset between 50 and 60 years and 83 in the group with disease onset after 60 years.

Disease characteristics at baseline

At baseline, mean age (±SD) was 54.3 (13.9) years, whereas mean disease duration (±SD) was 8.5 (9.0) years. Lung fibrosis was detected in 3507/8574 patients, with a diagnosis based on HRCT in 2659 patients (1190 patients had lung fibrosis on HRCT) and on X-rays for the remaining 2915 patients (2317 with lung fibrosis). Right heart catheterisation had been performed in 195 patients (2% of the cohort), revealing pre-capillary PH in 54 patients. However, as right heart catheterisation was only performed in patients with a suspicion of PH, we considered the entire cohort to estimate prevalence of PH.

In univariate analysis, a large number of characteristics were associated with male sex. There was no high association between variables (Cramer's V <0.6).

In multivariate analysis, only variables with >70% of the data available were included. In the multivariate model, adjusted on age, disease duration and anti-Scl70 antibodies, male sex was independently associated with a more severe phenotype as reflected by a higher risk of diffuse cutaneous form (OR: 1.68; 95% CI (1.45 to 1.94), p<0.001), a more active disease (Valentini score ≥3) (OR: 1.39 (1.13 to 1.70), p<0.003) and a higher risk of creatine kinase elevation (OR: 1.93 (1.58 to 2.36), p<0.001). Men were also characterised by a more severe vascular phenotype with an independent association with DU (OR: 1.28 (1.11 to 1.47), p<0.001) and PH (OR: 3.01 (1.47 to 6.20), p<0.003). Women had higher frequencies of anticentromere antibodies (ACA) positivity and of gastrointestinal involvement. Further details are provided in table 1.

Concerning nailfold capillaroscopy results (information available for 20% of the cohort), 264/305 (86.6%) men and 1411/1559 (90.5%) women had a scleroderma pattern (p<0.05). Women displayed more frequently an early pattern (279/1085 (25.7%) vs 40/210 (90.5%); p<0.05), whereas men were characterised by an active pattern (103/210 (49.0%) vs 458/1085 (42.2%); p<0.05). There was no significant difference regarding the late pattern (67/210 (31.9%) vs 348/1085 (32.1%); p=NS) (information missing in 54 men and 326 women). After adjusting for disease duration, sex was not associated with a capillaroscopic pattern.

Table 1 Results of the univariate and multivariate analyses (adjusted on age, disease duration and anti-Scl70 antibodies) comparing men and women with SSc at baseline (n=9182 patients)

	Univariate analysis			Multivariate analysis		
Characteristics	**Men**	**Women**	**p Value**	**N available data (%)**	**OR, 95% CI**	**p Value***
Age at disease onset (years) (mean (SD)) (n available)	47.1 (14.2) (1153)	45.7 (14.2) (6810)	0.002	7963 (86.7%)		NS
Age (years) (mean (SD)) (n available)	52.7 (13.8) (1319)	54.5 (13.9) (7858)	<0.001	9177 (99.9%)		NS
Disease duration (years) (mean (SD)) (n available)	5.1 (6.5) (1152)	8.1 (8.2) (6808)	<0.001	7960 (86.7%)		NS
Diffuse cutaneous subtype	721/1317 (54.7%)	2638/7832 (33.7%)	<0.001	9149 (99.6%)	1.68 (1.45 to 1.94)	<0.001
Modified Rodnan skin score ≥14†	274/681 (40.2%)	1327/4531 (29.3%)	<0.001	5212 (56.8%)		
Raynaud's phenomenon	1253/1305 (96.0%)	7509/7781 (96.5%)	NS	9086 (98.9%)		
Scleroderma puffy fingers	296/657 (45.0%)	1450/3385 (42.8%)	0.314	4042 (44.0%)		
ACA antibodies	195/1248 (15.6%)	2647/7748 (34.2%)	<0.001	8996 (98.0%)	0.45 (0.37 to 0.54)	<0.001
Anti-Scl70+ antibodies	573/1247 (46.0%)	2540/7367 (34.5%)	<0.001			
Valentini score ≥3[24]	221/1321 (16.7%)	740/7861 (9.4%)	<0.001	9182 (100%)	1.39 (1.13 to 1.70)	<0.003
CRP elevation†	200/622 (32.1%)	643/3196 (20.1%)	<0.001	3818 (41.6%)		
Oesophageal symptoms	791/1314 (60.2%)	5230/7822 (66.9%)	<0.001	9136 (99.5%)	0.80 (0.69 to 0.93)	<0.003
Stomach symptoms	255/1305 (19.5%)	1909/7792 (24.5%)	<0.001	9097 (99.1%)	0.74 (0.61 to 0.88)	<0.003
Intestinal symptoms	239/1310 (18.2%)	1935/7804 (24.8%)	<0.001	9114 (99.3%)	0.68 (0.57 to 0.82)	<0.001
Joint synovitis	205/1312 (15.6%)	1208/7791 (15.5%)	0.944	9103 (99.1%)		
Joint contracture	487/1310 (37.2%)	2368/7788 (30.4%)	<0.001	9098 (99.1%)		NS
Tendon friction rubs	178/1305 (13.6%)	679/7748 (8.8%)	<0.001	9053 (98.6%)		NS
Muscle weakness	352/1312 (26.8%)	1793/7763 (23.1%)	0.004	9075 (98.8%)		NS
Muscle atrophy	179/1306 (13.7%)	868/7748 (11.2%)	0.010	9054 (98.6%)		NS
CK elevation	193/1238 (15.6%)	547/7386 (7.4%)	<0.001	8724 (95.0%)	1.93 (1.58 to 2.36)	<0.001
Digital ulcers	535/1304 (41.0%)	2649/7774 (34.1%)	<0.001	9078 (98.9%)	1.28 (1.11 to 1.47)	<0.001
Scleroderma renal crisis	45/1310 (3.4%)	147/7796 (1.9%)	<0.001	9106 (99.2%)		NS
Proteinuria	122/1238 (9.8%)	389/7467 (5.2%)	<0.001	8705 (94.8%)	1.54 (1.21 to 1.97)	<0.001
LVEF<50%†	55/797 (6.9%)	133/4733 (2.8%)	<0.001	5530 (60.2%)		
Pericarditis	39/521 (7.5%)	174/2727 (6.4%)	NS	3248 (35.4%)		
Diastolic dysfunction	222/1204 (18.4%)	1253/7193 (17.4%)	NS	8397 (91.4%)		
Pulmonary hypertension	16/1321(1.2%)	38/7861 (0.5%)	0.003	9182 (100%)	3.01 (1.47 to 6.20)	<0.003
Lung fibrosis	603/1231 (49.0%)	2904/7343 (39.5%)	<0.001	8574 (93.4%)		NS
Dyspnoea class III or IV	80/598 (13.4%)	355/3145 (11.3%)	NS	3743 (40.8%)		
DLCO<60†	387/974 (39.7%)	1631/5233 (31.2%)	<0.001	6207 (67.6%)		
FVC<70†	97/537 (18.1%)	357/2771 (12.9%)	0.002	3308 (36.0%)		
Arterial hypertension	287/1312 (21.9%)	1630/7811 (20.9%)	NS	9123 (99.4%)		

Results are presented as number/number of available data (%) unless stated otherwise.
Only variables with >70% of the data available were entered in multivariate analysis.
*p: significance after Bonferroni correction was obtained for a p value <0.003.
†Variables not entered in the multivariate model since the number of available data concerned <70% of the cohort.
ACA, anticentromere antibodies; disease was active if the Valentini score was ≥3; CK, creatine kinase; CRP, C-reactive protein; DLCO, carbon monoxide diffusing capacity test; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; pulmonary hypertension was diagnosed on right heart catheterisation; lung fibrosis was considered if present on X-rays and/or high-resolution CT; NS, not significant; SSc, systemic sclerosis.

Impact of sex on disease outcomes

Follow-up data

In all, 4499/9182 (49.0%) patients with SSc had a recorded follow-up visit at least 2 years after inclusion. Among them, there were 652 men (14.5%) and 3847 women, resulting in a sex ratio of six women affected for one man. There were 1658/4485 (40.0%) diffuse cutaneous forms. After a mean follow-up of 4.9 (2.7) years, mean age was 58.9 (13.5) years and mean disease duration was 12.7 (8.0) years.

The sample had sufficient power for detecting impact on studied outcomes (see online supplementary table S1). Variables tested in univariate Cox proportional models were those with more than 70% of the data available in the follow-up cohort, resulting in 25 variables tested and four excluded (ie, C-reactive protein elevation, modified Rodnan skin score, LVEF below 50% and FVC below 70%). There was no significant association (Cramer's V<0.60) between all the variables tested.

Organ involvements

In univariate Cox proportional models, male sex was not predictive of either occurrence of new DU or lung progression during the follow-up.

For new onset of PH, we excluded patients with PH at baseline (ie, 22 patients). New occurrence of PH during the follow-up was recorded in 71/4477 (1.6% of the cohort) (right heart catheterisation was performed in 96 patients). In the multivariate analysis, male sex appeared as a predictor of new onset of PH during the follow-up (HR: 2.66 (1.32 to 5.36); p=0.006) together with carbon monoxide diffusing capacity test (DLCO) below 60% predicted (table 2).

For cardiac progression, we excluded patients with previous reduction of the LVEF to below 50%, that is, 126 patients. New onset of reduction of LVEF was observed in 41/2784 (1.5%) (data available in 63.7% of the cohort). In the multivariate model, male sex was independently predictive of heart dysfunction (HR: 2.22 (1.06 to 4.63); p=0.035) (table 3).

In univariate Cox proportional model, male sex was predictive of new onset of SRC, but not in multivariate Cox proportional model. Further information is provided in online supplementary information.

Mortality

Overall, 908 deaths were recorded (217 (33.1%) men vs 691 (18.0%) women; p<0.001). Men died younger than women (60.4 (13.1) years vs 63.9 (13.6) years; p<0.001) and their disease duration was shorter at death (8.6 (7.9) vs 12.3 (9.3) years; p<0.001) (information available respectively for 908 and 816 dead patients). Death was considered to be SSc-related in 445/665 cases (cause of the death not provided in 243 patients): 115/165 (69.7%) men and 330/500 (66.0%) women; p=0.44. The mean time to death after study inclusion was 2.5±2.2 years. The Kaplan–Meier survival curve displayed a higher survival probability in women compared with men (figure 2A). In multivariate Cox proportional hazard model adjusted on age, disease duration, diffuse cutaneous subtype and positivity of anti-Scl70 antibodies, male sex was identified as an independent predictor of death (HR: 1.48 (1.19 to 1.84); p<0.001). Other independent predictors were musculoskeletal involvement and severe organ involvements (ie, DU, PH and lung fibrosis) (table 4).

We then focused on SSc-related deaths and observed no significant difference between men and women (figure 2B). Independent predictors for SSc-related mortality were an active disease, muscle weakness, DLCO below 60% and proteinuria at baseline (see online supplementary table S2).

Table 2 Results of the multivariate Cox proportional model for predictors of new onset of pulmonary hypertension during the follow-up (adjusted on age, disease duration, diffuse cutaneous subtype and positivity of anti-Scl70 antibodies)

Predictors (at baseline)	p Multivariate	HR, 95% CI
Male sex	0.006	2.66 (1.32 to 5.36)
DLCO <60%	<0.001	8.96 (4.11 to 19.53)
Lung fibrosis	NS	
Muscle weakness	NS	
Oesophageal symptoms	NS	
Arterial hypertension	NS	

Pulmonary hypertension was diagnosed on right heart catheterisation; predictors were identified in univariate Cox proportional model with a p value<0.1; DLCO, carbon monoxide diffusing capacity test; lung fibrosis was considered if present on X-rays and/or high-resolution CT; NS, not significant.

DISCUSSION

In this study, we analysed the impact of sex on SSc, taking advantage of the largest series of (European) patients with SSc ever reported. Our main results are: (i) sex ratio (women/men) in SSc is about 6:1 whatever age at disease onset; (ii) men with SSc have a more severe phenotype and (iii) the prognosis of SSc is worse in men with an increased risk of occurrence of cardiovascular disease (PH and heart dysfunction).

It was already well documented that SSc was associated with a strong female predominance. Our results were concordant with literature data with a sex ratio equal to six affected women for one man.[7–11] It has been suggested that the sex ratio in SSc could be higher in the childbearing years and decreased during the postmenopausal years.[25] This was also demonstrated in other autoimmune diseases, such as SLE and rheumatoid arthritis.[26–28] We did not observe any difference in sex bias according to age at disease onset, suggesting that the female hormonal milieu and the pregnancy-related events were not responsible for this difference in disease susceptibility.[29] Other hypotheses have been proposed to explain this sex imbalance in

Table 3 Results of the multivariate Cox proportional model for predictors of new occurrence heart dysfunction during the follow-up (adjusted on age, disease duration, diffuse cutaneous subtype and anti-Scl70 antibodies)

Predictors (at baseline)	p Multivariate	HR, 95% CI
Male sex	0.035	2.22 (1.06 to 4.63)
Valentini score ≥3	0.011	3.49 (1.34 to 9.07)
Tendon friction rubs	NS	
Muscle weakness	NS	
Joint contracture	NS	
Joint synovitis	<0.001	3.31 (1.71 to 6.40)
CK elevation	0.017	2.64 (1.20 to 5.81)
Lung fibrosis	NS	
Pulmonary hypertension	0.010	14.40 (1.91 to 108.71)

Heart dysfunction was defined as left ventricular ejection fraction below 50% predicted. Predictors were identified in univariate Cox proportional model with a p value<0.1. CK, creatine kinase; lung fibrosis was considered if present on X-rays and/or high-resolution CT; pulmonary hypertension was diagnosed on right heart catheterisation; NS, not significant; disease was active if the Valentini score was ≥3.

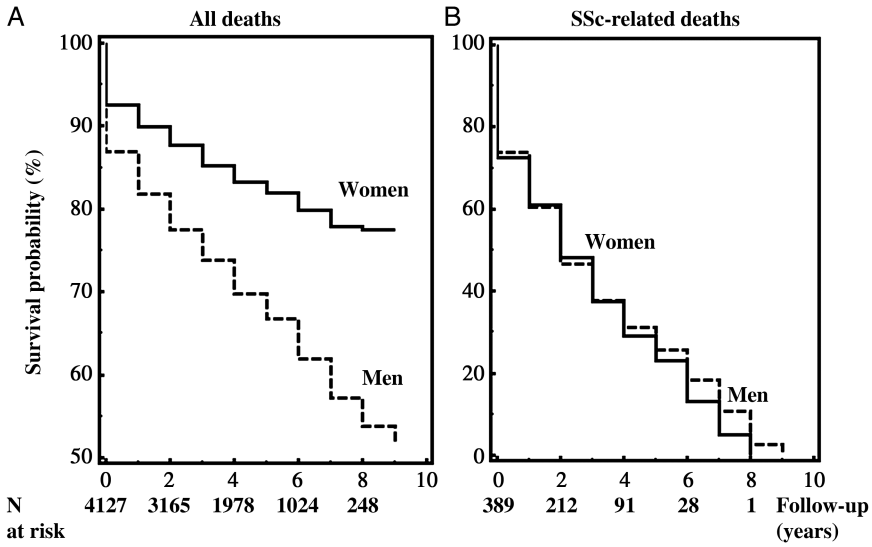

Figure 2 Kaplan–Meier survival for all deaths (A) and systemic sclerosis (SSc)-related (B) deaths according to sex during the follow-up period. The dotted line represents survival probability in men, whereas the solid line represents survival probability in women. In the bottom, the number of patients with SSc at risk can be noticed.

autoimmune diseases, such as sex-specific environmental exposure, foetal microchimerism, skewing in X-chromosome inactivation patterns and X-linked genetic susceptibility risk factors.[6 30 31] This latter factor is supported by a reproducible association between a sex chromosome gene IRAK1 and SSc in two independent studies.[31 32]

In this study, we showed that the disease was strikingly more severe in men, as reflected by an independent association with the diffuse cutaneous subtype, an active disease assessed by Valentini score and with creatine kinase elevation. Conversely, women were characterised by ACA antibodies positivity and a more frequent gastrointestinal involvement. Our results confirm and extent previous studies, reporting a higher frequency of ACA antibodies in women and a higher risk of diffuse cutaneous forms in men.[12 15 33]

Table 4 Results of the multivariate Cox proportional model for predictors of all causes of death (adjusted on age, disease duration, diffuse cutaneous subtype and anti-Scl70 antibodies)

Predictors (at baseline)	p Multivariate	HR, 95% CI
Male sex	<0.001	1.48 (1.19 to 1.84)
ACA antibodies	NS	
Valentini score ≥3	NS	
Tendon friction rubs	NS	
Muscle weakness	0.019	1.31 (1.05 to 1.63)
Muscle atrophy	0.013	1.40 (1.08 to 1.82)
CK elevation	NS	
Joint contracture	0.015	1.29 (1.05 to 1.57)
Joint synovitis	NS	
Digital ulcers	0.003	1.34 (1.11 to 1.62)
Scleroderma renal crisis	NS	
Proteinuria	<0.001	1.93 (1.44 to 2.60)
Pulmonary hypertension	0.010	2.56 (1.26 to 5.20)
DLCO<60%	<0.001	2.61 (2.12 to 3.22)
Lung fibrosis	0.002	1.39 (1.13 to 1.71)
Oesophageal symptoms	NS	
Stomach symptoms	NS	
Intestinal symptoms	0.006	1.34 (1.09 to 1.66)
Arterial hypertension	NS	

Predictors were identified in univariate Cox proportional model as predictors of death with a p value<0.1.
ACA, anticentromere antibodies; disease was active if the Valentini score was ≥3; CK, creatine kinase; pulmonary hypertension was diagnosed on right heart catheterisation; DLCO, carbon monoxide diffusing capacity test; lung fibrosis was considered if present on X-rays and/or high-resolution CT; NS, not significant.

Our group previously reported that women with SSc were characterised by polyautoimmunity, ACA positivity and limited cutaneous subtype.[34 35] However, prevalence of polyautoimmunity could not be assessed in the present study because this information was available only in a small proportion of patients.

Our study was the first to rigorously demonstrate that men have a more severe vasculopathy. Indeed, male sex was independently associated with both DU and PH at baseline.

A previous study suggested a higher frequency of DU in men in line with our results.[16] However, the sample size and the lack of multivariate analysis in this report could not allow firm conclusions. Herein, we could confirm that male patients have more frequently DU at baseline using multivariate analysis (OR: 1.28 (1.11 to 1.47), p<0.001). However, our prospective analysis failed to demonstrate any association between new occurrence of DU and sex during the follow-up.

Strengthening the relationships between male sex and vasculopathy, male sex was identified as an independent predictor of new occurrence of PH and heart dysfunction during the follow-up, with HR equal to 2.66 and 2.22, respectively. In a previous study, male sex was independently associated with PH assessed by echocardiography.[33] However, this study was biased because PH was not confirmed by right heart catheterisation, which is the gold standard for the diagnosis. Our study is the first to demonstrate that male sex is independently associated with PH, but is also predictive of new occurrence of PH during the follow-up, with a stringent definition of PH. It is of interest to notice that usually idiopathic pulmonary arterial hypertension occurs more frequently in women.[36] This underlines the specificity of SSc-PH characterised by higher prevalence and incidence in men.

Men were characterised by an active pattern at nailfold capillaroscopy and women by the early one. Some studies suggest that the active pattern is at higher risk of severe peripheral vascular involvement than the early one, which is in accordance with our results.[37] However, we did not succeed to demonstrate any association after adjusting for disease duration, probably because of the small size of the sample.

A previous study in EUSTAR cohort reported that male sex was independently associated with left ventricular dysfunction.[38] Herein, male sex was identified as an independent predictor of new occurrence of heart dysfunction during the follow-up. These results are of major interest since PH and heart dysfunction are the leading causes of death in SSc[39] and herein we show, for the first time, in a prospective study, that male sex is predictive of these two life-threatening outcomes. Note that we could not assess the association of heart dysfunction and outcome during the follow-up or male sex at baseline because LVEF was available for <70% of the cohort. Another critical issue is survival in SSc.[40] We herein observed that male sex was independently predictive of death. This is concordant with few previous cohort studies reporting a better survival for female patients.[8 12 14 16 41] In a preliminary EUSTAR study, male sex appeared as a risk factor to predict mortality.[18] Our results obtained through the largest worldwide database confirmed these data by showing a higher mortality in affected men with 1.8-fold more deaths in men compared with women. However, when we stratified on SSc-related mortality, there was no significant difference between men and women. Several hypotheses might be driven to explain this discrepancy. First, this difference might be related to the inherent difference between men and women regarding SSc-unrelated mortality.[42] This underlines the bias of considering all deaths instead of SSc-related deaths to estimate the impact of sex on mortality. In the same way, observational studies, which used the standardised mortality ratio, adjusted on sex and age, did not find any difference between men and women or suggested an increased risk of death among women.[9 43–45] However, the mean follow-up (5 years) might be too short to allow an accurate detection of predictive factors of death and SSc-related deaths. With this follow-up, we observed that severe organ involvements were more prevalent in men, but deaths related to these organ involvements might occur several years later.

Our study should be interpreted within some limitations: first, the exact cause of death could not be analysed because these data were not available. Furthermore, we could not perform adjustment for comorbidities, except arterial hypertension, which was as prevalent in men and women (table 1). Moreover, despite all the efforts made by EUSTAR to homogenise the care of patients with SSc, the participation of several centres might have introduced some heterogeneity in their assessment and some factors could not be included in the analysis because of missing values. Finally, our findings appear as robust in white Europeans but might not be applied generally to other ethnicities.

However, our study has several strengths: data were derived from a large, multicentre cohort, with an extensive list of clinical, laboratory and diagnostic parameters. Furthermore, unlike previous retrospective and cross-sectional clinical studies, our data collection was prospective to identify the impact of sex on disease progression and outcomes. In addition, most of the variables were available for more than 80%–90% of the cohort and thus analysed in our different multivariate models, which confirm the robustness of our study (table 1). Finally, in contrast to previous studies, we used the new ACR/EULAR classification allowing increasing the number of patients included and the representativeness of our cohort.

Novelty in our analysis lies on the identification of a more severe vasculopathy in men. The mechanisms that explain these discrepancies are still unknown and very challenging.

Our results suggest taking sex into account (i) for the patient management with a particular attention to vascular manifestations in men, (ii) for the analysis of drug effects in clinical trials and (iii) may open new avenues for SSc research, which needs to evaluate both genetic and environmental influences according to sex. Stratification or adjustment according to sex should allow identifying which therapeutic strategy has the greatest benefit for men and women, leading to the development of sex-tailored treatment regimens, as it has been recently demonstrated in depression and hepatitis C.[46 47]

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A gender gap in primary and secondary heart dysfunctions in systemic sclerosis: a EUSTAR prospective study

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SUPPLEMENTARY MATERIALS:

In November 2013, 10'928 patients from 120 centres were included in the EUSTAR database. Patients were retrospectively classified as responding to 2013 ACR/EULAR criteria for SSc or not, despite information regarding telangiectasia missing in most of them. In all, 9185 fulfilled the 2013 ACR/EULAR criteria for SSc. Only patients responding to the 2013 ACR/EULAR classification criteria for SSc were included in the present analysis [1]. In all, 9185 fulfilled the 2013 ACR/EULAR criteria for SSc. Information related to sex was missing in three patients, who were excluded from the analysis; therefore the sample size was of 9182 for baseline analysis. The structure of the database, the minimum essential data set (MEDS), and the inclusion criteria have been previously described in details [2–6]. Each participating centre obtained approval of the local ethics committee and all registered patients gave informed consent.

Impact of sex on phenotype at baseline

We looked at sex influence on age at disease onset, disease subtype (limited or diffuse SSc according to Leroy's criteria [7]), disease phenotype looking in particular at organ involvement, auto-antibodies (presence of anti-centromere (ACA) and anti-topoisomerase-I (anti-Scl-70) antibodies). Pulmonary hypertension (PH) was defined by pre-capillary pulmonary hypertension on right heart catheterization (resting mean pulmonary artery

pressure ≥25 mmHg together with a pulmonary capillary wedge pressure of ≤15 mmHg) [8,9]. For interstitial lung disease, we considered the presence of pulmonary fibrosis on X-rays and/or high resolution (HR) computed tomography (CT). The disease was considered as active if the Valentini score was ≥ 3 [10].

Impact of sex on disease outcomes

Patients with active digital ulcer (DU), PH confirmed on right heart catheterization, reduction of the left ventricular ejection fraction (LVEF) to below 50% as assessed by echocardiography and scleroderma renal crisis (SRC) at baseline were excluded from the analyses of respectively peripheral vascular worsening, lung vascular, cardiac and renal progressions. Peripheral vascular worsening was defined by new DU, which had to be distal to, or at, proximal interphalangeal joints and not thought to be due to trauma. Lung vascular progression was defined as the new onset of pre-capillary pulmonary hypertension on right heart catheterization. Cardiac progression was defined as the new onset of reduction of the LVEF to below 50% as assessed by echocardiography. Renal progression was defined by the new occurrence of SRC. Interstitial lung disease progression was defined as apparition or worsening of pulmonary fibrosis on X-rays and/or high HRCT and the deterioration of lung volume (≥10% of FVC) during the follow-up.

Statistical analysis

All data analyses were performed using MedCalc v11.4.4 and XL STAT v2013.6.02. Data were presented as mean (standard deviations (S.D.)) for continuous variables and numbers (percentages) for categorical variables. Data at baseline were statistically analysed using chi-square tests for differences in frequency and the Student's t-test for comparison between two normally distributed continuous variables. The relationship between baseline nominal variables was measured by the Cramer's V test. Variables identified by univariate analysis as

having a p value<0.10 were included in the multivariate model. Variables with a high association (Cramer's V>0.60) and with less than 70% of available data were not entered in the different multivariate models.

To note, heart dysfunction was not entered in the different multivariate models as an independent parameter since it was not available for >70% of the cohort. However, we assessed the association of different independent parameters (with more than 70% of the data available) with this outcome (i.e. new occurrence of heart dysfunction).

XLSTAT-Power was used to estimate the power observations associated with Cox regression model. Statistical power of this sample has been determined, taking into account our sample size, a type I error of 5% and the observed frequency of each outcome. Survival was also analysed by Kaplan Meyer survival technique.

SUPPLEMENTARY RESULTS:

At baseline, among patients with pulmonary hypertension (PH) (n=54), 5/41 (12.2%) with available data had PH secondary to lung fibrosis (FVC < 70%).

Impact of sex on organ involvements:

For new onset of DU, we excluded patients with DU at baseline (1651 patients). New onset of DU was noticed in 479/2580 (18.6%) patients (data missing in 268 patients, i.e. 6.0% of the patients).

SRC was recorded at baseline in 89 patients. New occurrence of SRC was recorded in 45/4114 (1.1%) patients (data available in 93.3% of the cohort).

Lung fibrosis was diagnosed at follow-up in 560 patients (492 by HCRT and 68 by X-rays). Interstitial lung disease progression was recorded in 105/1194 patients (data missing in 3305 patients).

In the follow-up, 71 developed PH. Among them, 19/57 (33.3%) with available data had pulmonary hypertension secondary to lung fibrosis.

Supplementary Table 1: Statistical power of the study sample, determined taking into account the sample size, a type 1 error of 5% and the observed frequency of each outcome

Outcome	Sample size	Type one error	Observed frequency (%)	Power
Mortality	4499	5%	20	1
Occurrence of new digital ulcer	2580		19	1
Occurrence of precapillary pulmonary hypertension	4477		2	1
Occurrence of reduction of left ventricular ejection fraction	2847		3	1
Occurrence of scleroderma renal crisis	4114		1	1
Interstitial lung disease progression	1194		9	1

Supplementary Table 2: Results of the multivariate Cox proportional model for predictors of SSc-related death (adjusted on age, disease duration, diffuse cutaneous subtype and positivity of anti-Scl70 antibodies)

Predictors (at baseline)	P multivariate	HR, 95% CI
ACA antibodies	NS	
Valentini score ≥3	0.016	1.56 [1.09-2.24]
Tendon friction rubs	NS	
Muscle weakness	0.036	1.33 [1.02-1.73]
CK elevation	NS	
Joint contracture	NS	
Scleroderma renal crisis	NS	
Proteinuria	0.002	1.86 [1.26-2.73]
DLCO<60%	0.023	1.38 [1.05-1.83]
Lung fibrosis	NS	
Stomach symptoms	NS	

Predictors were identified in univariate cox proportional model as predictors of death with a p-value<0.1; HR: Hazard ratio; 95% CI: 95% confidence interval; NS: not significant; ACA: anti-centromere antibodies; disease was active if the Valentini score was ≥ 3; CK: creatine kinase; DLCO: carbon monoxide diffusing capacity test; lung fibrosis was considered if present on X-rays and/or high resolution computed tomography.

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