Changes in the pattern of death of 987 patients with systemic sclerosis from 1990 to 2009 from the nationwide Spanish Scleroderma Registry (RESCLE)

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ABSTRACT

Objective. *To determine the changes in the pattern of death of patients with systemic sclerosis (SSc) throughout 20 years.*

Methods. *Data were collected from the Spanish Scleroderma Registry (RESCLE), retrospective multicentre database from 1990 to 2009. SSc-related and SSc-non related causes of death were assessed.*

Results. *987 patients were recruited. Overall standardised mortality ratio (SMR) was 2.34 (2.24-2.44). SSc-related causes of death were responsible of 72% of all deaths of those patients diagnosed within 1990-99 vs. 48% within 2000-09 (p=0.006). Relative pulmonary death rate was stable over time (68.1% within 1990-99 vs. 63.9% within 2000-09, p=0.815). Relative renal death rate was decreasing over time (17% within 1990-99 vs. 5.5% within 2000-09, p=0.175). Heart distribution tripled its ratio (12.8% within 1990-99 vs. 30.6% within 2000-09, p=0.058).*

Conclusion. *SSc-related causes of death were decreasing over time and, among them, pulmonary involvement was the leading cause of death in both decades. The ratio of renal causes decreased since 1990 at the time that the ratio of cardiac causes increased.*

Introduction

Systemic sclerosis (SSc) represents one of the autoimmune systemic diseases with a dire prognosis. Several studies from the 1960's were performed reflecting a higher mortality rate between 1.05-fold and 7.2-fold (1, 2) compared with the general population. The standardised mortality ratio (SMR) (3) has been assessed in 5 different meta-analyses (Table I), ranging from 2.72 (95%CI 1.93-3.83) to 3.53 (95%CI 3.03-4.11) (2, 4-7).

Interestingly, the pattern of death in patients with SSc has changed in the last 3 decades after the introduction of new therapies, mainly after the introduction of angiotensin-converting enzyme inhibitors (this is the main reason for decrease in mortality related to scleroderma renal crisis) and endotelin receptor antagonists and phosphodiesterase 5 inhibitors for the treatment of pulmonary arterial hypertension (PAH). Currently, the pulmonary involvement in the form of interstitial lung disease (ILD) or PAH, has been described the leading cause of death in the majority of SSc patients according to the findings from a US-based single centre longitudinal cohort (8). Main causes of in-hospital death of SSc patients from a nationwide US study were cardiopulmonary diseases in 25.8% and 23.9% respectively (9).

The main objective of the present study was to identify the changes in the pattern of death of the patients affected with SSc from the nationwide Spanish Scleroderma Registry in the last 20 years.

Materials and methods

The present study was based on data from the Spanish Scleroderma Registry (RESCLE) (10), created by the Spanish Internal Medicine Society in 2006. This is a retrospective and multicentre database in Spain, encompassing 20 referral nationwide centres for diagnosis and management of SSc. All phy-

Table I. Meta-analyses on SSc and mortality.

Study	Year of publication	Number of studies included	SMR (95% CI)
Ioannidis *et al*. (2)	2005	7	–
Elhai *et al*. (4)	2012	9	3.53 (3.03-4.11)
Toledano *et al*. (5)	2012	7	3.51 (2.74-4.50)
Komócsi *et al*. (6)	2012	10	3.24 (NA)
Rubio-Rivas *et al*. (7)	2014	17	2.72 (1.93-3.83)

NA: non available.

sicians involved have been trained on SSc and the registry is currently coordinated from a single centre. Database variables are clear and objective in order to minimise heterogeneity among centres. Furthermore, a patient cannot be included in further analyses if there are missing data. In order to avoid excluding patients with clear diagnosis of SSc who did not fulfil the American College of Rheumatology (ACR) preliminary classification criteria (11), we also considered the diagnosis following a modification of the classification proposed by LeRoy and Medsger (12). Demographic, clinical, immunological and capillaroscopy data encompassing 90 variables were collected according to a standard protocol and then entered into a SPSS database.

Disease onset was defined as the first symptom presented (including Raynaud's phenomenon) and the time of diagnosis the accurate date in which the first physician determined SSc. Although the Spanish Registry was created in 2006, prior dead patients were also included in the registry after a thorough search in each centre in order to avoid any kind of inclusion bias on mortality.

All patients were classified as prescleroderma (defined as the presence of Raynaud's phenomenon plus abnormal nailfold capillaroscopy and/or specific autoantibodies), scleroderma sine scleroderma, limited cutaneous Systemic sclerosis (lcSSc) and diffuse cutaneous Systemic sclerosis (dcSSc), according to previous reported studies of our Registry (10, 13, 14). For comparisons among them, lcSSc and sine scleroderma were assessed as pertaining to the same group, given the evidence that they share clinical spectrum, laboratory findings and prognosis.

Causes of death

All death certificates were checked out by the scleroderma-trained physician from every centre for those patients diagnosed from 1990 to 2009. As SSc-related causes of death we focused on pulmonary, cardiac, renal and gastrointestinal involvements. Pulmonary involvement was described as the presence of ILD or PAH. ILD was defined by restrictive pulmonary pattern with forced vital capacity (FVC) <70% of expected value on pulmonary function tests or pulmonary interstitial pattern evidenced by chest radiograph or high-resolution computed tomography scan or alveolitis confirmed by bronchoalveolar lavage (defined as neutrophilia ≥3%, eosinophilia ≥2% or lymphocytosis ≥15%). Therefore, death caused by ILD was due to advanced respiratory failure in absence of other explanatory cause of death. PAH was defined by systolic pulmonary arterial pressure (PAP) >40 mmHg by Doppler-echocardiography corresponding to maximum tricuspid regurgitant jet velocity of 3.0 to 3.5 m/s and confirmed by a mean PAP ≥25 mmHg at rest by right-sided heart catheterisation. Therefore, death caused by PAH was also due to advanced respiratory failure related to right ventricle failure in absence of other explanatory cause of death. Scleroderma renal crisis (SRC) was defined following Traub criteria (15) by the presence of renal function impairment in the last month in the absence of other renal diseases and potentially accompanied by malignant hypertension. Thus, a normal arterial pressure did not rule out the diagnosis of SRC. Cardiac involvement as a cause of death was defined by ischaemic cardiomyopathy of unknown cause (defined by reversible perfusion defects on Thallium gammagraphy or structural deformities on Doppler-echocardiography) in patients without classical vascular risk factors as smoking behaviour, diabetes mellitus, hyperlipidemia and arterial hypertension (all patients were checked on this classical risk factors). Arrhythmia and heart failure (defined as right heart failure with ejection fraction <40% by ecocardiography or ventriculography or left heart failure with ejection fraction <50% by ecocardiography or ventriculography) were also considered. Finally, gastrointestinal involvement as a cause of death was considered when starvation due to malabsortion syndrome.

As to SSc-non related causes of death, we focused on cancer (with histologic confirmation), infections, cardiovascular diseases and respiratory disorders (chronic obstructive pulmonary disease or COPD and pulmonary thromboembolism). We considered SSc-related cardiovascular involvement in those patients without other classical known risk factors. Although it was described a larger incidence of cancer related to SSc (16), it was not considered into the SSc-related causes of death.

We showed crude data (absolute number of deaths and percentage) for every period and relative frequencies among the four major SSc-related causes of death.

Temporal pattern of death

The whole cohort was split up in two in order to compare the causes of death and according to the decade in which the patient was diagnosed with SSc (1990-99 vs. 2000-09). Arbitrarily, three different times after diagnosis were created to assess mortality after diagnosis, "early" the first 5 years, "intermediate" between 5-10 years and "late" beyond 10 years after diagnosis. In contrast, in order to assess the SMR we chose those deaths that occurred in both decades, independently of the time of diagnosis.

Statistical analysis

The SMR was calculated taking into account persons at risk per year compared with the published Spanish population mortality rates from the Spanish Statistical National Institute (17).

Table II. Descriptive general data of the cohort. Visceral involvement is referred to any time during follow-up. Chi-square test for categorical variables and T-test for quantitative variables.

	1990-99	2000-09	*p*-value
Patients diagnosed in every decade	392	595	
Women absolute number (%)	362 (92%)	521 (88%)	**0.019**
Age at onset mean (SD)	44 ± 15	47 ± 17	**<0.001**
Age at diagnosis mean (SD)	51 ± 15	53 ± 16	**0.007**
Time from onset to diagnosis mean (SD)	8.9 ± 10	6.6 ± 9.3	**0.006**
dcSSc absolute number (%)	99 (25%)	151 (25%)	1.000
lcSSc absolute number (%)	249 (64%)	339 (57%)	**0.047**
ACR 1980 criteria absolute number (%)	261 (67%)	363 (61%)	0.092
ACR 2013 criteria absolute number (%)	329 (92%)	470 (88%)	0.070
Sine scleroderma absolute number (%)	30 (7.7%)	58 (9.7%)	0.304
ACR 2013 criteria among sine-scleroderma patients absolute number (%)	8 (33.3%)	8 (22.2%)	0.383
Pre-scleroderma absolute number (%)	14 (3.6%)	47 (7.9%)	**0.006**
ACR 2013 criteria among pre-scleroderma patients absolute number (%)	1 (7.7%)	2 (5.6%)	1.000
ANA + absolute number (%)	357 (91%)	543 (91%)	0.909
ACA + absolute number (%)	182 (51%)	229 (43%)	**0.014**
Anti-Topoisomerase + absolute number (%)	86 (24%)	128 (24%)	0.873
Gastrointestinal involvement absolute number (%)	292 (75%)	372 (63%)	**<0.001**
Pulmonary involvement absolute number (%)	173 (44%)	250 (42%)	0.511
Pulmonary hypertension (catheterism confirmation) absolute number (%)	71 (21%)	109 (21%)	1.000
Heart involvement absolute number (%)	104 (27%)	111 (19%)	**0.004**
Scleroderma renal crisis absolute number (%)	11 (3.1%)	13 (3.3%)	1.000
Osteomuscular involvement absolute number (%)	265 (68%)	336 (57%)	**0.001**

SD: standard deviation; DcSSc: diffuse cutaneous systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; ACR: American College of Rheumatology; ANA: antinuclear antibodies; ACA: anticentromere antibodies; NA: non available.

Categorical variables were described as absolute number and percentage. Continuous variables were described as mean and standard deviation. Univariate analysis was performed by Chi-square test for categorical variables and T-test for quantitative variables. A multivariable logistic regression was performed in order to assess those factors related to SSc-related death. Statistical analysis was performed by SPSS 18.0.

Results

At the time of the recruitment a total of 987 patients diagnosed with SSc from 1990 to 2009 were included in the study. Patients' features are shown in Table II.

General features

Three hundred and ninety two patients were diagnosed within 1990–99 and 595 patients within 2000-09. Both age at onset (44±15 *vs*. 47±17 years-old, $p<0.001$) and age at diagnosis (51±15 *vs*. 53±16 years-old, $p=0.007$) increased in the last two decades. In contrast, time from onset to diagnosis decreased (8.9±10 *vs*. 6.6±9.3 years, $p=0.006$).

Overall SMR for the period 1990-2009 was 2.34 (95%CI 2.24–2.44). We assessed SMR for different subsets, sex and age at the time of diagnosis according to previous studies (7). SMR for dcSSc patients was 2.13 (95%CI 2.04–2.23) compared to 2.06 (95%CI 1.96–2.15) for lcSSc/sine scleroderma patients, 3.62 (95%CI 3.50–3.74) for male gender compared to 2.29 (95%CI 2.18–2.39) for female gender and 7.06 (95%CI 6.71–7.41) for patients <65 years-old compared to 1.29 (95%CI 1.26–1.33) for patients ≥65 years-old.

Causes of death

Overall, 149 deaths (15.1%) were recorded in those patients diagnosed with SSc between 1990 and 2009, 72 (18.4%) within 1990-99 and 77 (12.9%) within 2000-09. In 9 patients (0.9%), the cause of death was undetermined (Fig. 1).

For the assessment of causes of death we differentiated SSc-related and SSc-non related causes of death (Table III and Fig. 1). SSc-related causes of death were responsible of 47 (72%) of all deaths within 1990-99 *vs*. 36 (48%) within 2000-09 ($p=0.006$). On the other hand, SSc-non related causes of death were responsible of 18 (28%) of all deaths within 1990-99 *vs*. 39 (52%) within 2000-09 ($p=0.006$). Among SSc-non related causes of death we did not find relevant changes over time (Table III). Among SSc-non related causes, 21 deaths out of 57 were due to cancer (9 deaths within 1990-99 *vs*. 12 within 2000-09, $p=0.814$). In particular, within 1990-99 these were 2 lung cancer, 2 breast cancer, 1 cancer of the uterus, 1 gastric cancer, 1 haematological cancer (this patient had been under treatment with cyclophosphamide) and two cancers were not specified in the database. Only 1 out of these 9 cancers was diagnosed within the first 3 years after the diagnosis of SSc. In contrast, within 2000-09 there were 3 lung cancers (1 patient had been under treatment with cyclophosphamide), 2 breast cancers, 2 carcinomas of unknown origin, 2 renal cancers, 1 oesophagus cancer, 1 haematological cancer and in 1 patient the cancer subtype was not specified in the database. Six out of these 12 cancers were diagnosed within the first 3 years after the diagnosis of SSc. We performed this analysis also in those patients fulfilling only the 2013 criteria, achieving similar results (data not shown).

Causes of death according to the clinical subset, dcSSc and lcSSc/sine scleroderma, were analysed (Table IV and Fig. 2). SSc-related causes of death were more prevalent in dcSSc (65% dcSSc vs. 56% lcSSc) although these differences did not achieve statistical significance ($p=0.377$). Lung-related death rate was similar in both groups, however death due to PAH was more prevalent in lcSSc/sine scleroderma (5.6% *vs*. 22%, $p=0.009$) and ILD in dcSSc subset (22% *vs*. 8.1%, $p=0.023$). Renal-related death rate in the form of SRC was mainly in dcSSc (13% *vs*. 3.5%, $p=0.045$). Heart-related death rate was mainly in lcSSc/sine scleroderma (7.5% *vs*. 15.1%), mostly due to ischaemic cardiomyopathy (0% *vs*.

Table III. Causes of death in 149 patients. In 9 patients the cause of death was uncertain. Chi-square and Fisher's Exact Test.

	1990-99	2000-09	*p*-value
Deaths absolute number	72	77	
SSc-related deaths absolute number (%)	47 (72%)	36 (48%)	**0.006**
Gastrointestinal	1 (1.5%)	0 (0%)	0.464
ILD	11 (17%)	8 (11%)	0.328
PAH	10 (15%)	12 (16%)	1.000
PAH (diagnosis by RHC)	6 (9.2%)	8 (11%)	1.000
ILD+PAH	11 (17%)	3 (4%)	**0.021**
Pulmonary involvement	32 (49%)	23 (31%)	**0.037**
SRC	8 (12%)	2 (2.7%)	0.045
Ischaemic cardiomyopathy	2 (3.1%)	3 (4%)	1.000
Heart failure	4 (6.2%)	4 (5.3%)	1.000
Arrhythmia	0 (0%)	4 (5.3%)	0.123
Relative frequencies			
Lung	32 (68.1%)	23 (63.9%)	0.815
Kidney	8 (17%)	2 (5.5%)	0.175
Heart	6 (12.8%)	11 (30.6%)	**0.058**
Gastrointestinal	1 (2.1%)	0 (0%)	1.000
SSc-non related deaths absolute number (%)	18 (28%)	39 (52%)	**0.006**
Cancer	9 (14%)	12 (16%)	0.814
Cardiomyopathy	0 (0%)	0 (0%)	-
Stroke	0 (0%)	1 (1.3%)	1.000
Chronic renal failure	0 (0%)	2 (2.7%)	0.499
COPD	0 (0%)	0 (0%)	-
Infection	4 (6.2%)	4 (5.3%)	1.000
Pulmonary embolism	0 (0%)	1 (1.3%)	1.000
Others	5 (7.7%)	19 (25%)	**0.007**

ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; RHC: right heart catheterisation; SRC: scleroderma renal crisis; COPD: chronic obstructive pulmonary disease. In 9 patients the cause of death was undetermined.

5.8%, p=0.156). Gastrointestinal involvement as cause of death was only present in 1 patient (1.2%) with lcSSc/sine scleroderma. On the other hand, SSc-non related causes of death were more prevalent in lcSSc/sine scleroderma subset than in dcSSc (35% *vs*. 44%, p=0.377).

After a multivariate logistic regression, older age at onset, female gender and sine scleroderma subset were found predictors of SSc-related death, although none of them achieved statistical significance (Table V).

Early, intermediate and late deaths after diagnosis were assessed. As previously reported, in total 149 deaths were registered in those patients diagnosed between 1990 and 2009. In 9 patients the cause of death was unknown and in 1 patient the accurate diagnosis date was not reported, so we could not determine the moment of death. Early mortality due to SSc-non related causes was described in 3 patients (17.6%) in 1990–99 *vs*. 23 patients (48.9%) in 2000–09 (p=0.042), whereas among SSc-related causes, pulmonary causes were

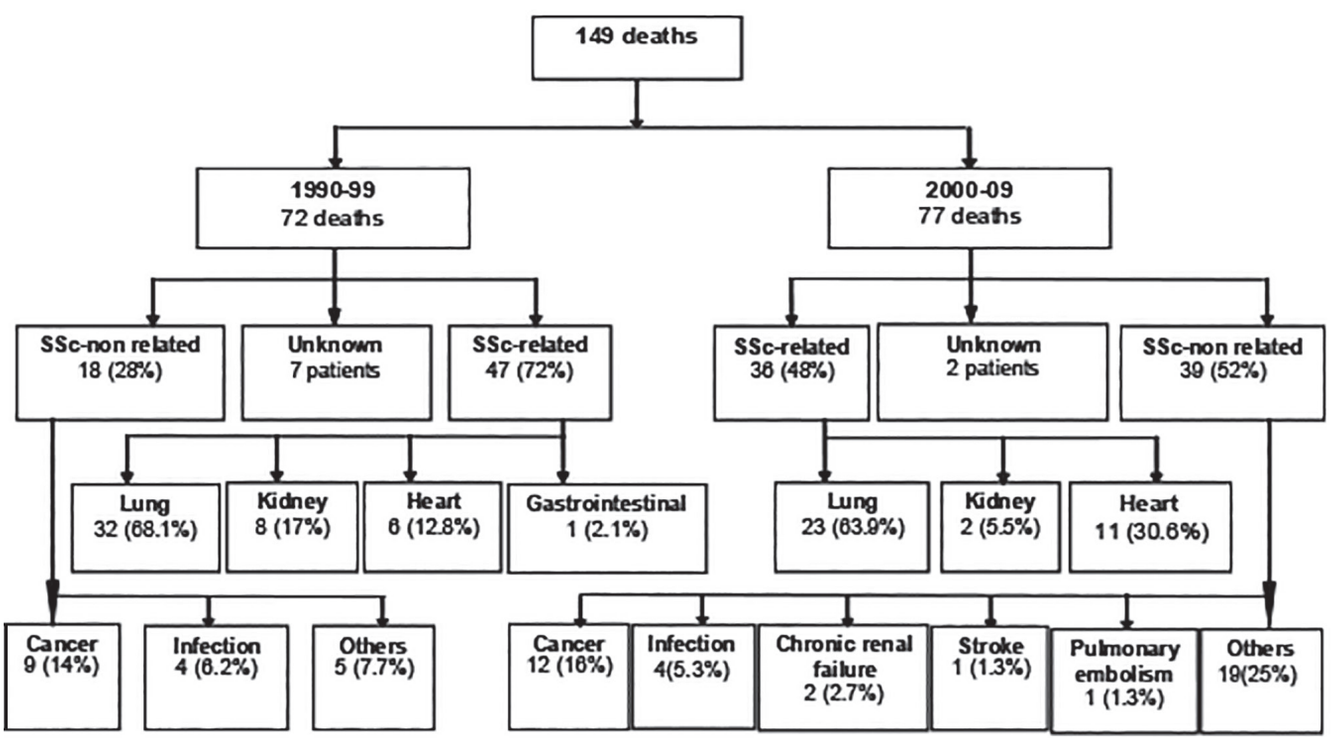

Fig. 1. Causes of death per decades. Chi-square and Fisher's exact test. Percentages were calculated excluding those patients whose death was of unknown cause. Among SSc-related causes, we showed relative percentages. SSc-non related causes vs. SSc-related causes (p=0.006). Lung (p=0.815), kidney (p=0.175), heart (p=0.058) and gastrointestinal (p=1.000). COPD: chronic obstructive pulmonary disease.

Table IV. Causes of death between cutaneous subsets. In 9 patients the cause of death was uncertain. Chi-square and Fisher's exact test.

	dcSSc	lcSSc/sine scleroderma	*p*-value
Deaths absolute number	58	91	
SSc-related deaths absolute number (%)	35 (65%)	48 (56%)	0.377
Gastrointestinal	0 (0%)	1 (1.2%)	1.000
ILD	12 (22%)	7 (8.1%)	**0.023**
PAH	3 (5.6%)	19 (22%)	**0.009**
PAH (diagnosis by RHC)	2 (3.7%)	12 (14%)	0.079
ILD+PAH	9 (17%)	5 (5.8%)	**0.046**
Pulmonary involvement	24 (44%)	31 (36%)	0.375
SRC	7 (13%)	3 (3.5%)	**0.045**
Ischaemic cardiomyopathy	0 (0%)	5 (5.8%)	0.156
Heart failure	1 (1.9%)	7 (8.1%)	0.152
Arrhythmia	3 (5.6%)	1 (1.2%)	0.298
Others	0 (0%)	0 (0%)	-
Relative frequencies			
Lung	24 (69%)	31 (65%)	1.000
Kidney	7 (20%)	3 (6%)	0.089
Heart	4 (11%)	13 (27%)	0.100
Gastrointestinal	0 (0%)	1 (2%)	1.000
SSc-non related deaths absolute number (%)	19 (35%)	38 (44%)	0.377

DcSSc: diffuse cutaneous systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; ILD: interstitial lung disease; PAH: pulmonary hypertension; RHC: right heart catheterisation; SRC: scleroderma renal crisis.

described in 8 patients (47.1%) *vs*. 16 (34%) (p=0.390), renal in 6 patients (35.3%) *vs*. 1 (2.1%) (p<0.001), cardiac in 0 patients *vs*. 7 (14.9%) (p=0.175) and gastrointestinal in 0 *vs*. 0 patients. Intermediate mortality due to SSc-non related causes was described in 5 patients (23.8%) in 1990-99 *vs*. 11 patients (50%) in 2000-09 (p=0.116), whereas among SSc-related causes, pulmonary causes were described in 13 patients (61.9%) *vs*. 6 (27.3%) (p=0.033), renal in 1 patient (4.8%) *vs*. 1 (4.5%) (p=1.000), cardiac in 2 patients (9.5%) *vs*. 4 (18.2%) (p=0.664) and gastrointestinal in 0 *vs*. 0 patients. Late mortality due to SSc-non related causes was described in 10 patients (37%) in 1990-99 *vs*. 5 patients (83.3%) in 2000-09 (p=0.070), whereas among SSc-related causes, pulmonary causes were described in 11 patients (40.7%) *vs*. 1 (16.7%) p=0.379, renal in 1 patients (3.7%) *vs*. 0 patients (p=1.000), cardiac in 4 patients (14.8%) *vs*. 0 patients (p=1.000) and gastrointestinal in 1 patient (3.7%) *vs*. 0 patients (p=1.000).

Discussion

The present study constitutes an important assessment of SSc-related and non-related changes in the pattern of death and the first nationwide in Spain. The patients' features from the two decades compared were similar. The age at onset and diagnosis are noteworthy, since they increased over time. We do not know if there were factors delaying the presentation of the disease. It is clear that the time from onset to diagnosis is decreasing, possibly because physicians are more aware of the disease and screening for autoimmune disorders after the presentation of Raynaud's phenomenon. Pre-scleroderma and sine-scleroderma are accepted and well-known subtypes today in contrast to old times and it explains

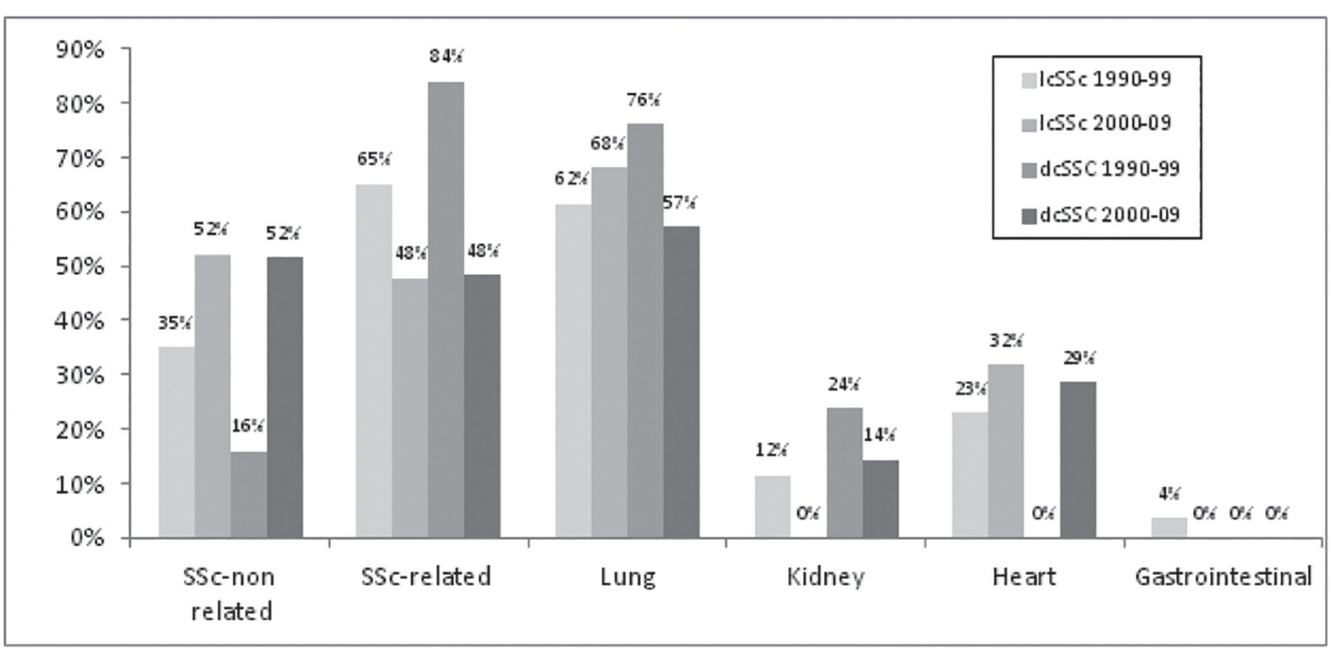

Fig. 2. Causes of death according to the skin subset. Chi-square and Fisher's exact test. In dcSSc patients: SSc-non related causes *vs*. SSc-related causes (p=0.010), lung (p=0.283), kidney (p=0.676), heart (p=0.019). In lcSSc/sine scleroderma patients: SSc-non related causes *vs*. SSc-related causes (p=1.000), lung (p=1.000), kidney (p=0.200), heart (p=0.474), gastrointestinal (p=1.000).

Table V. Predictors of SSc-related death. Multivariable logistic regression.

	OR (95% CI)	*p*-value
Gender (female)	2.84 (0.89-9.03)	0.077
Age at onset	1.04 (1.00-1.09)	0.057
Age at diagnosis	0.98 (0.94-1.02)	0.279
Skin subset		0.132
lcSSc	1 (ref.)	-
dcSSc	1.88 (0.65-5.47)	0.247
sine scleroderma	8.22 (0.85-79.71)	0.069
Anti-cm	1.27 (0.50-3.18)	0.616
Anti-topoisomerase	1.06 (0.35-3.16)	0.919

DcSSc: diffuse cutaneous systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; Anti-cm: anticentromere antibodies.

the increasing number of these patients over time.

We found an overall SMR of 2.34 (95%CI 2.24-2.44) in accordance with previous publications (2, 4-7). The latest and largest meta-analysis (7) showed an overall SMR 2.72, but after 1990 there was an estimated SMR of 2.42, that was certainly similar to our result. We suggest that there might be a few missing dead patients at the time of their inclusion in our registry, so that the SMR found in our cohort might be mildly lower than reality. Similar SMR was shown in recent single series (18-22). It is noteworthy that there was a worse SMR for male gender and dcSSc subset, as expected, so they are known factors related to poor outcome (19-29). Furthermore, male gender has been recently described not only as isolated factor of poor prognosis but also as predictive factor of pulmonary arterial hypertension and heart failure (30). Nevertheless, there were not huge differences on SMR in our study between dcSSc and lcSSc subsets, SMR 2.13 (95%CI 2.04-2.23) vs. SMR 2.06 (95%CI 1.96-2.15). Previous published SMR for lcSSc subset are quite similar but certainly not previous SMR published for dcSSc (18, 20-21, 23-26, 28-29), so we suggest that those patients presumably not registered in the past probably belonged to the dcSSc subset. As recently reported (13), SMR in those patients diagnosed before 65 years-old was much worse (SMR 7.06 *vs*. SMR 1.29). Since these data were based on trained centres they can be too optimistic when talking about survival or mortality, so that real mortality rate can be a bit higher. However, in our opinion, the pattern of death over time does not depend on the centre but the self nature of the disease.

A recent publication from our group (31) focused on survival and prognostic factors in SSc, showed preliminary data about causes of death from Spanish scleroderma population, being pulmonary causes the leading cause of death as well. The number of deaths was half the deaths we show in the present manuscript, with report neither on changes over time or data about early, intermediate and late death.

It is noteworthy that among SSc-related causes of death, cardiopulmonary involvement was the leading cause of death, representing 95% of all SSc-related deaths, and their percentages were increasing over time. Perhaps, a more accurate diagnosis of pulmonary and cardiac disease in the last decades might have been part of the explanation for these changes. These data could be enough to recommend a closer screening for pulmonary and cardiological involvement even much more often than what we do today and maybe to be more aggressive in terms of treatment of pulmonary hypertension/fibrosis and cardiological involvement. By seeing Figure 2, it seemed that pulmonary death was stable in lcSSc, but increasing in dcSSc, possibly because of the poor prognosis of ILD, more prevalent in this subset. Renal ratio exhibited a decline in the last 2 decades in all subsets, being a residual cause of death nowadays in lcSSc patients. Cardiac death was increasing in both subsets, but mainly in lcSSc. These changes in the pattern of death were described before in a single cohort (8), but never before from a nationwide study. Steen *et al*. (8) demonstrated a decreased percentage of death due to SRC from early 70s to early 90s of all SSc-related causes, and an increased pulmonary fibrosis and pulmonary hypertension rate in the same period. In our study, changes in lung death over time were notorious but did not achieve significance. ILD and SRC were more prevalent in dcSSc as cause of death as expected, and PAH in lcSSc/sine scleroderma. Heart involvement as cause of death was mainly in lcSSc/sine scleroderma, mostly due to heart failure and ischaemic cardiomyopathy. It was reported previously a subclinical coronary stenosis in 60% of lcSSc patients compared to 0% of dcSSc patients from a short asymptomatic cohort undergoing coronary catheterisation (32). It is required to be clarified that although heart involvement seemed to be increasing over time in the lcSSc/sine scleroderma subset it might be due to the fact that nowadays screening is similar for both diffuse and limited forms but it was not in the past for lcSSc/sine scleroderma subset. In accordance to medical literature, arrhythmias were not a great contributor to death rate in our cohort (32). As It was stated before, mortality in dcSSc patients was higher than in lcSSc and, in accordance with previous studies, pulmonary fibrosis and SRC were the leading cause of death in those patients (34).

Among SSc-non related causes of death cancer must be pointed out as well. Several studies focused on this topic and showed a higher incidence in these patients. A recent meta-analysis described a standardised incidence ratio (SIR) 1.41 (95%CI 1.18-1.68) (16). We also found a relevant ratio cancer as cause of death in the last two decades, representing today the third cause of death in our cohort after lung and heart-related death. This trend was even more important when compared to our population, since incidence of cancer is increasing but mortality due to cancer in Spain is stable or even decreasing (35). Recently, another study found association between cancer and anti-RNA polymerase III antibodies, most of all with breast

cancer, haematological, gastrointestinal and gynaecological (36, 37). In the present study, these antibodies were not assessed to confirm these findings. Although not significant, it was relevant and showed a trend the fact that SSc-non related causes of death were more prevalent in lcSSc/sine scleroderma subset than in dcSSc.

We cannot forget the potential inconsistency of clinical findings when compared to autopsy findings, as it was described in a recent publication (38). In over 18% of patients, the autopsy revealed that inconsistency, mainly in the case of the heart and renal involvement that were found affected more frequently in autopsies than expected previously.

As limitations of our study, we found difficulties in order to differentiate heart death due to SSc or not. Both conditions are clinically undistinguishable and sometimes only the clinical context was handy at the time of concluding that the affection was due to SSc. EUSTAR definition was used for SSc-cardiomyopathy (39), adding ischaemic cardiomyopathy in patients without other risk factors since there is an increasing evidence of such an affection in SSc patients compared with controls. We checked out all our patients for classical cardiovascular risk factors to minimise this potential bias and, in general, since these patients were relatively young without other risk factors, SSc was interpreted as the main cardiovascular risk factor. Furthermore, diastolic heart failure was not included as cardiac cause of death. Another limitation of every retrospective registry is the potential loss of information that can underestimate the SMR. We cannot rule out the possibility that a few patients who died in the early 90s were not included, but they should be certainly just a few since they were thoroughly searched for. They were supposed to be patients presenting factors of worse prognosis such as dcSSc subset, so this bias might be higher in the case of this subset. This is a common scenario for any multicentre and retrospective registry and we think this missing information did not bias the assessment of causes of death.

Conclusion

In conclusion, the present study constitutes the first nationwide study in Spain assessing the changes in the pattern of death and focusing on SSc-related and SSc-non related causes. Global mortality in our cohort showed a SMR 2.34 (95%CI 2.24–2.44). Among SSc-related causes of death, lung involvement was the first cause in the two decades. In contrast, renal involvement as cause of death decreased dramatically since 1990, after the introduction of ACE inhibitors and was more related to dcSSc subset and early mortality after diagnosis. SSc-non related death ratio was increasing over time and, among them, cancer represents nowadays the third cause of death in these patients.

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