Clinical and epidemiological differences between men and women with systemic sclerosis: a study in a Spanish systemic sclerosis cohort and literature review

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ABSTRACT

Objective. *The low overall prevalence of systemic sclerosis (SSc) and the low proportion of male patients have resulted in a scarcity of studies assessing sex differences in Ssc patients, and contradictory results have often been show among those studies that have been performed.*

Methods. *A prospective study was conducted with the Spanish RESCLE register to analyse the influence of gender on survival of SSc patients.*

Results. *In total, 1506 SSc patients (1341 women, 165 men) were recruited from 21 centres. Older age at onset (OR 1.02), shorter time from onset to diagnosis (OR 0.96), smoking (OR 2.57), interstitial lung disease (ILD) (OR 1.58), less predisposition to sicca syndrome and to antinuclear antibody positivity (OR 0.29 and 0.43, respectively), and higher compliance with the ACR 1980 criteria (OR 1.79) were independently associated with the male sex. During follow-up, 30.4% of men versus 14.6% of women died (p<0.001). Survival at 10 years from the onset of symptoms was 75.3% for men and 92.9% for women (p<0.001), and the difference remained after selecting only SSc-related deaths (85.6% vs. 96.1%, p<0.001). The mortality predictive factors were diffuse SSc (OR 2.26), ILD (OR 1.82), digital ulcers (OR 1.38), tendon friction rubs (OR 1.74), male sex (OR 1.53), increased age at onset (OR 1.13) and isolated PH (considering only deaths from diagnosis), both in the overall (OR 3.63) and female cohorts (OR 3.97). The same risk factors were observed in the male cohort, except for isolated PH and ILD.*

Conclusion. *The present study confirms the existence of epidemiological, clinical, laboratory and prognostic gender differences in systemic sclerosis patients.*

Introduction

Systemic sclerosis (SSc) is a complex systemic autoimmune disease of unknown origin. Excessive collagen storage occurs following an endotheliopathy that can alter the function of almost any organ including the skin, gastrointestinal tract, lungs, heart and kidney (1).

Hormonal, genetic, and environmental exposure factors have different effects on the clinical phenotype according to the sex of SSc patients. *In vitro*, 17β-estradiol appears to have a profibrotic effect in normal and SSc-cultured fibroblasts (2). Recent studies have found higher levels of prolactin in women with SSc than in control women, which also correlates with the aggressiveness of skin thickening (3). It has been further observed that in patients with SSc, lymphocytes are capable of producing prolactin, which stimulates the synthesis of the IL-2 receptor by these lymphocytes (4). To avoid protein overexpression in women, one of the X chromosomes is randomly silenced during chromosomal inactivation early in female embryogenesis. There have been at least 13 X-linked genes associated with the development of SSc of certain clinical subtypes, several of which escape inactivation pro-

cesses (*e.g.* TIMP1, IRAK1, IKBKB) (5). There is epidemiological evidence of occupational exposure to organic solvents and silica in patients with SSc, related to professions classically populated by men (6).

Evidence for the role of sex in the clinical manifestations of SSc in patients is scarce (7-15). The first study specifically designed to assess differences by sex in SSc was published in 1996 by Simeon *et al*., with a small number of patients (7). The two multicentre studies assessing clinical differences between men and women with SSc were made from the Toronto Systemic sclerosis Program (Canadian patients) and the EUSTAR cohort (mixture of patients from 23 European countries, the USA, Canada, Dominican Republic, Argentina, Brasil, South Africa, New Zealand, Russia, Israel and China) (12,13). Also, Ferri *et al*. in 2002 evaluated differences by gender in some clinical, analytical and prognostic aspects of their series of 1012 patients belonging to 3 Italian centres (15). These studies yielded mixed results in terms of sex predisposition for several relevant clinical manifestations including digital ulcers, pulmonary hypertension (PH), and cardiac involvement. In addition, it was unclear whether differences in age of onset existed between the sexes. Finally, there were conflicting results regarding gender differences in the survival when considering SSc-associated causes of death (12, 13). Many of these issues may be subject to geographical variations and environmental factors that varied between studies.

The aim of the present study was to assess the clinical manifestations and prognosis in a cohort of Spanish SSc patients according to gender. Notably, no similar studies in our geographical area exist.

Materials and methods

Patients

The Spanish Systemic Sclerosis Study Group (SSSG) was created by the Spanish Internal Medicine Society in 2006 with the aim of compiling a large series of patients with SSc in a registry named RESCLE (Registro de ESCLErodermia, the Spanish acronym). It collects 254 variables including clinical, immunological and capillaroscopic data, as well as treatments used. All patients provided informed consent to participate in the study, according to the requirements of the Ethics Committees of each hospital. The cut-off date for data collection was May 2014. On that date, there were 21 participating centres (listed on page 8).

Definitions

The definitions of the analysed variables are specified in the Supplementary material.

Capillaroscopy pattern

Periungual capillaroscopy was performed, and the systemic sclerosis patterns obtained were classified according to the two types described by Maricq (16): "Active", with predominance of capillary loss (extensive avascular areas) and neovascularisation, and "Slow", with predominance of giant capillary loops (mega-capillaries) and minimal loss of capillaries.

Immunologic findings

Antinuclear antibodies (ANA) were identified by an indirect immunofluorescence (IIF) assay using Hep-2 cell lines or by IIF using triple tissue cryostat sectioning (liver-stomach-kidney). We also measured SSc-related autoantibodies: anti-Centromere (ACA), anti-Topoisomerase I, anti-RNA-polymerase III, anti-PM-Scl, anti-Ku, anti-U1 RNP, and other autoantibodies including anticardiolipin, anti-SSA/Ro, anti-SSB/La, and anti-Sm.

Statistical analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables were expressed as the mean and standard deviation or as median and interquartile range in those variables with non-normal distributions. To analyse differences between categorical variables, the chi-squared test was used. The *t*-test was used to compare quantitative variables. To calculate the strength of a relationship between two or more variables, the Cramer's V coefficient was used. $p<0.05$ was considered statistically significant. Survival analysis was performed using Kaplan-Meier curves, and the log-rank test was used to compare survival curves. Cox regression was used to identify the prognostic factors for various interest groups. In the final multivariate model, only the significant variables from the univariate analysis were included, in a step-wise process. All analyses were performed using SPSS 18.0 for Windows.

Results

In May 2014, 1506 patients were included. Overall, the female/male ratio was 8/1. For lcSSc 9/6 (1.5/1), 4/7 (1/1.75) for dcSSc, 10/7 (1.4/1) for ssSSc and 16/6 (2.7/1) for preSSc (Supplementary material).

Clinical differences between men and women

Regarding age of onset, men had later SSc onset than women. Examining age of onset by sections (<30 years, 30-50 years, >50 years), there were fewer men than women with disease onset for ages less than 30 years and more men than women with onset after age 50. The time from SSc onset to diagnosis was lower in men than in women (Supplementary material).

The proportion of men who met the preliminary criteria for SSc classification according to ACR 1980 was higher than that of women. No significant differences were observed in fulfilling 2013 ACR/EULAR classification criteria, observing a very high compliance in both sexes. The frequency of smoking was higher in men than in women.

By cutaneous subtypes, dcSSc was more frequent in men, and lcSSc was more frequent in women. There were no significant differences between the proportions of men and women with preSSc or ssSSc. No statistically significant differences in age at onset of symptoms were observed. Regarding the accumulated clinical manifestations, no differences by sex were observed for peripheral vascular or GI involvement (Table I). Within the musculoskeletal manifestations, the two significantly more common ones in men than in women were the presence of myositis and tendon friction rubs.

ILD was more frequent in men than in women; the median of the expected values of FVC were significantly lower in men than in women. Furthermore, there was a higher percentage of men than women with a predicted FVC <70%. Ground glass opacity on HRCT was visualised more frequently in men than in women. No differences in the percentages of either sex were observed regarding DLCO/VA data or the radiological reticular pattern (Table I).

Considering all clinical conditions with PH, there were no differences between the proportion of affected men and women. No significant differences regarding parameters obtained by echocardiography or RHC were observed according to sex. However, analysing only cases of isolated PH, the difference between men and women was significant, with women showing a predisposition for isolated PH three times higher than men (Table I).

Conduction disturbances and systemic sclerosis renal crisis were significantly more frequent in men than in women, while sicca syndrome was more prevalent in the female group (Table I).

We found a higher frequency of anti-Topo I and anti-RNA pol III antibodies in men than in women. However, ANA, ACA and anti-Ro/SSA antibodies were significantly more frequent in women than in men. No significant differences in capillaroscopic patterns (according to Maricq) were observed by gender (Supplementary material).

Table I. Accumulated clinical symptoms.

	n	Total	Male	Female	*p*-value
Peripheral vascular					
Raynaud's phenomenon	1523	1.432 (95)	154 (93)	1.278 (96)	0.123
Digital ulcers	1523	620 (41)	80 (47)	540 (40)	0.068
Telangiectasia	1501	900 (60)	98 (59)	802 (60)	0.867
Musculoskeletal					
Calcinosis	1489	277 (19)	27 (17)	250 (19)	0.523
Arthritis	1125	226 (20)	31 (25)	195 (20)	0.192
Myositis	1128	289 (26)	47 (37)	242 (24)	**0.002**
Tendon friction rubs	1122	63 (5.6)	16 (13)	47 (4.7)	**0.001**
Acroosteolysis	1121	97 (8.7)	12 (9.6)	85 (8.5)	0.735
Gastrointestinal					
Oesophagus	1481	899 (61)	99 (60)	800 (61)	0.866
Stomach	1047	207 (20)	27 (23)	180 (19)	0.327
Malabsorption	407	69 (17)	7 (14)	62 (17)	0.689
Pulmonary					
ILD	1506	651 (43)	95 (57)	556 (42)	**<0.001**
FVC %*	1278	87.6 (70.6-101.0)	80.8 (60.0-94.5)	88.9 (72.0-102.0)	**<0.001**
DLCO/VA%*	1134	72.4 (59.0-87.0)	71.8\ (50.1-86.0)	73.0 (59.5-87.0)	0.197
FVC<70%*	1278	308 (24)	55 (40)	253 (22)	**<0.001**
Ground glass (HRCT)	938	333 (36)	53 (44)	280 (34)	**0.042**
Reticular pattern (HRCT)	1050	327 (31)	50 (38)	277 (30)	0.070
PH	1162	284 (24)	31 (25)	253 (24)	0.825
Isolated HP	1198	78 (6.5)	3 (2.3)	75 (7.0)	**0.038**
sPAP	652	34.0 (28.0-41.0)	36.5 (28.0-42.8)	34.0 (28.0-41.0)	0.529
mPAP	145	35.8 (15,3)	31.9 (15,8)	36.4 (15,2)	0.215
TRV	380	2.40 (2.11-2.78)	2.47 (2.20-2.76)	2.40 (2.10-2.80)	0.414
mPAP ≥25	145	108 (74)	15 (75)	93 (74)	1.000
Cardiac					
LVEF <60	1121	172 (15)	20 (16)	152 (15)	0.793
Pericarditis	865	67 (7.7)	13 (12)	54 (7.1)	0.086
Ischaemia	866	112 (13)	14 (13)	98 (13)	1.000
Intracardiac conduction disturbance	865	168 (19)	31 (28)	137 (18)	**0.020**
Diastolic LV dysfunction	750	132 (18)	16 (21)	116 (17)	0.427
Renal					
Renal crisis	912	38 (4.2)	9 (8.7)	29 (3.6)	**0.030**
Other manifestations					
Peripheral neuropathy	1139	123 (11)	18 (15)	105 (10)	0.116
Sicca	1494	466 (31)	23 (14)	443 (33)	**<0.001**

Data expressed as (n, %), quantitative variables as the mean and standard deviation (normal distribution) or median and interquartile range (non-normal distribution); n: number of patients with variable recorded; *Percentage of the expected value; ILD: Interstitial lung disease; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; DLCO/VA: diffusing capacity divided by the alveolar volume; HRCT: resolution CT; PH: pulmonary hypertension; Isolated PH: PH without or with mild ILD with FVC> 60%; sPAP: systolic pulmonary artery pressure estimated by echocardiography, in mmHg; mPAP: mean arterial pulmonary artery pressure measured by right heart catheterisation, in mmHg; TRV: tricuspid regurgitation velocity, in m/s; LVEF: left ventricular ejection fraction; LV: left ventricle.

Epidemiological and clinical findings associated with sex

Multivariate analysis was performed using all statistically significant parameters identified in the univariate analysis. The epidemiological clinical manifestations that were independently associated with men were smoking and older age at onset of disease. The independent factors associated with women were sicca syndrome, ANA positivity and longer time from onset to diagnosis (Table II).

Differences in causes of death according to sex

The age at death did not differ between men and women, but the median time from onset of symptoms to death was shorter in the male than in the female group (Table III). Overall, the proportion of deaths was higher in the male than in the female group.

When analysing the SSc-related and unrelated causes of death separately, no significant differences were observed between the percentages of men and the percentage of women who died from SSc-related or SSc-unrelated causes.

The most frequent cause of death was different in each sex group, although both were SSc-related: ILD was the most frequent cause in men and PH in women. As a cause of death, PH was more frequent in women than in men, both as global PH and as isolated PH (Table III).

Survival analysis

Cumulative survival curves were calculated by taking into account the time elapsed from the onset of symp-

Table II. Clinical and epidemiological characteristics associated with men.

	n	Total	Male	Female	Odds ratio univariate	*p* univariate	Odds ratio multivariate	*p* multivariate
		1506	165	1341				
dcSSc	1506	355 (24%)	62 (38%)	293 (22%)	2.15 (1.53-3.03)	<0.001		
Age at onset	1430	45.6 (16.2)	48.0 (16.2)	45.3 (16.2)	1.01 (1.00-1.02)	0.042	1.02 (1.00-1.03)	0.025
Time onset-diagnosis	1384	6.4 (9.0)	3.9 (6.7)	6.7 (9.2)	0.95 (0.92-0.98)	<0.001	0.96 (0.92-0.99)	0.022
Smoking habit	1214	145 (12%)	26 (20%)	119 (11%)	2.01 (1.25-3.21)	0.006	2.57 (1.53-4.31)	0.000
Myositis	1128	289 (26%)	47 (37%)	242 (24%)	1.87 (1.27-2.76)	0.002		
Tendon friction rubs	1122	63 (5.6%)	16 (13%)	47 (4.7%)	2.97 (1.63-5.41)	0.001		
ILD	1506	651 (43%)	95 (57%)	556 (42%)	1.83 (1.32-2.53)	<0.001	1.58 (1.03-2.43)	0.035
FVC (%)[1]	1278	85.5 (22.7)	77.5 (22,8)	86,4 (22,5)	0.98 (0.98-0.99)	<0.001		
FVC <70 (%)[1]	1278	308 (24%)	55 (40%)	253 (22%)	2.32 (1.61-3.36)	<0.001		
Ground glass	938	333 (36%)	53 (44%)	280 (34%)	1.49 (1.02-2.20)	0.042		
Isolated PH	1198	78 (6.5%)	3 (2.3%)	75 (7.0%)	0.32 (0.10-1.02)	0.038		
Intracardiac conduction disturbance	865	168 (19%)	31 (28%)	137 (18%)	1.75 (1.11-2.75)	0.020		
SRC	912	38 (4.2%)	9 (8.7%)	29 (3.6%)	2.58 (1.18-5.61)	0.030		
Sicca	1494	466 (31%)	23 (14%)	443 (33%)	0.33 (0.21-0.51)	<0.001	0.29 (0.17-0.52)	0.000
ANA	1512	1,390 (92%)	142 (85%)	1,248 (93%)	0.44 (0.28-0.71)	0.001	0.43 (0.22-0.83)	0.012
Anti-Topo I	1373	301 (22%)	44 (29%)	257 (21%)	1.53 (1.05-2.23)	0.029		
ACA	1348	615 (46%)	41 (30%)	574 (47%)	0.47 (0.32-0.69)	<0.001		
Anti-RNA pol III	222	37 (17%)	9 (36%)	28 (14%)	3.40 (1.37-8.43)	0.018		
Anti-Ro	1356	179 (13%)	11 (7.3%)	168 (14%)	0.49 (0.26-0.92)	0.021		
Follow-up[2]	1430	14.2 (11,7)	11.6 (10,2)	14,5 (11,9)	0.98 (0.96-0.99)	0.001		
ACR 1980 criteria	1504	942 (63%)	128 (76%)	814 (61%)	2.05 (1.42-2.98)	<0.001	1.79 (1.11-2.88)	0.017

Data expressed as (n, %), quantitative variables as the mean and standard deviation (normal distribution) or median and interquartile range (non-normal distribution); n: number of patients with variable recorded; Age/time in years; lcSSc: limited systemic sclerosis; dcSSc: diffuse systemic sclerosis; ILD: Interstitial lung disease; FVC: forced vital capacity; PH: pulmonary hypertension; SRC: systemic sclerosis renal crisis; [1]percentage of the expected value; [2]follow-up time from diagnosis.

toms and after diagnosis. Initially, all causes of death were considered, and in a secondary analysis only causes directly related to SSc were considered. The differences between groups at all stages of follow-up remained statistically significant except for the 5-year survival when taking into account the time from diagnosis and only the SSc-related deaths (Fig. 1).

Prognostic factors

Death prognostic factors are detailed in Table IV as calculated by Cox regression in the overall cohort and in the male and female cohorts, taking into account both the time from the onset of symptoms and the time from diagnosis.

• *Prognostic factors in the male cohort*

In the male cohort, taking into account deaths from the onset of symptoms, the most important prognostic factor was dcSSc, followed by the presence of tendon friction rubs and an older age at onset of symptoms. Protective factors were older age at diagnosis and the presence of Raynaud's phenomenon.

Given the deaths from the date of diagnosis, dcSSc and the presence of tendon friction rubs were the most relevant prognostic factors. The age at diagnosis provided a very weak risk. No protective factors were identified in this group.

• *Prognostic factors in the female cohort*

In the women's cohort, taking into account deaths from the onset of symptoms, the most important prognostic factor was dcSSc, followed by ILD, digital ulcers and age at onset of symptoms. Protective factors were older age at diagnosis and the presence of Raynaud's phenomenon.

Given the deaths from the date of diagnosis, dcSSc and PH (with or without associated ILD) were the most relevant risk factors. Age at diagnosis provided a weak risk. Raynaud's phenomenon was identified as a protective factor.

Discussion

The results of the current study are based on a large number of SSc patients (165 men and 1341 women) that are representative of the Spanish territory. With the data obtained in our series and those obtained in the literature review, summarised in Table V, we confirm the existence of epidemiological, clinical, biochemical and prognostic gender differentials in SSc patients. To our knowledge, the present study is the first to identify sex-related prognostic factors.

In our series, the female/male ratio was 8:1, consistent with previous studies in several geographic areas of Spain (17,18). Considering other studies conducted at the national level, we have observed a higher female/male ratio in series from Spain and other southern countries, such as Brazil (7.7:1) or Italy (7.8:1) (19, 20), than in northern countries, such as France (5:1), Germany (4.8:1), the USA (6:1) or Canada (5.8:1) (9, 10, 21, 22).

The men of the present cohort were diagnosed with SSc significantly later than women, in agreement with data from other patient series (14, 23-25). This finding may be related to hormonal influences, as suggested by Steen (23).

In the RESCLE cohort, it took more than twice as long to diagnose women with SSc than to diagnose men, which is consistent with data from the two

Table III. Causes of death, age at death, time from onset and from diagnosis to death.

	n	Total	Male	Female	*p*-value
Deaths	1523	247 (16.4)	51 (30.4)	196 (14.6)	**<0.001**
Age at death	256	66.3 (13.1)	66.1 (12.8)	66.4 (13.2)	0.881
Time from SSc onset to death	249	12.50 (5.08-21.99)	8.33 (3.87-12.66)	14.06 (5.95-24.29)	**<0.001**
Time from diagnosis to death	245	7.22 (2.95-12.80)	4.51 (2.90-11.39)	8.11 (2.94-13.75)	0.066
SSc-related	247	113 (46)	22 (43)	91 (46)	0.753
Isolated ILD	247	29 (11.7)	10 (19.6)	19 (9.7)	0.084
Isolated PH	247	39 (15.8)	0 (0.0)	39 (19.9)	**<0.001**
ILD plus PH	247	21 (8.5)	4 (7.8)	17 (8.7)	1.000
ILD (with or without PH)	247	50 (20.2)	14 (27.5)	36 (18.4)	0.172
PH (with or without ILD)	247	60 (24.3)	4 (7.8)	56 (28.6)	**0.002**
Arrhythmia	247	5 (2.0)	3 (5.9)	2 (1.0)	0.061
Ischaemic heart disease	247	1 (0.4%)	0 (0.00%)	1 (0.51%)	1.000
SRC	247	18 (7.3)	5 (9.8)	13 (6.6)	0.544
Non SSc-related	247	134 (54.3)	29 (56.9)	105 (53.6)	0.753
Cancer	247	32 (13.0)	5 (9.8)	27 (13.8)	0.640
Ischaemic heart disease (with other cardiovascular risk factors)	247	5 (2.0)	1 (2.0)	4 (2.0)	1.000
Stroke	247	2 (0.8)	0 (0.0)	2 (1.0)	1.000
CRF	247	2 (0.8)	1 (2.0)	1 (0.5)	0.371
COPD	247	1 (0.4)	1 (2.0)	0 (0.0)	0.206
Sepsis	247	15 (6.1)	4 (7.8)	11 (5.6)	0.520
VTE	247	2 (0.8)	1 (2.0)	1 (0.5)	0.371
Other	247	75 (30.4)	16 (31.4)	59 (30.1)	0.865

Data expressed as (n, %); quantitative variables in mean and standard deviation (normal distribution) or median and interquartile range (non-normal distribution); n: number of patients with variable recorded; Time in years; ILD: Interstitial lung disease; PH: pulmonary hypertension; SRC: systemic sclerosis renal crisis; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; VTE: Venous thromboembolic disease; SSc: systemic sclerosis.

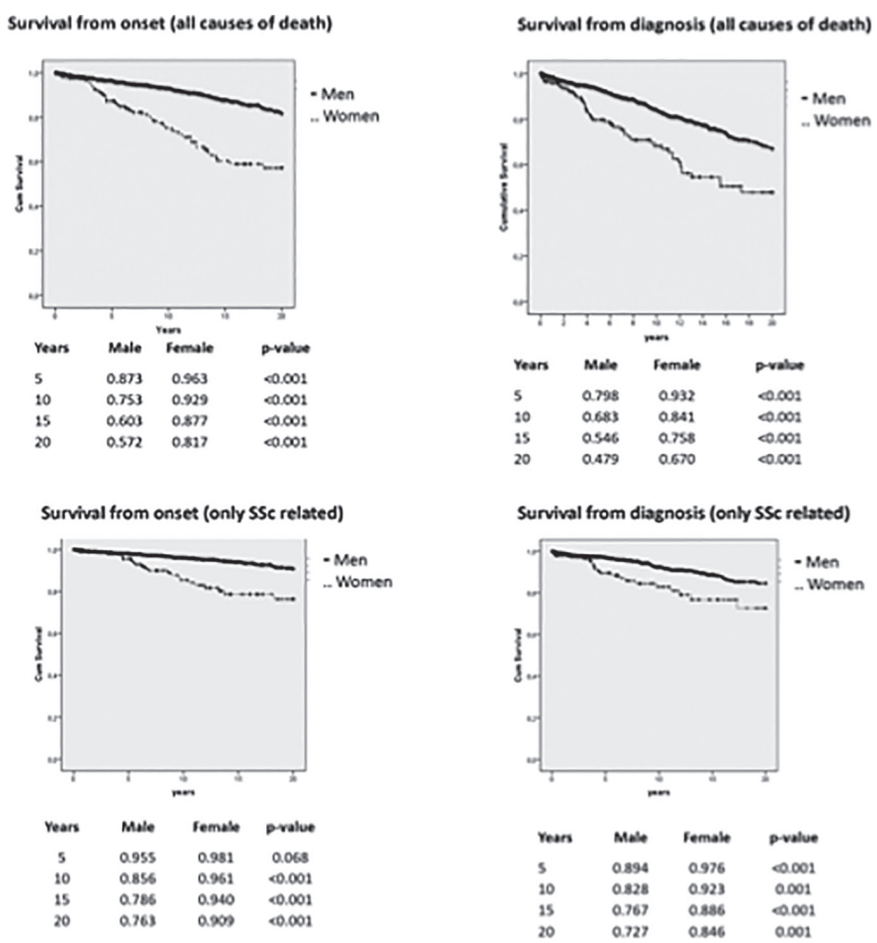

Fig. 1. Five-year survival rates.

previous multicentre studies (12,13). Symptomatic dcSSc, which is more common in men, allows the clinician to make a quick diagnosis given the aggressiveness of this form, but this is not the only reason for the difference in time between onset and diagnosis. In the study conducted via the Canadian Systemic sclerosis Research Group (CSRG) registry in 2009, the difference in time from the onset of Raynaud's phenomenon to diagnosis between men and women remained significant even after adjusting for skin subtype (26). It is also possible that a trend exists towards more comprehensive studies in men than in women with the same symptom (27). Furthermore, primary Raynaud's phenomenon is more common in females, so when this sign occurs in women, the conduction of a comprehensive study searching for systemic sclerosis is not likely (28). Jewett et al showed in addition that SSc women were substantially more likely than men to have appearance concerns (74.5 % female *vs*. 53.2 % male, $p<0.001$), which may condition a higher demand for medical care (29). Finally, there are gender differences in terms of early disease progression. The CSRG study

Table IV. Multivariate Cox regression. Prognostic factors in the overall cohort and male and female cohorts, from the onset of symptoms and since diagnosis.

SSc patients, patients evaluated (%)	OR (95% C.I.)	*p*-value
Overall cohort: Death from any cause from the onset of symptoms		
Male	1.53 (1.06-2.19)	0.022
dcSSc	2.26 (1.65-3.10)	<0.001
Age at SSc onset	1.13 (1.11-1.16)	<0.001
Age at SSc diagnosis	0.94 (0.93-0.96)	<0.001
Raynaud's phenomenon	0.42 (0.24-0.73)	0.002
Digital ulcers	1.38 (1.03-1.86)	0.031
Tendon friction rubs	1.74 (1.10-2.74)	0.017
ILD	1.82 (1.32-2.50)	<0.001
Sicca	0.66 (0.49-0.90)	0.009
Overall cohort: Death from any cause from diagnosis:		
Male	1.47 (0.99-2.18)	0.055
dcSSc	1.88 (1.35-2.61)	<0.001
Age at SSc diagnosis	1.06 (1.05-1.07)	<0.001
Raynaud's phenomenon	0.44 (0.25-0.78)	0.005
Tendon friction rubs	1.75 (1.08-2.84)	0.023
ILD	3.23 (2.04-5.12)	<0.001
Isolated PH	3.63 (1.84-7.16)	<0.001
Sicca	0.70 (0.51-0.96)	0.028
Male cohort: Death from any cause from SSc onset		
dcSSc	2.06 (1.05-4.06)	0.036
Age at SSc onset	1.17 (1.09-1.27)	<0.001
Age at SSc diagnosis	0.91 (0.85-0.98)	0.016
Raynaud's phenomenon	0.36 (0.14-0.95)	0.038
Tendon friction rubs	2.32 (1.10-4.89)	0.027
Male cohort: Death from any cause from diagnosis		
dcSSc	2.21 (1.14-4.27)	0.019
Age at SSc diagnosis	1.07 (1.04-1.09)	<0.001
Tendon friction rubs	2.64 (1.37-6.15)	0.010
Female cohort: Death from any cause from onset of symptoms		
dcSSc	2.31 (1.65-3.24)	<0.001
Age at SSc onset	1.14 (1.11-1.16)	<0.001
Age at SSc diagnosis	0.94 (0.93-0.96)	<0.001
Raynaud's phenomenon	0.28 (0.16-0.51)	<0.001
Digital ulcer	1.46 (1.07-1.98)	0.016
ILD	1.85 (1.33-2.57)	<0.001
Female cohort: Death from any cause from diagnosis.		
dcSSc	2.09 (1.48-2.96)	<0.001
Age at SSc diagnosis	1.06 (1.04-1.07)	<0.001
Raynaud's phenomenon	0.31 (0.17-0.56)	<0.001
ILD	3.17 (1.98-5.07)	<0.001
Isolated PH	3.97 (2.11-7.45)	<0.001

dcSSc: diffuse systemic sclerosis; ILD: interstitial lung disease; PH: pulmonary hypertension.

reported a larger elapsed time between the onset of Raynaud's phenomenon and subsequent non-Raynaud's symptoms in women than in men (26).

In our series, the presence of ulcers did not differ between the sexes. The same was observed in the aforementioned CSRG and in other single centre studies (9, 11, 13). However, other groups have reported more distal vascular involvement in men (8,11,13, 22, 30-32), and the study by Manfredi *et al*., conducted in 219 Italian patients, identified the male gender as an independent risk factor for the appearance of skin ulcers over a follow-up period of 6 months (33). In a study conducted on 231 Greek patients (31 men), Panopoulos *et al*. reported a higher incidence of digital ulcers in men during the first three years after the onset of the disease, but the incidence was similar later on (34). Therefore, vasculopathic involvement may be more closely matched in series with a long follow-up period because it is more associated with dcSSc and present in the early years (35, 36).

ILD such as smoking were associated with the male gender in our cohort which can lead to a hypothesis of an association between the two variables. However, the predominant SSc-related ILD is nonspecific interstitial pneumonia with a predominance of ground glass opacity areas (37), whereas bronchiolitis and desquamative interstitial pneumonia are the typical radiologic patterns related to smoking (38). In the current study, we have observed the presence of ground glass opacity in 222 patients (33%) and a reticular pattern in 327 patients (31%), with a predominance of the ground-glass opacity pattern in the male group. Our data are consistent with those obtained in the two previous multicentre studies (12, 13).

Upon assessing PH in men and women, we have observed a clear predominance in the female group, especially when analysing the isolated PH. This result is similar to that published by Hussein *et al*. (12), whereas the EUSTAR study observed a PH predominance in the male group (13). The rest of the studies conducted to date have compared only the prevalence of overall PH (not isolated PH), and they have found no statistically significant differences between sexes. Pasarikovski *et al*. recently compared 378 patients (58 men and 320 women) with SSc and PH and observed a greater coexistence of PH associated with ILD in the male group (67% in men *vs*. 48% in women, RR: 1.41, 95% CI: 1.14–1.74) (39). The increased presence of lcSSc in women and of ILD in men might be predisposing factors for the higher prevalence of isolated PH in the former.

The current study is the first to analyse separately the differences between men and women with SSc in terms of heart rhythm disorders, with an overall higher male prevalence.

ANA positivity was higher in the current cohort of women than in men. Salazar *et al*. also detected, in a sample of 3249 patients, a greater proportion of men within the group negative for ANA (40).

The clinical course of the men from the RESCLE cohort was faster and more aggressive than that of the women. A higher percentage of men died in a shorter period of follow-up because the onset of symptoms in men was later, despite the age of death being the same in men and women.

The most common cause of death in men and women was different: ILD in men (27.5%) and PH in women

Table V. Major studies examining clinical, epidemiological and prognostic differences between SSc male and female patients.

	Male/female	Onset	Classification criteria	dcSSc	Digital ulcers	GI	PH	Heart	Sicca	Myopaty	ILD	Kidney	Antibodies	Capillaroscopy	Mortality	Poor prognostic factors	Survival
Simeón[1]1996 (7)	9/82	NS	-	NS	-	NS	NS	NS	NS	M	NS	NS	NS	NS	-	-	-
Ferri[2]2004(15)	115/897	-	-	M	-	-	-	-	-	-	-	-	ACA: F SCL70: M	-	M		F
Gaultier[1] 2007 (8)	36/85	NS	M	M	M	NS	NS	NS	-	-	M	-	ACA: F	NS	-	-	NS
Al-Dhaher[1] 2010 (9)	27/158	-	-	M		NS	NS	NS	-	-	NS	NS	NS	-	NS	-	-
Nguyen[1] 2011 (10)	62/319	NS	-	M	NS	NS	M	-	-	NS	M	NS	-	-	-	-	-
Panopuolos[1]2013 (34)	31/200	NS	-	NS	M	NS	NS	NS	-	NS	NS	M	NS	-	-	-	
Hussein[3]2014 (12)	168/791	-	-	M	NS	NS	F	-	-	-	M	M	-	M	NS	-	F
Elhai[4]2014 (13)	1321/7861	NS	-	M	M	F	M	M [a]	-	-	-	-	ACA: F SCL70: M	-	M	-	NS
Peoples[1] 2016 (14)	542/2144	M	-	M	M	NS	NS	M [b]	-	NS	M	NS	ACA: F SCL70: M Anti-U3RNP: M	-	ILD: M PH: F	-	F
Freire[5] 2017	165/1341	M	M	M	NS	NS	F	M [c]	F	M	M	M	ANA: F ACA: F SCL70: M RNA pol III: M	NS	ILD: M PH: F	M: dcSSc, age onset, tendon friction rubs. F: dcSSc, age onset, digital ulcers, ILD, Isolated PH.	F

M: male predominance in this item; F: female predominance in this item.
[1]: unicentric; [2]: multicentric, Italy; [3]: multicentric, Canada; [4]: multicentric, patients from 23 European countries, USA, Canada, Dominican Republic, Argentina, Brazil, South Africa, New Zealand, Russia, Israel and China; [5]: multicentric, Spain.
NS: not significant; dcSSc: diffuse systemic sclerosis; GI: gastrointestinal; PH: pulmonary hypertension; ILD: interstitial lung disease; a: left ventricular ejection fraction <50%; b: left-sided heart failure (clinical) or estimated ejection fraction <45%, pericarditis, or arrhythmia requiring treatment; c: conduction disturbances.

(28.6%). There were no sex differences in the proportion of deaths due to ILD, but there were in terms of death by PH, which was more common in women than men, both overall and for isolated PH. It is also important to note that every man who died due to PH had associated ILD. The People series, analysing a series from Pittsburgh, yielded the same findings (13).

In the current cohort with long-term follow-up, survival curves showed lower cumulative survival in men than in women. This difference remained when the causes for SSc-related deaths were analysed separately, but began to be significant at 5 years after diagnosis. A study of the data extracted from the EUSTAR cohort showed that sex survival differences in the Kaplan Meier curves for overall death disappeared when they were further analysed for SSc-related deaths (13). Their mean follow-up period was only 5 years, which is very limited in regard to assessing differences in cumulative survival time.

In the RESCLE cohort, predictive factors for overall mortality from the date of onset were, in order of relevance, dcSSc, ILD, presence of digital ulcers and tendon friction rubs, male sex and older age at onset. In the meta-analysis conducted by Rubio *et al*. in 2014, the ILD showed an overall HR of 2.89 for unfavourable outcomes in patients with SSc (41). The finding of digital ulcers and tendon friction rubs as prognostic factors is directly related to their association with dcSSc. In our series, we found a strong association between these two variables and that SSc type (dcSSc/digital ulcers: V-Cramer 0.240, $p<0.001$; dcSSc/tendon friction rubs: V-Cramer 0.241, $p=0.001$) (data not shown). Regarding the age at symptom onset (Raynaud or non-Raynaud), the EUSTAR 2010 study on mortality in SSc also found it to be a poor prognostic factor (42).

In our series, older age at diagnosis was a protective factor. This fact is controversial in the literature. Several authors have described it as a poor prognostic factor, but Perez-Bocanegra reported that when the data are adjusted to those expected in the general population, mortality was only very slightly increased in patients with SSc over 65 years (SMR: 1.2) (43). Alba *et al*. also noted that higher SMR values were found in younger SSc patients aged ≤30 years (26.22; 95% CI, 14.43–38.01), followed by patients aged 31–59 years (13.32; 95% CI, 10.55–16.08). The lowest SMR was found in older patients ≥60 years (1.78; 95% CI, 1.17–2.39) (44). In the RECLE cohort, the presence of Raynaud's phenomenon at any stage of the disease course was identified as a protective factor. In the 2010 EUSTAR study, late onset of Raynaud's phenomenon was associated with increased mortality (42).

When the analysis was made taking into account deaths from the date of diagnosis, isolated PH was identified as a prognostic factor in addition to the previous ones. In his meta-analysis, Rubio *et al*. described PH as one of the main factors for poor prognosis in patients

with SSc, with an overall HR of 2.62 (95% CI: 1.64 to 4.17) (41).

The present study is the first to evaluate sex-related prognostic factors for SSc. The risk factors identified when studying the male patients separately in our cohort were similar to those of the overall cohort, although in the case of men ILD had no clear prognostic value. Therefore, the increased presence of ILD in men and the highest percentage of ILD-related deaths in the male population do not justify the worse survival rates. However, later diagnosis and the increased presence of diffuse cutaneous manifestations are responsible for poorer survival in men.

Limitations and strengths of the current study

The current study has the following limitations: Multicentre registries have a greater heterogeneity in collecting and entering data. To try to minimise this limitation, clear definitions of variables were set and followed by the Registration Centres, and the Coordinating Centre performed periodic quality controls. On the other hand, both right heart catheterisation and echocardiography were used for inclusion of patients with PH; therefore this diagnosis may have been overestimated in our study. However, the overestimation would have equally influenced the data from men and women, and thus it would not bias the sex differences found. Although this probably did not interfere with the global results of the present study, it is appropriate from a conceptual point of view that the definition used for pre-systemic sclerosis patients could include patients who should be classified as SSc according to the 2013 ACR/EULAR SSc classification criteria. Since the registry started in 2006, years before the new criteria were published, we have seen in a recent study that 8.3% of the very early and 24% of the early SSc patients met the ACR/EULAR 2013 criteria during the follow-up (45).

In terms of strengths, the current study is based on a range of men and women with systemic sclerosis who are representative of the Spanish territory, since data were collected from 21 participating institutions from almost all regions of the country. Numerous differences have been described in the clinical expression and laboratory data of patients with SSc from different sites in Europe, Asia and America. In fact, Galluccio *et al*. comments that international registries have utility to understand the overall behaviour of SSc, but national registries are essential to define the behaviour of systemic sclerosis in a specific population and can reveal variations that arise from environmental or genetic conditions (46). In addition, the median follow-up of our cohort is more than 11 years, long enough to assess differences in survival curves.

Conclusions

The clinical course in men in the RESCLE cohort was faster and the prognosis worse, with a higher proportion of deaths with respect to the female group. The most common cause of death in men was ILD, whereas it was PH in women. Isolated PH was a more frequent cause of death in women. In fact, all men who died of PH had an associated ILD. Survival curves showed a lower survival rate in men at 5 years from diagnosis that remained when assessing only SSc-related causes of death. Our work is the first to analyse independent prognostic factors by gender. Therefore, in the RESCLE cohort, men die faster because the disease occurs most often as the diffuse subtype and symptoms appear later in life.

Knowledge of the distinguishing sex-related features in systemic sclerosis is very important, not only because it allows for better understanding of the pathogenesis of this complex disease but also because it helps establish monitoring protocols and specific treatments adapted to the needs of each group and to establish prognostic subgroups.

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