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Original article

Survival in Swedish patients with systemic sclerosis: a nationwide population-based matched cohort study

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Abstract

Objectives. To conduct the first-ever nationwide, population-based cohort study investigating survival patterns of all patients with incident SSc in Sweden compared with matched individuals from the Swedish general population.
Methods. We used the National Patient Register to identify patients with incident SSc diagnosed between 2004 and 2015 and the Total Population Register to identify comparators (1:5), matched on sex, birth year and residential area. We followed them until death, emigration or the end of 2016. Follow-up of the general population comparators started the same date as their matched patients were included. We estimated all-cause survival using the Kaplan–Meier method, crude mortality rates and hazard ratios (HRs) using flexible parametric models.
Results. We identified 1139 incident patients with SSc and 5613 matched comparators. The median follow-up was 5.0 years in patients with SSc and 6.0 years for their comparators. During follow-up, 268 deaths occurred in patients with SSc and 554 in their comparators. The 5-year survival was 79.8% and the 10-year survival was 67.7% among patients with SSc *vs* 92.9% and 84.8%, respectively, for the comparators ($P < 0.0001$). The mortality rate in patients with SSc was 42.1 per 1000 person-years and 15.8 per 1000 person-years in their comparators, corresponding to an HR of 3.7 (95% CI 2.9, 4.7) at the end of the first year of follow-up and 2.0 (95% CI 1.4, 2.8) at the end of the follow-up period.
Conclusion. Despite advances in understanding the disease and in diagnostic methods over the past decades, survival is still severely impacted in Swedish patients diagnosed with SSc between 2004 and 2015.

Key words: SSc, survival, mortality

CLINICAL SCIENCE

Rheumatology key messages

- Despite advances in understanding systemic sclerosis and in diagnostic methods, survival is still severely impacted.
- There is no significant difference in survival between men and women with SSc in Sweden.
- Variations in the chosen time point for the start of follow-up may explain variations in survival across studies.

Introduction

SSc is a rare rheumatic disease of the connective tissue, associated with a heterogeneous clinical presentation and multiple organ-based manifestations involving the skin, musculoskeletal system, lungs and kidneys [1, 2]. SSc carries one of the highest standardized mortality ratios (SMRs) compared with the general population among the rheumatic diseases [3]. Renal involvement, pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are the main fatal manifestations of SSc [2]. SSc is much more common in women than men, however, male sex has been described as a poor prognostic factor [4].

Estimates of survival vary noticeably in the literature. This is partially due to disease rarity and heterogeneous presentation, the evolution of classification criteria over time [5–8] and that follow-up is started at different time points in relation to disease onset. The 5-year survival rate ranges from 68% to as high as 95% and 10-year survival ranges from 55% to 86% [9–13]. In Sweden, the only study where the survival of SSc was investigated included patients diagnosed between 1983 and 1995 and was mostly confined to the southern part of Sweden

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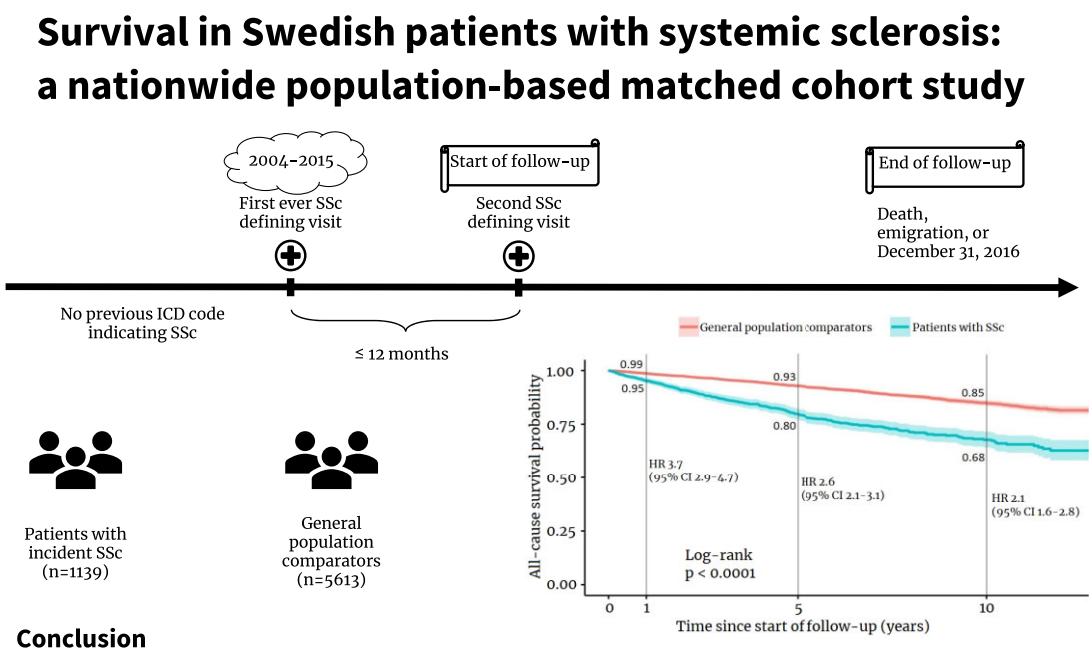
Graphical abstract



Conclusion

Despite advances in understanding the disease and in diagnostic methods, survival is still severely impacted in Swedish patients diagnosed between 2004–2015.

(Skåne) [14]. The 5-year all-cause survival was 86% while 10-year all-cause survival was 69%, with a standardized mortality ratio of 4.6 compared with the general population. Since improved diagnostic tools, novel treatment options and more inclusive classification criteria have emerged during recent decades, an up-to-date study to investigate survival of SSc covering all of Sweden and the patients diagnosed with SSc in recent years is needed and indispensable.

Herein we aim to conduct a nationwide, population-based cohort study investigating the survival patterns of all patients with incident SSc in Sweden compared with a matched cohort from the Swedish general population.

Materials and methods

Study design

This is a population-based matched cohort study.

Setting

Residents in Sweden are entitled to a national tax-funded healthcare system with equal accessibility for all residents. In Sweden, patients with SSc are followed by rheumatologists, usually in a tertiary care setting, with several visits during the first year after diagnosis.

Data sources

The National Patient Register (NPR) comprises information on hospitalizations with complete coverage since 1987 and information on diagnosis according to the International Statistical Classification of Diseases and Related Health Problems (ICD) codes is available for almost 99% of all hospitalizations [15]. Since 2001 the NPR also comprises information on outpatient specialist care, with coverage of almost 97%. With respect to rheumatology, the NPR is thought to have high coverage, as only 7% (16/246) of active rheumatologists in Sweden are private practitioners (data from 2015) [16]. The Total Population Register (TPR) contains information on sex, date of birth, address, date and country of emigration and date of death of all residents [17]. The Cause of Death Register (CDR) captures data on the date and causes of death of almost all residents since 1952 using death certificates submitted by physicians. The causes of death are recorded according to ICD codes. As defined in the ICD, both the underlying cause of death and the contributing causes of death are recorded in the CDR [18].

Participants

We used the NPR to obtain information on visits for SSc. To identify patients with incident SSc, we considered individuals $\geq$18 years of age registered as living in Sweden with at least two visits with SSc listed as the main diagnosis (ICD-10 codes: M34.0, M34.1, M34.8, M34.9), the first visit between 1 January 2004 and 31 December 2015 without any previous ICD code given for SSc and the second visit within 12 months of the first. At least one of the two ICD codes for SSc had to be given by a rheumatologist or internist. These criteria ensure a clear definition of incident SSc in order to avoid including patients misclassified as having SSc. The national board

of health and welfare provided us with data on all hospitalizations from 1997 and on all outpatient non-primary specialist care visits from 2001. By starting the study in 2004, when we had observation time in the inpatient register for 7 years, and in the outpatient register for 3 years, we ensured that included patients were incident cases, not prevalent cases, minimizing the risk of classifying prevalent SSc as incident SSc. Using the TPR, we identified sex, birth year and residential area–matched individuals (1:5) from the Swedish general population resident in Sweden and alive on the date of the second disease-defining visit. We obtained information on sex, birth year, residential area and date of death for all participants from the TPR. To identify baseline comorbidities, we collected data from the NPR on main and secondary diagnoses from all visits that ever occurred prior to the start date of follow-up for each participant. We obtained information on the underlying cause of death using the CDR.

Exposure and other variables, outcome definition and follow-up

The exposure was an incident SSc diagnosis. Potential confounders include sex and age, as increasing age and male sex have previously been described to be associated with higher mortality [19]. Start of follow-up was the date of the second disease-defining visit for each patient with SSc. The general population comparators were given the corresponding date as their matched patient. We followed all participants until our primary outcome (death), emigration or 31 December 2016, whichever occurred first. Baseline comorbidities were grouped according to ICD-10 codes into diseases of the circulatory system [cardiovascular disease (CVD); I00–I99], neoplasm (C00–D48), respiratory diseases (J00–J99) and renal diseases (N00–N19). We grouped underlying causes of death into SSc-related death in patients with SSc (M34.0, M34.1, M34.8, M34.9), CVD-related deaths in both patients with SSc and comparators (I00–I99), neoplasm-related death in both groups (C00–D48) and infectious diseases–related death in both groups (A00–B99, L00–L08 and J00–J22). As a secondary outcome, we estimated the risk of premature death in patients with SSc compared with their comparators and considered deaths that occurred at <70 years as premature, according to the definition of premature mortality by the Organization of Economic Co-operation and Development [20].

Statistical methods

The baseline characteristics of the study population were described using number (%), mean (S.D.) and median [interquartile range (IQR)], as appropriate. We used the Kaplan–Meier method to estimate all-cause survival in both SSc patients and their comparators. We estimated the empirical all-cause mortality rates and used Poisson models to estimate 95% CIs. We also estimated mortality rates stratified by sex, region and age at the start of follow-up (grouped into ages 18–49, 50–59, 60–69 and ≥ 70 years). We compared the risk of death in different groups of study participants by estimating hazard ratios (HRs) using flexible parametric models adjusted for age and sex [21]. In the analysis of premature death, we included only participants who were <70 years of age at start of follow-up. We followed them until turning 70 years, death, emigration or 31 December 2016, whichever occurred first. The outcome was death before 70 years. We estimated these HRs using flexible parametric models adjusted for age and sex. We performed the statistical analyses using the packages 'survival' [22], 'biostat3' [23], 'flexsurv' [24], 'survminer' [25] and 'rstpm2' [26] in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval information

An ethical permit to conduct this study was granted by the Swedish Ethical Review Authority (Dnr 2017/2000-31) and written consent was not needed since this study is register based.

Results

We identified 1139 patients with incident SSc and 5613 matched comparators from the general population between 2004 and 2015. The mean age at the start of follow-up was 58.7 years (S.D. 14.5) and 80% were women. The median follow-up was 5.0 years (IQR 5.6) and 6.0 years (IQR 5.7) for patients with SSc and their comparators, respectively. Summary characteristics and baseline comorbidities are presented in Table 1. Until 31 December 2016, 24% of all patients with incident SSc had died (268 deaths): 64 were men (28% of all men) and 204 were women (22% of all women). Ten percent of individuals from the matched comparators had died (554 deaths): 141 were men (13% of all men) and 413 were women (9% of all women). The mean age at death was 72.3 years in patients with SSc (71.4 in men and 72.6 in women) and 76.5 years in their comparators (75.1 in men and 77.0 in women).

All-cause survival

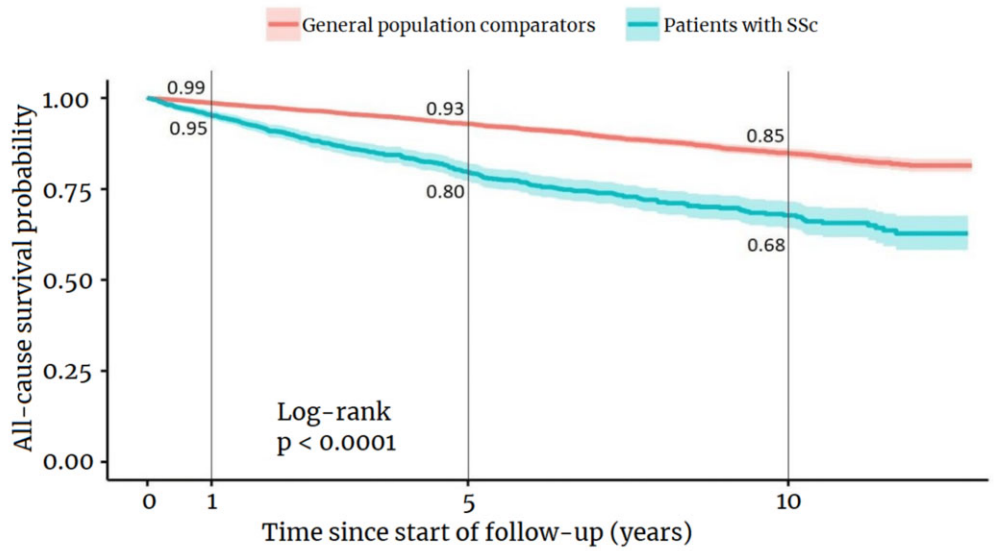
Survival among patients with SSc was lower than in the general population comparators ($P < 0.0001$). The Kaplan–Meier 1-year all-cause survival for patients with SSc was 95%, 5-year survival was 80% and 10-year survival was 68%. Corresponding estimates in the general population comparators were 99%, 93% and 85%, respectively (Fig. 1). Among patients with SSc, 1-, 5- and 10-year survival estimates in men were 94%, 78% and 63%, compared with 96%, 80% and 69% in women, respectively ($P = 0.14$) (Fig. 2). Survival estimates of men and women stratified by age group are presented in Supplementary Figs S1 and S2 (available at *Rheumatology* online), respectively.

Table 1 Baseline characteristics and comorbidities

Characteristics	Patients with SSc	General population comparators
N	1139	5613
Age at start of follow-up, years, mean (S.D.)	58.7 (14.5)	58.5 (14.5)
Sex[a]		
Female, *n* (%)	912 (80.1)	4499 (80.2)
Male, *n* (%)	225 (19.8)	1114 (19.8)
Follow-up, years, median (IQR)	5.0 (5.6)	6.0 (5.7)
Age at start of follow-up (years), *n* (%)		
18–49	308 (27.0)	1546 (27.5)
50–59	249 (21.9)	1234 (22.0)
60–69	313 (27.5)	1526 (27.2)
≥70	269 (23.6)	1307 (23.3)
Baseline comorbidities, *n* (%)		
Diseases of the circulatory system	619 (54.3)	1395 (24.9)
Neoplasms	357 (31.3)	1415 (25.2)
Respiratory diseases	331 (29.1)	806 (14.4)
Renal diseases	46 (4.0)	125 (2.2)

Baseline characteristics and comorbidities of patients with SSc diagnosed between 2004 and 2015 and their general population comparator cohort matched on sex, birth year and residential area. [a]Data on sex were missing in two patients with SSc.

Fig. 1 All-cause survival curves



Number at risk (cumulative number of deaths)

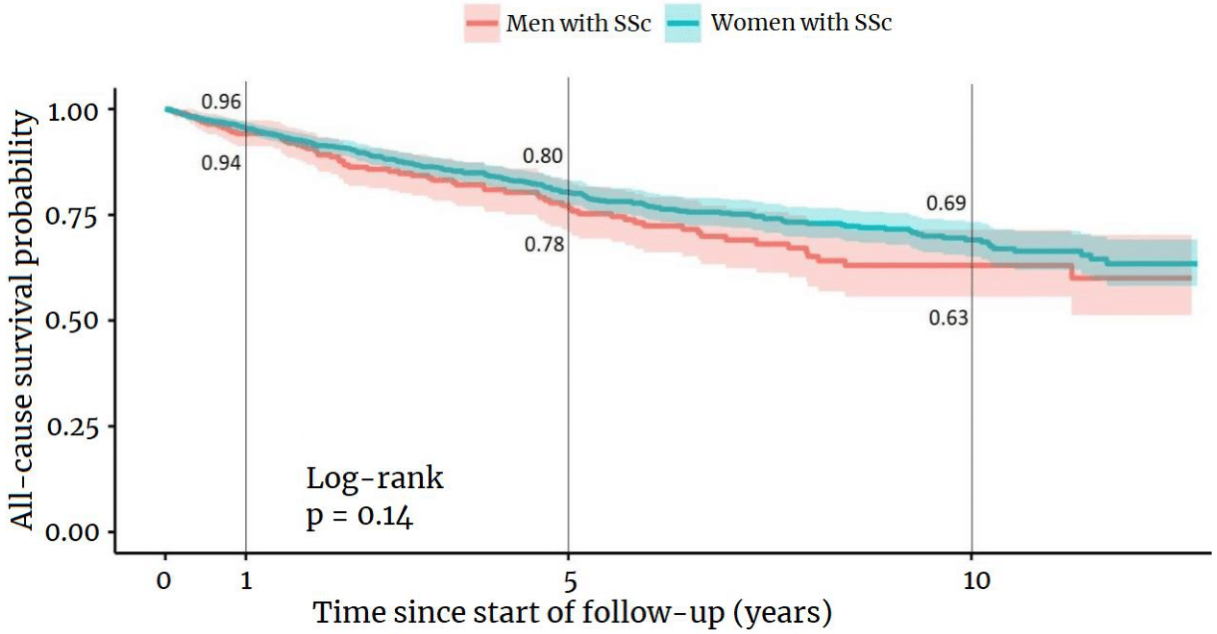
	0	1	5	10
Patients with SSc	1139 (0)	1084 (54)	567 (198)	177 (259)
General population comparators	5613 (0)	5518 (76)	3252 (337)	1071 (525)

All-cause survival in patients with SSc diagnosed between 2004 and 2015 and their general population comparator cohort matched on sex, birth year and residential area with follow-up until 31 December 2016.

All-cause mortality

The crude all-cause mortality rate in patients with SSc was 42.1 (95% CI 37.2, 47.4) per 1000 person-years and 15.8 (95% CI 14.5, 17.2) per 1000 person-years in their comparators (Table 2). This corresponded to an age- and sex-adjusted HR decreasing during follow-up from 3.7 (95% CI 2.9, 4.7) at the end of the first year of follow-up to 2.0 (95% CI 1.4, 2.8) at the end of follow-

Fig. 2 All-cause survival in patients with SSc, stratified by sex



Number at risk (cumulative number of deaths)

	0	1	5	10
Women with SSc	912 (0)	870 (41)	446 (152)	144 (196)
Men with SSc	225 (0)	212 (13)	119 (46)	32 (63)

Data on sex were missing in two patients with SSc.

up. The mortality rate in patients with SSc was lowest among younger patients: 7.6 (95% CI 4.3, 12.6) per 1000 person-years in those ages 18–49 years and 116.7 (95% CI 97.7, 138.2) in those ≥70 years. Patients with SSc had consistently higher mortality rates than their comparators in the respective age groups.

The mortality rate in women with SSc was higher than in women from the comparators: 40.3 (95% CI 35.0, 46.2) *vs* 14.9 (95% CI 13.5, 16.4) per 1000 person-years. In men with SSc, the mortality rate was 49.5 (95% CI 38.1, 63.2) compared with 19.1 (95% CI 16.1, 22.5) per 1000 person-years in their comparators. The age-adjusted HR in women decreased from 3.8 (95% CI 2.9, 5.0) at the end of the first year of follow-up to 2.0 (95% 1.4, 2.9) at the end of follow-up, and in men from 3.3 (95% CI 2.0, 5.4) to 2.1 (95% CI 1.0, 4.3).

Mortality rates differed widely between regions (Supplementary Fig. S3, available at *Rheumatology* online). Norrbotten had the highest mortality rate, 87.2 (95% CI 43.5, 156.1) per 1000 person-years, where 11 deaths occurred in the 27 patients with SSc during follow-up. Fewer than five deaths occurred in the 21 patients in Västmanland, which corresponded to the lowest mortality rate, 14.9 (95% CI 1.8, 53.7) (Supplementary Table S1, available at *Rheumatology* online).

Causes of death

Ninety-five (35%) of the 268 deaths among patients with SSc were attributed to SSc. Sixty-six (25%) of all deaths in patients with SSc and 170 deaths (31%) of all 554 deaths in the comparators were assigned to CVD. In patients with SSc, 51 (19%) of all deaths were assigned to neoplasms and the corresponding number in the comparators was 194 (35%) of all deaths. Nine deaths (3% of all deaths) in patients with SSc had an underlying cause of death indicating infectious diseases, compared with 20 deaths (4% of all deaths) in the comparators.

Premature death

Patients with SSc had a 373% higher rate of premature death at the end of the first year of follow-up compared with their comparators [HR 4.73 (95% CI 3.18, 7.04)]. It decreased to 181% [HR 2.81 (95% CI 1.91, 4.12)] at the end of the fifth year of follow-up, to 147% [HR 2.47 (95% CI 1.47, 4.17)] at the end of the tenth year of follow-up and to 131% [HR 2.31 (95% CI 1.28, 4.17)] at the end of follow-up.

Discussion

In this study we present data on survival for all patients with SSc in Sweden compared with a comparator cohort

TABLE 2 All-cause mortality rate and HR

Characteristics	Patients with SSc		General population comparators		HR (95% CI)			
	Deaths/total follow-up in person-years	Mortality rate (95% CI) per 1000 person-years	Deaths/total follow-up in person-years	Mortality rate (95% CI) per 1000 person-years	At end of 1 year of follow-up	At end of 5 years of follow-up	At end of 10 years of follow-up	At end of follow-up
Overall	268/6372	42.1 (37.2, 47.4)	554/35095	15.8 (14.5, 17.2)	3.7 (2.9, 4.7)	2.6 (2.1, 3.1)	2.1 (1.6, 2.8)	2.0 (1.4, 2.8)
Sex[a]								
Female	204/5062	40.3 (35.0, 46.2)	413/27718	14.9 (13.5, 16.4)	3.8 (2.9, 5.0)	2.6 (2.1, 3.2)	2.1 (1.5, 2.9)	2.0 (1.4, 2.9)
Male	64/1293	49.5 (38.1, 63.2)	141/7377	19.1 (16.1, 22.5)	3.3 (2.0, 5.4)	2.5 (1.8, 3.6)	2.2 (1.1, 4.1)	2.1 (1.0, 4.3)
Age at start of follow-up (years)								
18–49	15/1966	7.6 (4.3, 12.6)	13/10129	1.3 (0.7, 2.2)	2.8 (0.5, 15.1)	8.9 (2.0, 39.2)	5.9 (1.5, 23.3)	5.8 (1.2, 27.8)
50–59	27/1545	17.4 (11.5, 25.4)	47/8196	5.7 (4.2, 7.6)	6.7 (2.9, 15.1)	2.0 (1.0, 3.9)	1.5 (0.5, 4.1)	1.3 (0.4, 4.1)
60–69	92/1712	53.7 (43.3, 65.9)	150/9689	15.5 (13.1, 18.2)	4.1 (2.6, 6.3)	3.2 (2.3, 4.4)	3.0 (1.9, 4.7)	2.9 (1.7, 4.9)
≥70	134/1149	116.7 (97.7, 138.2)	344/7081	48.6 (43.6, 54.0)	3.1 (2.3, 4.3)	2.2 (1.7, 2.8)	1.8 (1.2, 2.7)	1.7 (1.0, 2.7)

All-cause mortality rate and HR with 95% CI of patients with SSc diagnosed between 2004 and 2015 and their general population comparator cohort matched on sex, birth year and residential area with follow-up until 31 December 2016. HRs were adjusted for age and sex with degree of freedom of 5 and allowing for time-dependent effect of SSc. [a]Data on sex were missing in two patients with SSc.

matched on sex, birth year and residential area identified from the Swedish general population. Our results demonstrate the significantly higher mortality associated with SSc compared with unexposed individuals from the general population.

Even though our study covered a more recent period, our survival estimates are lower than those reported by a previous study conducted in the southern part of Sweden (Skåne) between 1983 and 1995, where 5-year survival in Skåne was 86% *vs* 80% in the present study and 10-year survival was 69% *vs* 68% in the present study, respectively [14]. This could be due to an increased awareness of SSc in Skåne, which in turn may have led to a more established collaboration between primary care and practising rheumatologists, leading to patients with SSc being diagnosed in early stages and hence higher survival was observed among these patients. The mean age at enrolment in that study was 49.6 years, lower than the estimate of the present study. In the present study we found the all-cause mortality rate in Skåne to be 37.2 per 1000 person-years, which is lower than the overall mortality rate in Sweden of 42.1.

Several factors may have led to the noticeable variation in mortality rates on a regional level. Since Sweden is divided into 21 regions differing in population size, it was expected that we would observe relatively few patients with SSc in many regions and hence a low number of deaths. More than half of the regions had <10 deaths recorded during the entire follow-up period. This, in combination with large CIs, could have led to unreliable estimates that should be interpreted with caution. Moreover, SSc is probably more likely to be detected in regions where highly specialized rheumatology clinics are easily accessible—more specifically, in regions where university hospitals are located, like Skåne and Stockholm. On the other hand, patients with SSc in other regions may have had their disease undetected for a long time and been taken care of in other clinics due to the wide spectrum of SSc manifestations.

Our survival estimates differ from estimates from other parts of the world. In Brazil, 5- and 10-year all-cause survival was 90% and 84%, respectively, in a cohort of patients identified from a referral university, where patients had a mean age at disease onset of 42.6 years [27]. In Greece, 5- and 10-year survival of 83% and 70%, respectively, was reported in patients identified from referral centres and private rheumatologists [28]. Likewise, 5- and 10-year survival estimates in Hungary were 84% and 72.6%, respectively [29]. In contrast, 10-year survival in Japan was markedly higher, at 88% [30]. We observed high mortality in patients with SSc despite our study being conducted on a national level, unlike the majority of studies in the literature identifying patients from highly specialized referral centres. Even though our inclusion criteria required that at least one of the two listings was coded by a rheumatologist or an internist, we found no reason to believe that this requirement caused selection bias. As a rule, patients with SSc in Sweden are usually followed by rheumatologists.

An important factor to consider when comparing our results with other studies is that the start of follow-up differs considerably among studies. Starting follow-up from the debut of RP (which is considered the earliest event of SSc [31]) or other symptoms compared with starting from the date of diagnosis might lead to better survival estimates since patients are forced by the study design to survive until they are diagnosed with SSc in order to be included in the study population. Moreover, SSc is characterized by long diagnostic delay after the debut of RP, especially in women [32]. A French study reported 5- and 10-year survival of 86% and 72%, respectively, where the initial time point of follow-up was the debut of the first non-Raynaud's symptom [12]. A higher 5- and 10-year survival (98% and 95%, respectively) were reported in a cohort in China where patients with SSc were followed starting from the debut of the first SSc-related symptoms, including RP [33]. This might raise the question of whether included patients are in fact incident or prevalent. In a Canadian study, patients with incident SSc (defined as subjects recruited within 4 years of onset of the first non-Raynaud's symptom) had significantly lower survival than those with prevalent SSc (defined as all registered patients with SSc regardless of disease duration at study entry) [34], concluding that prevalent cohorts might underestimate mortality in SSc due to uncaptured early deaths. In our study, the start of follow-up was set at a second visit indicating SSc, but we do not know how long patients had had their symptoms before they came for their disease-defining visits. If we compare the estimates and generalize the findings from the Canadian study to our study, we might assume that patients in our cohort had even shorter disease duration when follow-up started. This could partially explain the relatively low survival estimates observed in our study.

HRs of the risk of death in patients with SSc compared with their comparators, both overall and when stratified by sex, were highest at the end of the first year of follow-up and exceeded 3.0. HRs decreased gradually under the follow-up period to reach 2.0 at the end of follow-up. However, this pattern was inconsistent in all age groups, most likely due to the low number of deaths, especially in the younger age groups.

Male sex was described to be associated with higher mortality in patients with SSc [35]. We observed worse survival associated with an SSc diagnosis in men compared with women, unadjusted for age, but with no statistical significance. A study in New Zealand also reported a non-statistically significant difference in survival between men and women [36], while data from Australia and the USA showed statistically significant worse survival in men [11, 37]. All those estimates were not adjusted for age either.

Increasing age has previously been associated with higher mortality in SSc [19]. In line with that, the all-cause mortality rate among patients with SSc in our study was lowest in those ages 18–49 years and increased with age to become highest in those $\geq$70 years at diagnosis (Table 2). In our cohort, patients 18–49 years of age at the start of follow-up had the highest contribution in total follow-up in person-years. However, we observed the lowest number of deaths during the study period in this age group. A similar observation was made in individuals ages 18–49 years from the comparators.

The reliability of the causes of death obtained from the CDR has been questioned and discussed. The agreement between the expected cause of death based on case summaries and the expected cause of death based on death certificates submitted to the CDR varied depending on age and some diagnostic groups [38]. Therefore our results on causes of death should be interpreted with caution. According to the underlying cause of death from the CDR, 35% of all deaths were related to SSc in our study, which is comparable to the above-mentioned Swedish study conducted in Skåne where 31% of deaths were definitely related to SSc [14]. Kuo *et al.* [39] and Strickland *et al.* [40] reported figures comparable to ours, where the cause of death was ascertained from death certificates assigned to the respective register in Taiwan and the UK. On the other hand, 55% of deaths among patients with SSc in Spain were related to SSc, where the cause of death was obtained from medical records or the patients' relatives [41].

We observed that patients with SSc not only have a higher mortality rate than their comparators, but also a higher rate of premature death. During the entire follow-up period, patients with SSc had a higher rate of premature death (defined as death before 70 years of age) than their comparators, which was highest at the end of the first year of follow-up. To the best of our knowledge, this issue has never been studied before in patients with SSc. This observation illustrates the impact SSc has on patients with respect to shortened life span.

A major strength of this study is its nationwide design, comprising an unselected cohort of patients with SSc and a group of matched comparators from the general population. Our stratification on age and sex allows physicians to provide their patients with more specific information with regard to prognosis based on sex and age at diagnosis. Our inclusion and exclusion criteria ensure a clear definition of incident SSc. Nonetheless, this study has limitations. One such limitation is that we had no access to medical charts and therefore could not verify the SSc diagnosis via chart review. However, requiring two visits, at least one in rheumatology or internal medicine, with SSc as the main diagnosis increases the probability that we only included patients who truly had SSc. We were also unable to investigate mortality in patients with SSc stratified by disease subset since there are no distinct codes unique for each subset of SSc (i.e. dcSSc and lcSSc). The pattern of autoantibodies, which is correlated to the subset and manifestation of SSc [31], could not be studied either, nor could the potential occurrence of overlap syndrome in our SSc cohort since we have no access to review the medical charts. Similarly, we were unable to explore the impact of serious organ-based manifestations such as PAH and ILD on survival.

In conclusion, this study demonstrates that the previously observed significantly higher mortality among patients with SSc is present also in Sweden today. Despite advances in understanding the disease and in diagnostic methods, survival is still severely impacted in Swedish patients diagnosed between 2004 and 2015.

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Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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