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ORIGINAL ARTICLE

Mortality in systemic sclerosis—a single centre study from the UK

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Abstract This study aims to determine the cause and predictors of mortality in a cohort of patients with systemic sclerosis (SSc) and assess whether the mortality rate differs significantly from the general population. Patients enrolled onto the Royal National Hospital for Rheumatic Diseases Connective Tissue Disease database between 1999 and 2010 were included in this study. The NHS Strategic Tracing Service and UK Registry of Births, Marriages and Deaths were used to establish date and cause of deaths. A retrospective case note review collected information on clinical phenotype and serology. A standardised mortality ratio (SMR) was calculated and survival was determined using Kaplan–Meier estimates. Univariate and multivariate predictors of survival were assessed using proportional hazards regression modelling. Amongst this cohort of 204 patients (25 males, 40 diffuse SSc), the mean age at diagnosis was 51.6 years (SD13.7) and the mean duration of follow-up was 12.5 years (SD 8.8 years). In the deceased group (53 patients), the mean age of death was 72.0 years (SD 12.3 years). The mean disease duration at death was 14.2 years (SD 8.5 years). The overall SMR was 1.34 (95 % confidence interval (CI) 1.00–1.75). The SMR was higher in males (1.54 [95 % CI 0.67–3.04] vs. 1.30 [95 % CI 0.95–1.74]). The leading causes of death in this cohort were infection, respiratory disease and malignancy. The most common cause of SSc-related mortality was pulmonary complications. Factors adversely affecting survival were older age at diagnosis, male gender, interstitial lung disease (ILD) and anti-RNA polymerase III antibody. The mortality rate of our cohort, who had predominantly limited disease, was higher than that of the general population; although not as high as reported in previous retrospective studies.

Keywords Cause of death · England · Mortality · Survival · Systemic sclerosis · Wales

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Introduction

Systemic sclerosis (SSc) is a chronic multi-system disease of unknown aetiology characterised by inflammation, vasculopathy and fibrosis. It is associated with increased morbidity and mortality and has the worst outcome of any of the connective tissue disorders [1]. A recent meta-analysis of nine cohort studies showed that patients with SSc have a 3.5-fold risk of death compared to the general population [2]. Complications of SSc that may be life threatening include pulmonary hypertension, pulmonary fibrosis, renal crises and cardiac involvement. Studies have suggested that the cause of death has changed over time [3, 4]. A recent analysis of 5,860 patients from the EULAR Scleroderma Trials and Research (EUSTAR) registry showed that SSc-related deaths (55 %) were mainly caused by lung and heart involvement whereas non-SSc (41 %) causes included infections (especially pneumonia), malignancies and cardiovascular disease [5]. Prior to the introduction of angiotensin-converting enzyme inhibitors, renal crisis was the most common cause of death in SSc [4]. In the present study, we have investigated the survival and causes

and predictors of death of SSc patients in a single tertiary referral centre in the UK.

Materials and methods

Patient selection

Patients registered on the RNHRD Connective Tissue Disease database between 1999 and 2010 were included in this study. All participants had provided written informed consent to be part of the database, as approved by the Bath Research Ethics Committee.

Patient demographics and clinical phenotype

Case notes were reviewed and scrutinised for patient demographics, disease duration, serology and clinical phenotype. The date of diagnosis was recorded as the time of first diagnosis by a rheumatologist. All patients fulfilled the 1980 ARA classification criteria for SSc [6] and/or the criteria for the classification of early SSc [7]. Patients were classified into disease subtypes based on cutaneous involvement according to LeRoy et al.'s criteria [8]. Pulmonary arterial hypertension (PAH) was diagnosed if patients had a mean pulmonary artery pressure of >25 mmHg on right heart catheter [9]. Cardiac involvement was based on a documented history of any cardiac involvement, other than ischaemic heart disease, and included left ventricular dysfunction, arrhythmias, myocardial fibrosis, or pericardial effusion. A diagnosis of interstitial lung disease (ILD) required previously reported characteristic findings on HRCT or lung biopsy. The results of most recent pulmonary function tests (forced vital capacity [FVC] and diffusing capacity [DLco]) undertaken within the last 5 years were documented (available for 149 patients). Upper gastrointestinal (GI) involvement was defined as a clinical history of gastro-oesophageal reflux (GORD) and/or dysphagia, endoscopic evidence of GORD or stricture, or abnormal peristalsis on oesophageal manometry and/or barium swallow. Patients were documented as having lower GI involvement if there was a history of frequent and/or loose stools, faecal incontinence or a history of intestinal pseudo-obstruction. Scleroderma renal crisis (SRC) was defined as the new onset of hypertension accompanied by acute renal failure. A past history of digital ischaemic complications was based on a documented history of digital ulceration, digital pitting, tissue necrosis, auto-amputation or pulp atrophy.

The results of serological analysis were recorded for all patients. This was based upon previous immunofluorescence studies using HEp-2 cells, followed, where appropriate, by immunoblotting and/or immunoprecipitation to aid further characterisation of SSc-specific autoantibodies.

Mortality data

Information on patient deaths was collected retrospectively. The National Health Service (NHS) Strategic Tracing Service was used to establish which patients had died and their date of death. Survival status was ascertained up until the end of December 2011. Date and cause of death were confirmed by death certificates from the Registry of Births, Marriages and Deaths. The cause of death was defined by the information provided on the death certificate alone. A standardised mortality ratio (SMR) was calculated separately for men and women in addition to the overall SMR for the cohort. The SMR assesses the relative mortality rate of a disease in comparison with the general population. It is calculated by comparing the observed number of deaths with the number of expected deaths, adjusted for age and gender, for the calendar years of follow-up. The SMR was calculated by matching the patient data to single-year, 5-year age-banded England and Wales data from the Office of National Statistics. The Office of National Statistics maintains population census data with annual adjustments according to birth, death and immigration/emigration status.

Statistical analysis

All analyses were carried out in the statistical package R (2011) with use of the 'survival' package [10]. Descriptive statistics for continuous variables were expressed as means ± SD. Categorical variables were expressed as a number and percentage. Univariate effects of covariates on mortality were assessed using Chi-squared tests and Kaplan–Meier curves and log-rank tests were used to assess differences in survival. A multivariate Cox proportional hazards model was used to assess multivariate predictors of survival, including all main effects and two-way interactions. Covariates that had more than 5 % missing values were excluded.

Results

A total of 223 patients were identified from the database. Sixty-seven were deceased and 156 were living. Five living and four deceased patients were excluded from further analysis due to insufficient information on date of disease onset and SSc subtype. Seven deceased patients were excluded from the analysis as the date of death and/or last known address could not be accurately confirmed via the NHS Tracing Service (and such information was required to obtain the death certificate). Three patients who died in 2011 could not be included as the matched population data from the Office of National Statistics for 2011 had not been released at the time of analysis. As a consequence, living patients at the time of the study had their survival time

censored as at the end of 2010. The cause of death was therefore established for 53 deceased patients.

The majority of patients were females (179/204, 87.7 %) and most had limited cutaneous involvement (164/204, 80 %). Anti-centromere antibody (ACA) was the most common autoantibody (47 %). The mean age at diagnosis was 51.6 years (SD 13.7) and mean duration of follow-up was 12.5 years (SD 8.8 years). The minimum duration of follow-up was 1 year. In the deceased group, the mean age of death was 72.0 years (SD 12.3 years). The mean age of death was higher in limited compared with diffuse cutaneous SSc (73.0 years vs. 65.7 years respectively). The mean disease duration at death was 14.2 years (SD 8.5 years). Thirty-two percent (8/25) of males vs. 25 % (45/179) of females died. Demographic and clinical features are presented in Table 1.

The leading cause of death was infection (13/53, 24.5 %) with pneumonia being the predominant cause (10/13, 76.9 %) (Table 2). Nineteen (35.8 %) deaths were SSc-related with pulmonary involvement being the predominant cause of death (47.4 % of SSc-related and 20.8 % of all deaths). Among the nine patients who died due to SSc-related pulmonary involvement, interstitial lung disease was the predominant cause (6/9, 66.7 %). Malignancy was the third most common cause of death, accounting for 18.9 % of deaths (lung 2, bowel 2, unknown primary 2, haematological 1, endometrial 1, pancreatic 1, peritoneal 1). Furthermore, two patients who died of pneumonia also had malignancy (lung 1, metastatic ovarian 1) and the patient who died of acute renal failure also had breast cancer. Other SSc-related causes of death were disease activity [3], cardiovascular [4], gastrointestinal [1], hepatic [1] and sepsis related to SSc [1].

Table 3 shows the sex-specific and overall SMR in our SSc cohort compared with the general England and Wales population for the study period 1972–2010. The SMR for the whole cohort was 1.34 (95 % CI 1.00–1.75). The SMR was higher in males (1.54 [95 % CI 0.67–3.04]) vs. females (1.30 [95 % CI 0.95–1.74]) and in patients with diffuse cutaneous disease (1.66 [95 % CI 0.83–2.97]) vs. limited disease (1.27 [95 % CI 0.92–1.72]). Univariate analyses of the effects of covariates on mortality showed significant effects of older age at diagnosis (x^2=12.42, p=0.006), PAH (x^2=8.55, p=0.003) and ILD (x^2=6.54, p=0.011) with older age at diagnosis (p <0.001) and ILD (p=0.04) having a significant effect on survival (based on log-rank tests). Kaplan–Meier cumulative survival curves for these significant covariates are shown in Fig. 1. No significant

Table 1 Demographic and clinical features of 204 patients with systemic sclerosis (SSc)

Characteristic	Whole cohort (n=204)	Living (n=151)	Dead (n=53)
Female sex, *n* (%)	179 (87.7)	134 (88.7)	45 (84.9)
Age at diagnosis, mean (SD)	51.6 (13.7)	49.8 (13.4)	56.9 (13.1)
Duration of follow-up, mean (SD)	12.5 (8.8)	11.9 (8.9)	14.2 (8.5)
Limited cutaneous SSc, *n* (%)	164 (80.4)	122 (80.8)	42 (79.2)
Serology, *n* (%)			
Anti-centromere	96 (47.1)	71 (47.0)	25 (47.2)
Anti-Scl-70	33 (16.2)	24 (15.9)	9 (17.0)
Anti-U1 ribonucleoprotein	10 (4.9)	9 (6.0)	1 (1.9)
Anti-RNA polymerase I–III	31 (15.2)	24 (15.9)	7 (13.2)
Anti-U3 ribonucleoprotein	6 (2.9)	6 (4.0)	0 (0.0)
PM-Scl	7 (3.4)	5 (3.3)	2 (3.8)
Ro/La	22 (10.8)	17 (11.3)	5 (9.4)
Other	20 (9.8)	15 (9.9)	5 (9.4)
Organ involvement, *n* (%)[a]			
Pulmonary hypertension	23/199 (11.6)	11/149 (7.4)	12/50 (24.0)
ILD	65/201 (32.3)	41/151 (27.2)	24/50 (48.0)
SRC	5/180 (2.8)	2/144 (1.4)	3/36 (8.3)
Cardiac involvement	25/190 (13.2)	20/148 (13.5)	5/42 (11.9)
Upper GI disease	137/192 (71.4)	108/148 (72.3)	29/44 (65.9)
Lower GI disease	50/180 (27.8)	41/144 (28.5)	9/36 (25.0)
Joint involvement	74/185 (40.0)	58/143 (40.6)	16/42 (38.1)
Myositis	12/181 (6.6)	10/144 (6.9)	2/37 (5.4)
Digital ischaemic complications	75/187 (40.1)	55/146 (37.7)	20/41 (48.8)
FVC (mean % predicted value), mean (SD)[b]	98.0 (21.5)	98.4 (21.7)	95.7 (20.9)
DLco (mean % predicted value), mean (SD)[b]	64.0 (20.4)	66.0 (20.5)	53.8 (16.7)

SD standard deviation, *ILD* interstitial lung disease, *GI* gastrointestinal

[a]Data on organ involvement was incomplete for some patients

[b]Data available for 149 patients

Table 2 Causes of death

Cause of death, *n* (%)	Number=53 (%)	Related to SSc (*n*=19)[a]
Infection	13 (24.5)	1 (5.3)
Septicaemia	1	0
Pneumonia	10	1
Other	2	0
Malignancy	10 (18.9)	0 (0.0)
Cardiovascular	8 (15.1)	4 (21.1)
Coronary heart disease	1	0
Heart failure	5	3
Other	2	1
Respiratory	11 (20.8)	9 (47.4)
Interstitial lung disease	6	6
Pulmonary hypertension	3	3
Chronic obstructive pulmonary disease	2	0
Cerebrovascular	3 (5.7)	0 (0.0)
Gastrointestinal	(3.8)	1 (5.3)
Hepatic	1 (1.9)	1 (5.3)
Renal	1 (1.9)	0 (0.0)
Disease activity	3 (5.7)	3 (15.8)
Other[b]	1 (1.9)	0 (0.0)

[a]Includes causes that are probably and possibly related to systemic sclerosis (SSc)

[b]This patient could not be classified into another category as the death certificate stated that the patient had died of "shock"

associations were found between mortality and disease subtype, gender, serology or other organ involvement. The multivariate Cox proportional hazards model indicated that significant predictors of reduced survival were older age at diagnosis, male sex, ILD and RNA polymerase III antibody (anti-RNA pol III), after adjustment for other covariates. PAH and the two-way interactions between subtype and age at diagnosis with ACA were borderline significant (Table 4).

Discussion

In this study, we have evaluated the clinical and serological factors influencing survival and the causes of death in a large single centre cohort of patients with SSc in the UK. A number of studies have investigated standardised mortality ratios in cohorts of SSc patients. Two international meta-analyses have shown that there is considerable heterogeneity in the SMRs across different settings. This may be because the clinical manifestations and severity of SSc are thought to vary among groups of different racial descent [11, 12]. The most recent international meta-analysis included nine studies (2,691 patients, 732 deaths) and calculated a pooled SMR of 3.53 with a range from 2.86–4.69 [2]. Another international meta-analysis from seven cohorts (different to the cohorts in the other meta-analysis) revealed SMRs ranging from 1.5–7.2 [13]. The SMR obtained for our whole cohort (1.34) was lower than that obtained in most published studies, although the ratio was higher for males

Table 3 Standardised mortality ratios (SMR) in the systemic sclerosis cohort compared with the general population

Characteristic	Observed number of deaths	Expected number of deaths	SMR (95 % CI)
Male	8	5.18	1.54 (0.67–3.04)
Limited SSc	7	4.91	1.43 (0.57–2.94)
Diffuse SSc	1	0.27	3.67 (0.09–20.44)
Female	45	34.49	1.30 (0.95–1.74)
Limited SSc	35	28.13	1.24 (0.87–1.73)
Diffuse SSc	10	6.36	1.57 (0.75–2.89)
Total	53	39.67	1.34 (1.00–1.75)
Limited SSc	42	33.04	1.27 (0.92–1.72)
Diffuse SSc	11	6.63	1.66 (0.83–2.97)

CI confidence interval

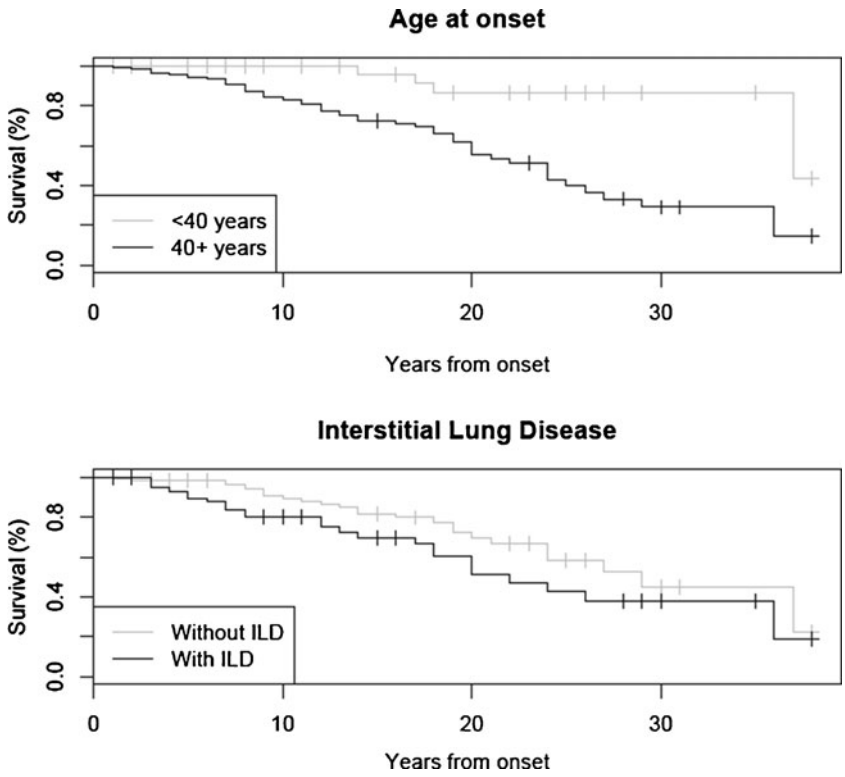

Fig. 1 Kaplan–Meier cumulative survival curves for the systemic sclerosis cohort stratified by age at onset and Interstitial Lung Disease. Log rank test p values were p <0.0001 for age at onset and p=0.04 for Interstitial Lung Disease

(1.54) and those with diffuse disease (1.66). The wide confidence intervals are likely to be related to the relatively small study size. It is possible that our database patients have less severe disease than patients in other mortality studies. This is supported by the fact that only 20 % of our cohort had diffuse disease compared to up to 51 % in other cohorts reporting significantly higher SMRs [13]. This is likely to reflect a greater recognition of early and limited cutaneous disease in contemporary cohorts such as ours in comparison with earlier studies. A South Australian population-based SSc registry studied over a similar period (1993–2007) has reported a similar SMR at 1.46 (95 % CI 1.28–1.69) [14]. Aside from the population-based registry, our patients' mean age of death (72 years, SD 12.3) was generally older than the mean age of death in other cohorts. As an example, the EUSTAR registry patients had a mean age of death of 61.7 (SD 13.3) [5].

Table 4 Summary of Cox regression modelling of predictors of survival

Risk factor	Hazard ratio	HR, 95 % CI	p value
Age at diagnosis (years)	1.07	1.02–1.11	0.002
Male gender	4.97	1.98–12.47	0.001
Diffuse SSc	2.31	0.85–6.33	0.102
Highest mRSS	0.70	0.37–1.33	0.279
Interstitial lung disease	3.76	1.66–8.51	0.001
Pulmonary arterial hypertension	1.98	0.95–4.12	0.069
Anti-centromere antibody (ACA)	0.28	0.01–7.86	0.457
Anti-Scl-70	1.44	0.57–3.67	0.446
Anti-RNA polymerase III	11.54	1.11–119.63	0.040
Anti-RNA polymerase I	0.25	0.01–7.83	0.429
Anti-RNA polymerase II	0.30	0.04–2.00	0.210
Pm-Scl	2.31	0.41–12.88	0.340
Subtype ACA[a]	8.85	0.89–87.69	0.062
Age at diagnosis ACA[a]	1.05	1.00–1.12	0.066

Covariates with more than ~5 % missing values were excluded. Anti-U1 ribonucleoprotein (RNP) and anti-U3 RNP were not included in the model as there was only 1 death in the anti-U1 RNP group and 0 deaths in the anti-U3 RNP group.

[a]Results are presented for all main effects and borderline significant (p <0.1) two-way interactions

The prevalence of SSc-related causes of mortality is similar to figures from other cohorts, with pulmonary (ILD and PAH) and cardiovascular disease being the most common cause of death [2, 5, 14–16]. However, the rate of SSc-related death (35.8 %) was lower than in many of the other cohort studies [17–24]. Of the non-SSc-related causes of death, infection (particularly pneumonia) and malignancy were the most common causes, in keeping with mortality data from the EUSTAR registry [5] and several other cohort studies from Japan [25], Hong Kong [26], Denmark [27], Sweden [21, 22], Canada [23] and Italy [24]. Several studies have suggested an increased incidence of cancer in patients with SSc [28, 29]. Only one of our patients died of renal disease which is consistent with the reported improvement in the prognosis of patients with SRC [30]. The death certificates of our patients were completed by doctors who were generally not involved in the care of their systemic sclerosis, and therefore, SSc and its complications may not have been mentioned or were underestimated as a contributing cause of death. It is possible that of the ten patients who died of pneumonia, GORD/aspiration and ILD may have contributed to this illness. Furthermore, it is not always possible to distinguish SSc-related or unrelated mortality.

Radiological ILD was confirmed as an important independent predictor of poor prognosis (hazard ratio 3.76, $p=0.001$). Although PAH caused 15.8 % of SSc-related deaths and 5.7 % of all-cause deaths, the presence of PAH was only found to be associated with death on the univariate analysis. Gastrointestinal involvement does not appear to be a prominent risk factor for mortality despite its significant morbidity. Aside from the finding for PAH, these findings are in keeping with other studies, including the meta-analysis by Ioannidis et al. [13].

The presence of anti-RNA pol III autoantibodies was the only serological predictor of worse survival. Although anti-RNA pol III is known to be associated with scleroderma renal crisis [31, 32], none of the three patient deaths were due to this condition. Previous studies have reached conflicting conclusions regarding the influence of auto-antibodies on mortality but some have indicated an association between mortality and RNA polymerase antibodies [33]. Anti-Scl-70 positivity has also been associated with poorer survival in previous studies [13, 34]. Although ACA did not have a significant effect on survival, the two-way interactions between subtype and age at diagnosis with ACA had a borderline significant effect, that is, those ACA-positive patients who were older at diagnosis or who had diffuse disease had a trend towards poorer survival ($p<0.1$). It is likely that this effect is due to the small number of deaths in the diffuse disease group and the large number of ACA-positive patients who were diagnosed at an older age.

We also found older age at diagnosis to be a poor prognostic factor and this has been described previously [14, 18, 23]. This is an expected finding given that life expectancy decreases with age. Male patients were found to have shorter survival than females and this is consistent with previous studies showing that male SSc patients have a higher age-adjusted mortality compared with females [14, 24].

Diffuse disease has previously been found to be a predictor of decreased survival [13]. Although the SMR for patients with diffuse SSc was higher than that for limited disease, we found no association with poorer survival, perhaps due to the low number of deaths in this group of patients (11/53, 20.8 %).

Our retrospective study has a number of limitations. Due to missing data, such as the date of disease onset and date of death, a number of alive and deceased patients needed to be excluded from the analysis. However, there was no loss to follow-up amongst the 204 included patients as their status was ascertained using the NHS Strategic Tracing Service. Use of such service provides more accurate data than mortality studies using only file reviews, registry data or questionnaires. Despite thorough file reviews, some clinical information, such as the presence or absence of visceral complications, was not available for a small number of patients. For this reason, when the regression analysis was performed, variables that had at least 5 % missing values were excluded. As our database is predominantly comprised of prevalent rather than incident cases of SSc, it is enriched with patients who had already survived long enough to be included in the study. The time of initiation of follow-up was considered to be the time of retrospective diagnosis (rather than the time of enrolment in the database), leading to a potential underestimation of the SMR. Furthermore, a number of severe cases are known to us who died early in the course of their disease without consenting to inclusion on our database.

Conclusions

The mortality rate of our cohort of patients with SSc is higher than that of the general population. Male gender, older age at diagnosis, a history of ILD and anti-RNA pol III all adversely affect survival. Pulmonary involvement in the form of PAH and/or ILD was the leading cause of SSc-related death in our cohort. Infection, malignancy and cardiovascular disease were predominant causes of non-SSc-related deaths. Prompt detection of pulmonary disease allows earlier initiation of therapy which may improve survival. Our findings provide further justification for existing recommendations on cardiopulmonary screening in SSc.

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