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Mortality and prognostic factors in Spanish patients with systemic sclerosis

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Objective. **To determine survival and mortality in a cohort of Spanish patients with scleroderma (systemic sclerosis, SSc) and to analyse whether survival is influenced by demographic, clinical or immunological variables or the extent of skin involvement.**
Methods. **The study included 79 patients diagnosed with SSc and taking part in a study to determine the extent of sclerosis, visceral involvement and immunological alterations. We studied the number of observed and expected deaths (the expected number being based on age- and sex-specific rates in the background population) and derived standardized mortality ratios with their 95% confidence intervals (CI). Cumulative survival after onset of the first symptom was estimated according to the Kaplan–Meier method. The Cox method was used to identify the prognostic factors.**
Results. **The mortality rate was 0.0249 deaths per person-year. Survival at 15 yr was 0.62 (95% CI 0.410–0.778). The standardized mortality ratio was 429.4% (95% CI 222–750). On crude analysis, lung involvement [forced vital capacity (FVC) $<70\%$, pulmonary hypertension], SSc renal crisis, an active capillaroscopic pattern, pericardial effusion and age over 60 yr at diagnosis were associated with shorter survival. On multivariate analysis, only age at diagnosis over 60 yr, FVC $<70\%$ and SSc renal crisis were independent prognostic factors.**
Conclusions. **The mortality rate associated with SSc showed a four-fold increase compared with the background population. Lung involvement and sclerodermal renal crisis were found to be independently associated with reduced survival.**

KEY WORDS: Scleroderma, Survival, Standardized mortality ratio, Prognostic factors.

Scleroderma or systemic sclerosis (SSc) is a multisystem disorder characterized by excessive accumulation of connective tissue components and structural vascular abnormalities. Its natural history varies from a relatively benign condition to a rapidly progressive disease with a high risk of mortality [1]. The relatively few studies examining survival report 5-yr survival rates of 34–73% [2]. This substantial variation is explained by the broad variation in the course of the disease, the fact that survival was estimated from different time points (from onset or from diagnosis of SSc) and because the populations studied included different proportions of patients with diffuse and limited SSc.

The extent of skin sclerosis has been considered an important prognostic factor by several authors [3–11] and SSc patients have been subdivided into two groups according to this factor. Patients with diffuse SSc have skin sclerosis both distal and proximal to the elbows and knees, and those with limited SSc have skin sclerosis only distal to the elbows and knees [3, 11]. In recent years the value of visceral involvement and skin sclerosis as prognostic factors has been assessed by the use of multivariate statistical methods [5–11]. Again, the results obtained in these studies are not always concordant, as not all types of SSc patients were included and the variables estimated were dissimilar.

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In this report we review the mortality of a cohort of patients referred to a single Spanish centre. We attempted to recruit a true inception cohort retrospectively, and determined survival according to the onset of symptoms as reported by the patients rather than with respect to the date of the first visit. Secondly, we estimated the mortality risk as related to the background population risk in both males and females. Finally, we analysed and identified the prognostic factors related to survival in SSc patients.

Patients and methods

This follow-up study included 79 patients diagnosed with SSc at the Internal Medicine Department of Vall d'Hebron Hospital, a referral centre for this disease, between 1976 and 1996. Sixty-five of the total fulfilled the American College of Rheumatology (ACR) classification criteria [12] for SSc, and the 14 patients who did not had Raynaud's phenomenon, anticentromere antibodies (ACA), capillaroscopic abnormalities, sclerodactyly and the characteristic visceral involvement of SSc. All patients referred to our centre with an interval of 15 yr or less between onset and diagnosis of the disease were included in the study. Disease onset was defined as the self-reported date of the first symptom (Raynaud's phenomenon in the majority of patients), as has been described in other work [13–15]. At the time of diagnosis, a standardized clinical protocol containing 150 items of information was filled in for each patient and appropriate tests were requested. The criteria for evaluating the manifestations of SSc are detailed below.

Clinical features

Skin involvement was considered present when cutaneous thickening was found. The extent of skin sclerosis was assessed at diagnosis and 6 months later by inspection and palpation of the entire body skin by two physicians. On the basis of the maximum extent of skin sclerosis, two separate groups of SSc patients were established: those with diffuse SSc, comprising patients with sclerosis distal and proximal to the elbows and knees, and those with limited SSc, comprising patients with sclerosis only distal to the elbows and knees or without skin involvement.

Muscle involvement was assessed from clinical symptoms (proximal muscle weakness), physical examination and muscle enzyme determination. When enzyme alterations were found, electromyography and muscle biopsy were performed.

Joint involvement was considered present when arthralgia, arthritis, tendon friction rubs or acro-osteolysis was observed.

Digestive tract involvement secondary to SSc was defined as hypomotility of the lower two-thirds of the oesophagus and/or decreased peristalsis confirmed by manometry or cine-radiography. Intestinal manifestations (diarrhoea, malabsorption syndrome) were also recorded and a breath test was performed when alterations were detected.

Pulmonary involvement was demonstrated by pulmonary fibrosis on chest radiography, pulmonary function testing, alterations on spirometry or less than 70% of predicted carbon monoxide diffusing capacity.

Cardiac involvement was established by one or more of the following: clinical symptoms; reversible thallium perfusion defects after cold stimulation [16]; any change on colour Doppler echocardiography; electrocardiographic signs of right ventricle enlargement; pulmonary hypertension (PHT) measured by Doppler ultrasonography in patients with tricuspid regurgitation [17]; and left ventricular ejection fraction lower than 50% or right ventricular ejection fraction lower than 40% on radionuclide ventriculography.

Renal involvement secondary to SSc was diagnosed when increased serum creatinine concentration or abnormal urine analysis (haematuria, proteinuria >500 mg/24 h) was detected in the absence of any other known cause, or when a sclerodermal renal crisis (SRC), defined according to Traub *et al.* [18], was noted.

Nailfold capillaroscopy was performed on each finger of both hands with a Wild M3 stereomicroscope and the use of a cold light lamp Intralux 5000 Volpi (Urdorf, Zurich, Switzerland). According to Maricq *et al.* [19], two capillaroscopic patterns were distinguished: an active pattern characterized by predominance of capillary loss, and a slow pattern characterized by megacapillaries with no capillary loss.

Laboratory analysis included determination of general haematological and biochemical parameters, antinuclear antibodies detected with an immunofluorescence assay, ACA determined by an immunofluorescence technique with Hep-2 cell substrate, and anti-topoisomerase I antibodies determined by immunoblotting.

Statistical analysis

The overall mortality rate was calculated as the ratio between the number of deaths and the cumulative follow-up time (expressed as person-years). The 1990 mortality data from Catalonia were used to estimate the standardized mortality ratio (SMR) [20]. Cumulative survival 5, 10 and 15 yr after SSc onset was estimated by the Kaplan–Meier method. The 95% confidence intervals (CI) were calculated with the Greenwood method. The Cox proportional hazards model [21] was used to identify the main SSc prognostic factors. The Stata software package [22] was used for statistical calculations.

Results

Clinical findings

The study included 68 (86%) women and 11 (14%) men. Twenty-two of the 79 patients had diffuse SSc and 57 limited SSc. Twelve patients died. Deaths were due to sclerodermal renal crisis in seven, progressive respiratory insufficiency due to lung fibrosis in two, PHT in two and lung cancer in one. The causes of death in each SSc group were as follows: in the diffuse SSc group, five from sclerodermal renal crisis, one from lung fibrosis and one from lung cancer; in the limited SSc group, two from sclerodermal renal crisis and three from lung involvement (one lung fibrosis and two PHT). The patients' demographic, clinical and immunological features are shown in Table 1.

Survival

The mean interval from the first symptom of SSc to diagnosis and the start of follow-up was 4.5 yr (S.D. 4.1, range <1 month to 14 yr). The median interval from first symptom to diagnosis and start of follow-up was 1 yr (S.D. 3.06) in the diffuse SSc patients and 4.7 yr (S.D. 4.20) in the limited SSc patients (Mann–Whitney U-test, 325; $P=0.001$).

Table 2 shows the distribution of the 79 patients according to the intervals from first symptom to diagnosis

TABLE 1. Basic clinical and demographic data of 79 Spanish patients with SSc

Variable	Value	%
Age at onset: yr [median (range)]	44.2 (7–72.6)	
Age at diagnosis: yr [median (range)]	48.8 (15.4–73)	
Disease duration at enrolment (yr)*	4.5	
Diffuse SSc	1	
Limited SSc	4.7	
Sex (no. of patients)		
Male	11	14
Female	68	86
Skin involvement (no. of patients)		
Diffuse	22	28
Limited	57	72
Capillaroscopy (no. of patients; not done for 10 patients)		
Active	20	29
Slow	49	71
Lung involvement (no. of patients)		
FVC <70%	8	10
DCO <70%	22	32
PHT	5	6
Oesophagus involvement (no. of patients)	69	87
SSc renal crisis (no. of patients)	8	10
Anti-topoisomerase I antibodies (no. of patients)	15	19
ACA (no. of patients)	25	32
Deaths (no.)	12	15
SRC	7	59
Respiratory insufficiency due to pulmonary fibrosis	2	17
PHT	2	17
Lung cancer	1	8

DCO, carbon monoxide diffusing capacity.
*Mann–Whitney *U*-test: 325, $P=0.001$.

TABLE 2. Survival and distribution of 79 SSc patients according to the intervals from first symptom to diagnosis and from first symptom to end of follow-up (strata of duration)

Strata of duration (yr)	Years between first symptom and diagnosis			Deceased	Cumulative survival (%): 95% CI
	0–5	5–10	10–15		
5	13			7	(71) 0.46–0.86
5–10	15	2		4	(64) 0.42–0.79
10–15	21	16	12	1	(62) 0.41–0.77

and from the first symptom to the end of follow-up. There were 481.8 person-years of follow-up. Twelve of 79 patients died during this period; nine deaths occurred in the first 6 yr after onset of the disease. The mortality rate was 0.024905 deaths per person-year. The life-table analysis shows a survival rate of 71% (95% CI 0.468–0.863) after 5 yr, 64% (95% CI 0.421–0.794) after 10 yr and 62% after 15 yr (95% CI 0.410–0.778) (Table 2 and Fig. 1). The SMR of the SSc cohort showed a four-fold increase (from 2.22 to 7.50) in mortality risk compared with the background population.

Prognostic factors

In the crude analysis the following variables were associated with shorter survival: patient age over 60 yr at diagnosis; lung involvement, defined by forced vital capacity (FVC) <70%; PHT; SRC; pericardial effusion and active capillaroscopic pattern (Table 3). After adjusting for the presence of FVC <70%, survival was shorter only among patients with age at diagnosis over 60 yr [incidence density ratio (IDR) = 12.3, 95% CI 2.4–62.5] and patients with SRC (IDR = 45.9, 95% CI 6.4–331.6). After adjusting for the presence of SRC, survival was still shorter among patients with FVC <70% (IDR = 22.2, 95% CI 4.4–111.7) and among patients with age at diagnosis over 60 yr (IDR = 24.7, 95% CI 2.9–205.1). However, when the other statistically significant variables in the crude analysis were added to the model with age at diagnosis, FVC <70% and SRC, the log-likelihood ratio χ^2 tests were not significant. Therefore, age at diagnosis over 60 yr, FVC <70% and SRC were independent prognostic factors in this cohort of patients with SSc.

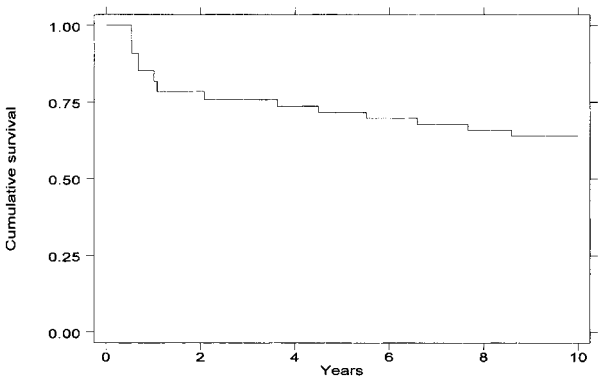

FIG. 1. Cumulative survival of SSc patients as determined by the Kaplan–Meier method.

Discussion

Reported survival rates in SSc differ considerably because of several factors, including the variable natural history of the disease and methodological differences between studies. One of the problems resides in selection bias. Patients with rapidly progressive disease and fatal outcome before referral to the hospital are not included in such analyses, and this can work to falsely improve survival rates. The initial time-point from which survival is estimated, i.e. from the onset of SSc or from its diagnosis, can also affect survival results. Delays in diagnosis may be lengthy and the calculation of survival from diagnosis may not provide a representative sample of the population with the disease. This report attempts to provide a representative cohort by determining survival from the first self-reported symptom of the disease and including those with fatal outcome at diagnosis. Survival in our series (5-yr survival 71%, 10-yr survival 64% and 15-yr survival 62%) was similar to that of several studies showing increased mortality associated with SSc.

Another relevant point in these studies is the difficulty in interpreting mortality rates without taking into account

TABLE 3. Fifteen-year survival of 79 Spanish patients according to demographic, clinical and immunological variables: crude analysis

	All patients	Surviving patients	Deceased patients	Cumulative survival	95% CI	*P*
No. patients	79	67	12	62%	0.410–0.778	
Gender: no. (%)						
Male	11 (14)	8	3	53%	0.132–0.806	
Female	68 (86)	59	9	65%	0.413–0.806	0.226
Skin involvement: no. (%)						
Limited	57 (72)	50	5	71%	0.343–0.899	
Diffuse	2 (28)	17	7	52%	0.254–0.734	0.126
Age at diagnosis (yr) (%)						
$\geqslant 60$	61 (77)	56	5	82%	0.610–0.920	
>60	18 (23)	11	7	24%	0.48–0.522	0.003
FVC: no. (%)						
$>70\%$	68 (86)	63	5	85%	0.607–0.952	
$<70\%$	8 (10)	2	6	2%	0.000–0.211	<0.001
PHT: no. (%)						
Absent	74 (94)	65	9	66%	0.419–0–833	
Present	5 (6)	2	3	33%	0.009–0.774	0.002
SRC: no. (%)						
Absent	71 (89)	66	5	86%	0.696–0.939	
Present	8 (11)	1	7	9%	0.002–0.402	0.027
Pericardial effusion: no (%)						
Absent	63 (78)	58	5	82%	0.622–0.924	
Present	15 (19)	8	7	24%	0.052–0.515	0.004
Capillaroscopic pattern (%)						
Active	20 (25)	15	5	52%	0.204–0–761	
Slow	49 (62)	47	2	91%	0.693–0.977	0.02
ACA (%)						
Absent	51 (65)	43	8	69%	0.476–0.833	
Present	25 (32)	24	1	93%	0.591–0.990	0.396
Anti-topoisomerase I antibodies (%)						
Absent	59 (75)	55	4	87%	0.688–0.949	
Present	15 (19)	11	4	53%	0.187–0.792	0.105

Survival was estimated by the Kaplan–Meier method. *P*-values were derived from the log-likelihood ratio χ^2 test.

the expected mortality in the background population. We have determined mortality risk over a long time-span and in relation to the background population of men and women. The results of this work show a four-fold increase in the mortality rate in SSc patients compared with an age- and sex-matched Spanish population. The four published studies using the SMR and whose results are directly comparable with ours provide the following data: SMR of 4 in an English SSc cohort [13], 4.7 in a Canadian SSc cohort [23], 3 in a Danish SSc cohort [14] and 4.6 in a Swedish SSc cohort [15]. The present work is the first to use this method to determine the risk of mortality in a Mediterranean sample.

Eleven of the 12 deaths registered in this study were directly related to SSc. The last death, by lung cancer, supports results from previous studies suggesting an increased incidence of lung cancer in patients with SSc [24, 25]. All the SSc-related deaths in the present study were due to kidney and/or lung involvement. Scleroderma renal crisis was the most important cause of death, even though all the patients with identified SSc that developed this condition received early treatment with ACE (angiotensin-converting enzyme) inhibitors. Four of the seven deaths due to SRC were of patients who were diagnosed with SSc at the moment they were admitted to hospital with renal failure.

The present work includes a large number of variables potentially related to survival in these patients (sex, age at diagnosis, extent of skin sclerosis, visceral involvement, ACA and anti-topoisomerase antibodies) in the analysis of prognostic factors. Lung involvement, SRC and age at diagnosis over 60 yr were the variables found to be associated with decreased survival. A greater percentage of women than men (69 *vs* 53%) and a greater percentage of limited than diffuse SSc patients (71 *vs* 52%) survived over the 15 yr since initiation of the disease. Nevertheless, sex and the extent of skin involvement were not among the prognostic factors. We believe that this can be explained by the relatively small number of men and of diffuse SSc patients in the series, which reduced the statistical power of these variables in the analysis.

Other authors have assessed the prognostic value of visceral involvement and skin sclerosis by multivariate statistical methods, but the results obtained in these studies are not applicable to the entire SSc population. Wynn *et al.* [7] and Altman *et al.* [4] included only diffuse SSc, and the prognostic factors identified relate only to this group. Peters-Golden *et al.* [6] studied pulmonary function alterations only in diffuse SSc patients. Ferri *et al.* [9] only considered skin involvement and immunological alterations. Bulppit *et al.* [10] included SSc

patients with a disease course of less than 1 yr; thus this series consisted entirely of diffuse SSc cases. Patients with limited SSc fulfil the diagnostic criteria more than 1 yr after the onset of the disease. Clements *et al.* [5] found that skin sclerosis and heart involvement were associated with poor prognosis. Finally, Jacobsen *et al.* [14] analysed only the influence of skin involvement on survival. Cox regression models were calculated after adjusting for sex and age at study end, and the risk ratio between limited and diffuse skin involvement was 1.3 ($P = 0.0002$).

In the present work we observed that a severe restrictive pattern and SRC were associated with poor prognosis after adjusting for age at diagnosis. In a previous study by our group to identify morbidity markers using a stepwise strategy to estimate a multiple logistic regression model, only diffuse sclerosis followed by pulmonary hypertension on Doppler echocardiography were found to be independent prognostic factors [11].

In summary, the data from this study demonstrate a four-fold increase in mortality among patients with SSc compared with the background population rate in our setting. Sclerodermal renal crisis was the most important cause and lung involvement the second most important cause of death in this group of patients. Among the numerous clinical and immunological variables studied, we found that FCV $<70\%$ and sclerodermal renal crisis were independently associated with poorer prognosis.

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