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Causes and predictors of death among Finnish patients with systemic sclerosis

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Original research article

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Abstract

Objective: The aim of our study was to assess causes and predictors of death among Finnish patients with systemic sclerosis (SSc).

Methods: Medical records of patients registered with the ICD-10 code M34 from 1996 to 2018 in two university hospitals were reviewed retrospectively. The clinical data were collected through end of 2020. The death certificates were obtained from Statistics Finland through August 2021. By using the death certificates and patient records, the cause of death for each subject was determined. The mean age at death, median times from SSc diagnosis, and factors predicting death were analyzed.

Results: Among 313 SSc patients, 91 deaths occurred between April 2000 and September 2020. The overall 5-year and 10-year survival rates were 88.4% and 80.2% respectively. SSc was the most common primary cause of death (n=35) and interstitial lung disease was the most common SSc-related cause of death (n=13). Fifty-two percent of the patients with diffuse systemic sclerosis (dcSSc) and 33% of the patients with limited cutaneous systemic sclerosis (lcSSc) died due to SSc itself. The patients who died due to SSc were significantly younger than those who died due to other causes; ages at death were 65.6 years (SD 12.7,CI=61.2–70.1) vs. 74.2 years (SD 9.6, CI=71.5-76.9), respectively, (p=0.0006). Interstitial lung disease, pulmonary arterial hypertension, gastrointestinal involvement, male gender and older age at disease onset predicted death.

Conclusion: The disease itself is the major cause of death among Finnish SSc patients, both in diffuse and limited forms of SSc.

Introduction

Systemic sclerosis (SSc) is a rare rheumatic autoimmune disease, characterized by vasculopathy and fibrosis of the skin and internal organs (1). The disease occurs more frequently in women than in men, with female to male ratio varying from 3:1 to 7–8:1 (2). Mortality of SSc is significant (3-12); the pooled over-all standardized mortality ratios (SMRs) vary from 2.72 to 3.53 in meta-analyses from the last decade (3,9-10).

Among SSc-related causes of death, scleroderma renal crisis (SRC) was the most common cause of death in past decades (13-14), but since the 1980s SRC has become rare and cardiopulmonary causes have become more common (7,9,14-18).

In the literature, many predictors of death in SSc are indicated. These are male gender, older age at disease onset, diffuse disease subtype, worsened pulmonary function, pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), high modified Rodnan skin score (mRSS), telangiectasias, digital ulcers (DUs), high C-reactive protein (CRP), anemia, cancer, proteinuria, SRC and overlap with myositis (5,7,15-17,19).

The studies assessing mortality have mainly been done using the classification criteria by the American College of Rheumatology (ACR) 1980 (20), LeRoy (21), LeRoy and Medsger (22) and ACR/European League Against Rheumatism (ACR/EULAR) 2013 (23). The majority of studies have been conducted using the older criteria. Two studies have been conducted using national registries (8,24).

The aim of our study was to examine the causes and predictors of death among patients with SSc in hospital-based data in two hospital districts in Finland using ACR/EULAR 2013 classification criteria for the basis of the diagnosis.

Methods

Patients over 16 years of age with a diagnostic code of SSc (ICD-10 codes beginning with M34) that appeared at least once in their medical records during the years 1996–2018 were identified from the hospital discharge registers of Turku and Oulu University Hospitals. The patient records were reviewed retrospectively. Wrong diagnoses and typing errors were excluded. The clinical data were collected to the end of 2020. Using ACR/EULAR 2013 criteria and the extent of skin fibrosis, the diagnoses were reclassified and divided into different subsets of the disease by two experienced physicians—i.e., a rheumatologist (S.K.) and a resident of internal medicine (M.K.). These subsets were diffuse cutaneous systemic sclerosis (dcSSc), limited cutaneous systemic sclerosis (lcSSc) and SSc without affected skin, sine scleroderma SSc (ssSSc). The validity of the diagnoses of our data was studied earlier (25). The death certificates including the primary and imminent causes of death were obtained from Statistics Finland through August 2021. The primary cause of death is the main reason leading to imminent cause of death. By examining patient records and death certificates, the primary cause of death for each subject was reevaluated. The primary causes of death were divided into four groups: SSc-related, cardiovascular disease, cancer, and other causes. The group of SSc-related causes of death were divided into groups by clinical manifestation that led to death. These were ILD, PAH, SRC, gastrointestinal (GI) tract involvement, myocardial and other SSc-related cause. The survival time was considered to be the time from the date of clinical diagnosis to death.

The predictors of death were determined as follows: PAH was diagnosed either by right heart catheterization (24 of 36) or with clinical examination supported by ultrasonography (12 of 36). ILD was diagnosed by typical findings in thorax x-rays or high-resolution computed tomography. GI-tract involvement included unintentional weight loss of at least 10% and other GI findings, such as watermelon stomach, esophageal dysmotility or pseudo-obstruction. Digital ulcers (DUs) were classified only if seen by a healthcare professional. Capillary abnormalities had to be seen by capillaroscopy, other microscopy or direct visual inspection. More extensive skin involvement was

defined by skin thickening proximal to metacarpophalangeal joints at the time of diagnosis. For the analyses, the two ssSSc cases were included in the lcSSc group of.

The study data were collected and managed using REDCap electronic data capture tools hosted at the University of Turku (26-27).

Statistics

Variables were summarized with descriptive statistics. Associations between death and categorical variables were studied by chi-square test, and by Fisher's exact test if the assumptions of the chi-square test were violated. The age at death and the time from diagnosis to death in relation to cause of death were studied with one-way analysis of variance (ANOVA) and the Kruskal-Wallis test (for non-normally distributed continuous variable).

Finally, the association between death and explanatory variables was analyzed using multinomial logistic regression. The model included age, gender, ILD, PAH, GI-tract involvement, disease subtype, teleangiectasiae, smoking (ever vs. never), skin involvement, DUs, anti-topoisomerase antibody (ATA) positivity and nailfold capillary abnormalities. Odds ratios (OR) with 95% Wald confidence intervals (95% CI) were reported. The Kaplan-Meier method was used to estimate overall survival time, and comparisons between female and male patients were made using log-rank test.

The normality of variables was evaluated visually and tested with the Shapiro-Wilk test. For the non-normality continuous variables, nonparametric methods were used. All tests were performed as two-sided with significance level set at 0.05. The analyses were carried out using the SAS system, version 9.4 for Windows (SAS Institute Inc., Cary, NC, US).

Ethical considerations and study permissions

This was a non-interventional retrospective study without direct patient contact. According to Finnish legislation, no patient consent or ethical committee approval was needed. Permissions for the study were obtained from the hospital district of Southwest Finland for Turku University Hospital and the hospital district of Northern Ostrobothnia for Oulu University Hospital.

Results

Among 313 SSc patients, 91 deaths occurred between April 2000 and September 2020. Table 1 shows the SSc-related and non-SSc-related causes of death by gender and disease subtype. Among these 91 patients, 23 had dcSSc, 66 had lcSSc and two had ssSSc.

For the 91 deceased patients, we have data for 34 patients from the beginning of the Raynaud´s phenomenon (RP) and for 51 patients beginning at the first non-RP symptom, respectively.

The overall 5- and 10-year survival rates in the whole SSc group were 88.4% and 80.2%, respectively. The female subjects had better prognoses: 5- and 10 -year survivals were 90.1% and 84.4%, respectively, for females and 75.2% and 64.0% for males (p=0.0008 between genders).

SSc-related cause of death was the most common cause of death (n=35). In the group of SSc-related deaths, ILD with or without secondary pulmonary hypertension (n=13) and PAH (n=11) were the leading causes of death (Table 1). In addition, one patient had both ILD and PAH contributing to death. One patient in the SSc-related death group had other defined complications with severe gangrene in fingers, osteomyelitis and recurrent septicemia. Twelve of 23 patients with dcSSc (52%), 22 of 66 patients with lcSSc (33%) and one of two (50%) patients with ssSSc died due to SSc. For these 12 deceased patients with dcSSc, diagnoses were made between 1987 and 2017. The diagnoses of these 22 deceased lcSSc patients were made between 1982 and 2016, with seven before 2000, nine between the years 2000 and 2013 and five between 2014 and 2016. For one subject, the time of diagnosis was not available. The diagnosis of the only ssSSc patient was made in 2006.

Autoantibody profiles among patients who died due to SSc were as follows: five were positive for antitopoisomerase antibodies (ATA), 18 for anticentromere antibodies (ACA) and one for anti-RNA polymerase III (anti-RNAP3) antibodies. Anti-RNAP3 antibodies were tested for only a few years at the end of follow-up. In ILD-related deaths, three were positive for ATA and four for ACA. In PAH-related deaths, ten were positive for ACA while in SRC-related deaths two were positive for ATA and one for anti-RNAP3.

The most common non-SSc-related cause of death was cardiovascular disease (n=20). Of these different types, coronary heart disease was the most common (n=13), followed by peripheral artery disease (n=4), essential hypertension (n=2) and stroke (n=1). There were 18 cancer-related deaths, with GI malignancies being the most common (n=6) followed by lung cancer (n=4). The other cancers were liver and biliary tract (n=2), lymphoma (n=2), malignant myeloma (n=1) and cancers from unknown origin (n=3). In the group of other causes of death, the most common was trauma (n=4), followed by chronic obstructive pulmonary disease (n=3), liver cirrhosis (n=2), Alzheimer′s disease (n=2), septicemia (n=1), long QT-interval (n=1), gut occlusion (n=1), meningioma (n=1), alcohol abuse (n=1), cerebral hemorrhage (n=1) and unknown (n=1).

Figure 1 presents the mean ages of death and the median times from SSc diagnoses to death for the groups organized by primary cause of death. The mean age at death of patients who died of an SSc-related cause was 65.6 years (SD 12.7, CI= 61.2–70.1) in contrast to 74.2 years (SD 9.6, CI= 71.5–76.9) for patients who died due to non-SSc-associated causes; the difference was statistically significant (p=0.0006). The median time from SSc diagnosis to death was 4.4 years [IQR 1.5, 11.8] in the SSc-related death group and 10.8 years [IQR 4.7, 17.1] for the non-SSc-related death group; the difference was statistically significant (p=0.0061). Table 2 presents the mean ages at death and the median times from the SSc diagnoses to death by different manifestations associated with SSc.

In multinomial logistic regression analysis, we found that ILD, PAH, GI involvement, older age at disease onset and male gender predicted death of all causes, and nailfold capillary abnormalities were associated with a more favorable outcome (Table 3).

Discussion

The major finding of this study was that almost half of Finnish men and one-third of Finnish women with SSc died due to the disease itself. These percentages for dcSSc and lcSSc patients were 52% and 33%, respectively. This raises the question of where these patients should be monitored. It must be noted that, currently, milder cases are monitored as the classification criteria have become more sensitive (23) and the incidence of SSc has been shown to increase (28). For the majority of the subjects who died due to SSc, the diagnosis was made before the year 2013, seven patients with dcSSc, 14 with lcSSc and one with ssSSc. This study did not answer the question if the mortality has decreased after 2013 classification criteria, because we did not have the mortality data for the background population.

The validity of SSc diagnoses in our data was studied from 2008-2018 (25). All patient records were reviewed and 253 of 385 patients (65.75%) fulfilled ACR/EULAR 2013 criteria. 37 (9.6%) subjects were considered as having early SSc and 95 subjects (24.9%) had another diagnosis. In our current study, all subjects fulfilled ACR/EULAR 2013 criteria, but most likely at the beginning of follow-up the milder cases were not detected and were not referred to a rheumatologist.

The primary causes of death in Finnish SSc patients are in line with previous studies (6,17). That is also true for deaths linked with SSc (14,16,18). ILD and PAH are the leading SSc-related causes of death in Finnish patients with SSc. SRC and GI-tract involvement were more rarely causes of death, but their time to death is even shorter than with PAH or ILD manifestations. SRC typically occurs at the early stage of the disease (29). During our study, the use of angiotensin-converting enzyme (ACE) inhibitors may have reduced the frequency of SRC as a cause of death. It is possible that SSc

had contributed to the death in a form of gut occlusion in the group of other causes, but we could not verify that.

It was previously reported that infections are common causes of death among patients with SSc (15,18). In Finnish death certificates, the primary and the imminent causes of death are reported, and in fact, the proportion of infections listed as a leading primary cause of death was low. Only one patient had septicemia listed as a primary cause of death. In three patients with pneumonia as an imminent cause of death, severe ILD was the primary cause of death.

Cardiovascular disease was the most common primary cause of death among the non-SSc-related deaths. SSc might have contributed to these deaths because it is recognized that SSc increases the risk of atherosclerosis (30-32).

Cancer was the second-most prevalent cause of non-SSc-related death in our study, with cancer of the GI-tract being the most frequently observed. Four of the cancer-related deaths were due to lung cancer, which is reported to be the most frequent type of cancer in patients with SSc (33-34). Of the four patients with lung cancer, three had underlying ILD; lung cancer is known to be associated with ILD in SSc patients (35-36). Two of four patients had a history of smoking, and for one patient the data on smoking history was unavailable. One patient who died due to adenocarcinoma of the lungs was a non-smoker.

We had limited data of the onset of either RP or the first non-RP symptom. For the analyses of time to death, we used the time of clinical diagnosis as a starting point. This leads to the shorter life expectancy in these analyses. In the literature, the starting point has been determined from the first RP symptom (19), from the time of the first non-RP symptom (5,16,19), from the development of cutaneous sclerosis (13,17,19), or from the initial evaluation in the clinic (14).

PAH is known to be a late manifestation of SSc (37). In our study,the median time from SSc diagnosis to death due to PAH was only 3.7 years. Among the eleven subjects with PAH as a

primary cause of death, data on the time of onset of RP were available for five subjects, and for these five subjects the mean time from RP to death was 18.2 years. Nine of those eleven subjects had information about the beginning of the first non-RP symptom, and the mean time from non-RP symptom to death was 5.1 years for these nine subjects. Seven of those nine patients had symptoms of pulmonary hypertension as their first non-RP symptom, six with dyspnea and one with severe fatigue. We assume that the delay of the SSc diagnoses explains the short time span from diagnosis to death in patients with PAH.

During the follow-up, the screening of organ involvements and also the treatment developed. For example, high-resolution computed tomography was routinely used to detect ILD at the end of follow-up. This allowed earlier detection of ILD and also milder cases were found. It is likely the use of immunosupressants was more common. National guidelines on screening and follow-up of the different manifestations of SSc were introduced in Finland in 2022, after the implementation of our study.

The analysis for autoantibodies against RNAP3 was available only during the last few years of the study, this leads to a fact that only one patient was positive for these antibodies. Twenty-two of 29 deceased subjects with negative result for SSc-spesific antibodies had ANA positivity. Ten of these had a speckled nucleolar pattern. At the time, these were not divided into coarse or fine speckled staining. Some of these could still present anti-RNAP3 positivity.

In the multinomial logistic regression analysis an older age at disease onset, male gender, ILD, PAH, and GI-tract involvement predicted death after adjustment. GI-tract involvement during the early course of the disease is known to be associated with worse survival (38). Male gender also predicted death even after adjustment for the disease subtype and ATA positivity. In a study of the EUSTAR database of 1072 deceased subjects out of a total of 11193, the male gender was also found to be an independent risk factor of early mortality (18). The nailfold capillary abnormalities seemed to be associated with a better prognosis in this model. These abnormalities were detected by

various methods. The nailfold capillaroscopy device was acquired by the study hospitals in 2010 and 2012. We assume that before this, the most common abnormalities were giant capillaries, which are easier to detect. In literature a worse prognosis is associated with the late pattern in the capillaroscopy compared to non-late pattern. In the dcSSc subtype the difference was statistically significant (39).

We had limited data on the affected skin areas outside the skin of the upper extremities, and the impact of the skin involvement was therefore deficient. The mRSS was not used in the clinical assessment and therefore was not available in this register data. The mRSS is known to have predicted mortality in previous studies (5,15). The assessment of skin thickening proximal to metacarpophalangeal joints was done at the time of diagnosis; this information was not available for 34 subjects.

Conclusion

Our study demonstrates that SSc is a severe disease in Finland and that a remarkable proportion of patients die due to the disease itself. SSc-related mortality is predominantly related to ILD and PAH. Based on these findings, monitoring of SSc patients through a predefined protocol by rheumatologists may be justified.

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Conflict of interest

S.K. is an investigator in clinical PsA drug studies funded by Abbvie, Pfizer, and BMS and a SSc drug study funded by Boehringer-Ingelheim, and has also received consulting and speaker fees from

UCB, Abbvie, Boehringer Ingelheim, Medac and scientific meeting attendance support from UCB, Roche, and Abbvie, which are all unrelated to this work. J.H. has attended advisory boards organized by Abbvie, Amgen, Boehringer Ingelheim, Fresenius Kabi, Janssen and Novartis and scientific meeting attendance support from Abbvie, Medac, Novartis and Pfizer, which are all unrelated to this work. M.K. has received scientific meeting attendance support from Pfizer, which is unrelated to this work. T.R. has declared no conflicts of interest. J.P. is an investigator in clinical PsA drug studies funded by Lilly, Boehringer-Ingelheim ,Abbvie, Pfizer and BMS; she has received a speaker fee from UCB and scientific meeting attendance support from Medac, Jansen-Cilag and UCB, which are all unrelated to this work. L.P. is an investigator in clinical PsA drug studies funded by Abbvie, Pfizer and BMS, and has also received consulting and speaker fees from Abbvie , Boehringer Ingelheim, Jansen-Cilag, Novartis Finland, Sandoz, Eli Lilly, UCB Finland, Celltrion, Fresenius-Gabi and Swedish Orphan Biovirtum, and scientific meeting attendance support from Orion, Sanofi and Amgen, which are all unrelated to this work. K.T. is an investigator in a clinical GCA drug study funded by Novartis, and has received consulting and speaker fees from Abbvie, Vifor Pharma and Pfizer, and scientific meeting attendance support from UCB and Pfizer, which are all unrelated to this work.

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Figure 1

Median times from diagnosis to death (a) and mean ages at death (b). Comparison is made between the groups.

Table 1 The primary causes of death

Causes of death	Deaths n (female/male)	Disease subtype (dcSSc/lcSSc/ssSSc)
All causes	91 (68/23)	23/66/2
SSc- related	35 (25/10)	12/22/1
ILD	13 (9/4)	5/8/0
PAH	11 (9/2)	0/10/1
Renal crisis	4 (2/2)	4/0/0
Myocardial	2 (2/0)	1/1/0
GI-tract involvement	3 (1/2)	2/1/0
Other	2 (2/0)	0/2/0
Cardiovascular disease	20 (16/4)	3/17/0
Cancer	18 (12/6)	4/14/0
Other causes	18 (15/3)	4/13/1

The primary causes of death grouped by gender and disease subtype. lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; ssSSc systemic sclerosis sine scleroderma; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension

Table 2. Mean ages at death and median time to death from the diagnosis of systemic sclerosis

SSc-related cause of death	**Deaths (n)**	**Median time from SSc diagnosis, years [IQR]**	**Mean age at the time of death, years (SD)**
ILD	13	11.8 [4.4, 14.1]	62.5 (13.4)
PAH	11	3.7 [1.5, 4.6]	72.4 (5.2)
Renal crisis	4	0.3 [0.1, 0.5]	62.0 (13.5)
Heart	2	12.2 [9.2, 15.3]	69.5 (23.3)
GI-tract involvement	3	1.5 [1.3, 8.1]	51.7 (6.7)
Other	2	12.3 [9.9, 14.7]	77.0 (14.1)

Mean ages at death and median times to death by different SSc-related complications: SSc, systemic sclerosis; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; GI, gastrointestinal; IQR, interquartile range; SD, standard deviation

Table 3. Risk factors for death in patients with systemic sclerosis

	Odds ratio (CI)	p-value
ILD	8.8 (2.7–29.3)	<0.001
PAH	9.4 (2.5–35.0)	0.001
Male gender	10.8 (2.4–48.3)	0.002
Older age at disease onset	1.1 (1.0–1.1)	0.003
GI-tract involvement	3.9 (1.2–12.3)	0.023
Nailfold capillary abnormalities	0.3 (0.1–0.9)	0.028
Telangiectasias	1.9 (0.7–5.3)	0.221
Smoking (ever vs. never)	1.5 (0.4–5.7)	0.392
Digital ulcers	0.4 (0.1–1.9)	0.259
dcSSc	3.8 (0.7–20.8)	0.119
Anti-topoisomerase-antibody positivity	0.5 (0.1–2.9)	0.422
Skin thickening	0.2 (0.04–1.1)	0.058

Independent risk factors of death analyzed by multinomial logistic regression: odds ratio (OR) and confidence interval (CI); ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; dcSSc, diffuse cutaneous systemic sclerosis; GI, gastrointestinal