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# Early mortality in a multinational systemic sclerosis inception cohort

## Running title: Early mortality in incident scleroderma

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**Abstract**

**Objective:** To determine mortality and causes of death in a multinational inception systemic sclerosis (SSc) cohort.

**Methods:** We quantified mortality as Standardized Mortality Ratio (SMR), Years of Life Lost (YLL) and percentage mortality in the first decade of disease. The inception cohort was comprised of patients recruited within 4 years of disease onset. For comparison, we used a prevalent cohort, which included all patients irrespective of disease duration at recruitment. We determined a single primary cause of death (SSc or non-SSc related) using a standardized case report form, and evaluated predictors of mortality using multivariable Cox regression.

**Results:** In the inception cohort of 1070 patients, there were 140 (13%) deaths over a median (IQR) follow-up of 3.0(1.0-5.1) years, with a pooled SMR of 4.06 (95% CI 3.39–4.85), up to 22.4 YLL in women and 26.0 YLL in men, and mortality in the diffuse disease subtype of 24.2% at 8 years. In the prevalent cohort of 3218 patients, the pooled SMR was lower at 3.39 (95% CI 3.06-3.71), and percentage mortality in diffuse disease was lower (9.3% at 8 years). In the inception cohort, 62.1% of the primary causes of death were SSc related. Malignancy, sepsis, ischemic heart disease and cerebrovascular disease were the most common non-SSc related causes. Predictors of early mortality included male, diffuse disease, pulmonary arterial hypertension and renal crisis.

**Conclusion:** Early mortality in SSc is substantial and prevalent cohorts underestimate mortality in SSc by failing to capture early deaths, particularly in men and those with diffuse disease.

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**Keywords**: Systemic sclerosis; Mortality; Inception cohort

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Systemic sclerosis (SSc) is characterized by immunologic abnormalities, microvascular dysfunction and tissue fibrosis (1-4), with potential involvement of vital organs including the heart and lungs resulting in substantial morbidity and mortality. Earlier studies reported a 10-year survival as low as 50% (5), whereas more recent studies including the EUSTAR registry, have reported survival of 90% at 5 years and 84% at 10 years (6).

A major methodological concern in these studies of 'prevalent' cohorts including the EUSTAR registry is underestimation of mortality due to left truncation, which occurs when early deaths are not captured, and survivor bias, which occurs from over-sampling of individuals who have survived initial disease and are therefore likely to have better overall outcomes. Studies of 'inception' cohorts where subjects are recruited at the time of disease onset have the potential to overcome these sources of bias. However, to date, there have been no reported studies of mortality in SSc in inception cohorts. Furthermore, there is little published on risk factors for, and causes of death in incident SSc.

In order to address these issues, we undertook a large multinational study of SSc subjects recruited from Australia, Canada and Spain for the purpose of estimating mortality and determining causes of death in those recruited within 4 years of disease onset ('inception' cohort), and compared this with a 'prevalent' cohort of patients in whom no restrictions were placed on disease duration at recruitment.

## SUBJECTS AND METHODS

### Subjects and cohorts

Subjects from the Australian Scleroderma Cohort Study (ASCS), the Canadian Scleroderma

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Research Group (CSRG) cohort study and the Madrid University Hospital 12 de Octubre Scleroderma Cohort were included. The ASCS and CSRG are multi-center Australian and Canadian cohorts, respectively, while the Madrid cohort is a single center Spanish cohort.. Ethics approval was obtained from the human research ethics committees of each of the participating sites. Subjects in these cohorts fulfilled the 1980 American College of Rheumatology (ACR) classification criteria for SSc (7) and provided written informed consent to participate at recruitment. No specific treatment algorithm was used in the three cohorts and subjects were followed up at least once a year.

We included adult (≥18 years) SSc subjects who had at least one follow-up visit in the ASCS between January 2007 and March 2014, in the CSRG cohort between January 2005 and March 2014, and in the Spanish cohort between January 2000 and March 2014.

The inception cohort was defined as a subset of subjects recruited within 4 years of onset of their first non-Raynaud symptom attributable to SSc. This inception cohort is referred to as the '4-year inception' cohort below. The prevalent cohort included all registered subjects, regardless of disease duration at cohort entry. Accordingly, the prevalent cohort was inclusive of subjects in the inception cohort. However, we undertook extra analyses wherein we removed the inception patients from the prevalent cohort, referred as 'non-inception' cohort below. We also undertook extra analyses using the definition of subjects recruited within one year of first non-Raynaud symptom onset for the inception cohort, referred to as the '1-year inception' cohort below.

**Mortality data**

Survival status was ascertained up until the end of April 2014 based on the records in the



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databases and telephone tracing of patients in whom no data had been entered for ≥24 months in the database. The final status of loss to follow-up was defined as one where no data had been entered for ≥ 24 months with a failure to contact the patient despite at least two attempts.

***Calculation of standardized mortality ratio (SMR)***

The SMR was used to compare the mortality of subjects with SSc relative to that of the general population of Australia, Canada and Spain, respectively. SMR and its 95% confidence interval (CI) were calculated as follows (8,9):

$$SMR = \frac{O}{E}$$

$$95\%CI = \left(SMR - 1.96 \times \frac{\sqrt{O}}{E}, SMR + 1.96 \times \frac{\sqrt{O}}{E}\right)$$

where O is the observed number of deaths in the study population and E is the expected number of deaths. The expected number of deaths is the product of the total number of person-years contributed by the study population of each cohort multiplied by the mortality rate of the general population. The age- and sex-adjusted SMRs were calculated similarly; the expected number of deaths was stratified by 10-year age groups and sex. The mortality rates of the general population were obtained from Australian Bureau of Statistics, Statistics Canada and Spanish National Statistics Institute respectively, and the most recent available data at the time of data analysis were up to December 2012. We calculated the SMR for the three national cohorts from the respective cohort start dates (January 2007 for Australia, January 2005 for Canada, and January 2000 for Spain) to December 2012. The SMRs of inception and prevalent cohorts of each country were calculated and compared. Extra SMR analyses for the 'non-inception' cohort and the '1-year inception' cohort were undertaken, wherein the 'non-inception' cohort included only patients with greater than 4 years disease duration at recruitment.

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In relation to losses to follow up, sensitivity analyses were performed to re-calculate SMR assuming that all of these patients were (i) alive and (ii) dead at the end of the study.

***Calculation of Life expectancy (LE) and years of life lost (YLL)***

LE for the study population as well as the general population of each country was calculated according to sex by a period abridged life table as described by Chiang and Newell (10,11) using 5-year age intervals up to the oldest age interval of 85+ years. The calculations used the same data as for SMR calculations above. YLL was calculated as follows:

$$YLL = LE_g - LE_s$$

where LE_g is life expectancy at the time of birth in the general population and LE_s is life expectancy at the time of birth in the study population.

***Causes of death***

A standardized death case report form (CRF) (Supplementary File) was completed by the treating doctor for all deaths in every center. Cause of death was then verified against source documents. The causes of death were categorized as a single primary cause (either SSc or non-SSc related) and all other SSc organ involvement that contributed to death. Each SSc organ involvement was defined using standard uniform definition as presented in the Supplementary File (pages 3-4)..

**Statistical analysis**

Data are presented as mean ± standard deviation (SD) for continuous variables, median (interquartile range) for abnormally distributed continuous variables and numbers (percentages or proportions) for categorical variables. Baseline characteristics were compared between



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subjects who were alive and those who had died. Normally distributed continuous variables were compared using the student t-test with unequal variances, whereas abnormally distributed continuous variables were compared using Kruskall-Wallis and Mann-Whitney U tests. The differences in frequency were determined using chi-square and Fisher's exact tests.

Meta-analysis was performed to pool the incident and prevalent SMRs, respectively, of the three national cohorts, wherein the 'weight' of every cohort was calculated based on sample size. Pooling was conducted on the natural logarithm of SMR (the log-SMR) and statistical heterogeneity was assessed using the $I^2$ statistic. As there was heterogeneity, we used a random effects model to estimate a pooled log-SMR, which we then back-transformed.

Survival analysis in the first decade was performed using the Kaplan-Meier method with comparisons performed using the log-rank test. The primary endpoint was all-cause death or data censoring. The follow-up period ended in March 2014. The duration of follow-up was defined as the time from onset of the first non-Raynaud manifestation until death or last follow-up. Extra Kaplan-Meier survival analysis for the '1-year inception' cohort was also undertaken.

Univariable and multivariable Cox proportional hazards models were used to determine the variables associated with mortality. Age, gender, disease duration, disease subtypes, antibodies, organ involvements and comorbidities were included in the univariable Cox hazards model. Variables with significance in the univariable analysis were then included in the multivariable Cox hazards regression analysis wherein we ensured the proportionality of hazard assumption was valid.

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A two-tailed p value ≤0.05 was used to indicate statistically significant differences. All statistical analyses were performed using STATA 13.1 (Statacorp, College Station, TX, USA).

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## RESULTS

### Characteristics of subjects

There were a total of 1070 subjects (389 Australian, 484 Canadian and 197 Spanish) in the combined inception cohort ($inception_{combined}$). There were a total of 3218 subjects (1411 Australian, 1465 Canadian and 342 Spanish) in the combined prevalent cohort ($prevalent_{combined}$). Baseline demographics, clinical characteristics, organ involvements and major comorbidities in the three individual national cohorts and the combined cohorts were summarized in Table 1. There were 140 deaths (36 Australian, 67 Canadian and 37 Spanish) in the $inception_{combined}$ cohort, and 440 deaths (157 Australian, 213 Canadian and 70 Spanish) in the $prevalent_{combined}$ cohort. In the $inception_{combined}$ cohort, compared with subjects who were alive to the end of follow-up, those who died were significantly older at disease onset (58.8±13.5 *vs* 50.8±13.6, $p<0.0001$) and recruitment, and were more likely to be men (30.0% *vs* 15.4%, $p<0.0001$). More of those who died had diffuse disease (54.3% *vs* 38.1%, $p<0.0001$) and anti-RNA polymerase (anti-RNAP) III antibodies (36.5% *vs* 20.2%, $p=0.005$), while more of the subjects who were alive had limited disease (60.8% *vs* 42.9%, $p<0.0001$) and anti-centromere antibodies (36.8% *vs* 25.8%, $p=0.018$). In the $inception_{combined}$ cohort, subjects who died had more organ complications than living subjects including pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), myocardial involvement, pericardial effusion, and renal crisis while the frequency of gut involvement in the two groups was similar. There were also significant differences in frequency of comorbidities including ischemic heart disease (IHD) between the two groups (Supplementary Table 1).



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In the prevalent$_{combined}$ cohort, the characteristics of patients who had died and those who were alive at the end of the study were similar to the dead and alive patients in the inception$_{combined}$ cohort, respectively, with the notable exception that in the prevalent$_{combined}$ cohort, those who died also had more frequent digital ulcers, cerebrovascular disease (CVD) and malignancy (Supplementary Table 1).

**SMR, LE and YLL results**

Because of the time limitation of matched general population data, there were a total of 942 subjects (339 Australian, 420 Canadian and 183 Spanish) in the inception$_{combined}$ cohorts and 2872 subjects (1252 Australian, 1325 Canadian and 295 Spanish) in the prevalent$_{combined}$ cohorts included in SMR and YLL analyses. Among them, 113 subjects (42 Australian, 62 Canadian and 9 Spanish) in the inception$_{combined}$ cohorts and 430 subjects (196 Australian, 214 Canadian and 20 Spanish) in the prevalent$_{combined}$ cohorts were lost to follow-up.

***SMR***

The age and sex adjusted SMRs of inception cohorts from Australia (3.4 [95% CI 2.3-4.5]) and Canada (5.1[95% CI 4.0-6.2]) were higher than the corresponding prevalent cohorts, while the age and sex adjusted SMR in the inception cohort from Spain (3.2 [2.3–4.2]) was lower than the corresponding prevalent cohort. Regardless of cohort type (inception *vs* prevalent), the crude (non-age-adjusted) and age-adjusted SMRs for men were higher than for women, in all nations. In men, SMRs in inception cohorts were consistently higher than the prevalent cohorts, in all nations (Table 2).



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*Pooled SMR*

The pooled age and sex adjusted SMR of the three inception cohorts was higher at 4.06 [95% CI 3.39, 4.85; $I^2$= 76.4%; *p*(het)=0.014] than that of the three prevalent cohorts, which was 3.39 [95% CI 3.06, 3.71; $I^2$= 84.9%; *p*(het)=0.001] (Figure1).

In extra SMR analyses, the pooled SMR of the 'non-inception' cohorts was even lower at 3.20 [95% CI 2.86, 3.58; $I^2$=90.2%; *p*(het)<0.0001].

*SMR sensitivity analyses*

In SMR sensitivity analyses, assuming all losses to follow-up were (i) alive or (ii) dead, the pooled SMR for the inception cohorts was higher than the pooled SMR for the prevalent cohorts (Supplementary Table 2).

*Extra SMR analysis for '1-year inception' cohorts*

The age and sex adjusted SMRs of the '1-year inception' cohorts were even higher than the corresponding '4-year inception' cohort SMRs from all three nations, and were much higher than the corresponding prevalent cohort SMRs from Australia and Canada. While the age- and sex-adjusted SMR of the '1-year inception' cohort from Spain was still lower than the corresponding prevalent cohort, the crude SMR in either men or women was higher in all three national '1-year inception' cohorts than the corresponding prevalent cohorts (Supplementary Table 3).

***LE and YLL***

The LE at birth of the Australian general population from 2007 to 2012 was 84.4 years for women and 79.9 years for men. The LE of the Australian SSc study population within the same



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time period was 73.1 and 72.5 years in the inception and prevalent cohorts, respectively, for women, and 54.1 and 62.7 years in the inception and prevalent cohorts, respectively, for men. The YLLs were 11.3 years (inception) and 11.9 years (prevalent) for women, and 25.8 years (inception) and 17.2 years (prevalent) for men. The findings were similar for the Canadian and Spanish cohorts (Table 2).

**Survival analysis**

The overall survival in the first decade of disease in the inception$_{combined}$ cohort was lower than the prevalent$_{combined}$ cohort (99.0%, 94.8%, 88.9% and 81.3% *vs* 99.5%, 98.0%, 96.7% and 94.6%, at 1, 3, 5 and 8 years respectively, $p$<0.0001) (Figure 2) and the 'non-inception$_{combined}$' cohort (100%, 100%, 99.8% and 98.8%, at 1, 3, 5 and 8 years, respectively, $p$<0.0001) (Supplementary Figure 1), and this difference was greater for men (97.0%, 89.4%, 80.8% and 65.8% in inception *vs* 99.4%, 95.6%, 92.1% and 86.8% in prevalent, at 1, 3, 5 and 8 years, respectively) (Supplementary Figure 2) and for diffuse disease subtype (98.4%, 92.1%, 85.5% and 75.8% in inception *vs* 99.2%, 96.8%, 94.3% and 90.7% in prevalent, at 1, 3, 5 and 8 years respectively) (Supplementary Figure 3). Kaplan-Meier analysis revealed lower survival in men than women and in those with diffuse versus limited disease subtype, regardless of cohort type (inception$_{combined}$ *vs* prevalent$_{combined}$) ($p$<0.0001) (Supplementary Figures 2 and 3).

*Extra survival analysis for '1-year inception$_{combined}$' cohort*

The survival of 'the1-year inception$_{combined}$' cohort (95.2%, 85.2%, 78.0%, and 70.8% at 1, 3, 5 and 8 years, respectively) decreased further compared with the '4-year inception$_{combined}$' and prevalent cohort$_{combined}$. Kaplan-Meier analysis revealed the survival of the '1-year inception$_{combined}$' cohort was significantly lower than the corresponding 'non-inception$_{combined}$'



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cohort (100%, 99.4%, 98.1% and 96.1% at 1, 3, 5 and 8 years, respectively, $p<0.0001$) (Supplementary Figure 4).

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**Causes of death**

Among the 140 deaths in the inception$_{combined}$ cohort, 62.1% of the principal causes were SSc related and 24.2% were non-SSc related. We were unable to determine causes of death for 13.7% of patients who died. The most common (55.2%) principal cause of SSc-related death was heart-lung disease including PAH (25.3%), ILD (20.7%) and PAH combined with ILD (9.2%), while other SSc-related principal causes in descending order of frequency were myocardial involvement (14.9%), gut involvement (13.8%), renal crisis (13.8%), pericardial effusion (1.1%) and sepsis due to ischemic digit or decubitus ulcer (1.1%). Malignancy (38.2%), sepsis (14.7%), CVD (11.8%) and IHD (8.8%) were the most common non-SSc related primary causes. Regardless of the primary cause, SSc organ involvement contributed to death in 50.1% of cases (Table 3). The causes of death in the three individual national inception cohorts were similar (Supplementary Table 4 and 6).

Among the 440 deaths in the prevalent$_{combined}$ cohort, proportionally fewer of the principal causes of death were SSc-related (55.5%) and more were non-SSc related (33.6%), compared with the inception$_{combined}$ cohort. We were unable to determine causes of death for 10.9% of patients who died. The most common principal cause of SSc-related death was also heart-lung involvement, accounting for proportionally more deaths than in the inception$_{combined}$ cohort (70.9% *vs* 55.2%), including PAH (36.1% *vs* 25.3%), ILD (21.7% *vs* 20.7%), and PAH combined with ILD (13.1% *vs* 9.2%). Other major SSc-related principal causes were gut involvement (9.8%), myocardial involvement (9.0%) and renal crisis (7.0%), which were less frequent than in the inception$_{combined}$



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cohort. As with the inception$_{combined}$ cohort, malignancy (37.1%) was also the most common non-SSc related primary cause in the prevalent$_{combined}$ cohort, with IHD and sepsis accounting for 12.2% and 9.5% of the non-SSc related deaths, respectively (Table 3). The causes of death in the three individual national prevalent cohorts were similar (Supplementary Table 5 and 6).

**Predictors of mortality**

In the inception$_{combined}$ cohort, univariable hazards analyses showed that male gender, older age at disease onset, diffuse disease subtype, subjects with PAH, renal crisis, myocardial involvement and IHD/CVD carried a higher risk of death (all $p<0.05$), whereas subjects with longer disease duration at recruitment had a lower risk of death ($p=0.001$). Anti-centromere, anti-Scl70, ILD, gut involvement and malignancy were not found to be significant predictors of mortality (Supplementary Table 7). Multivariable hazards regression analysis showed that male gender, older age at disease onset, diffuses disease subtype, PAH and renal crisis were independent predictors of risk, and longer disease duration at recruitment was an independent protective factor. Among the risk factors, PAH had the highest hazard ratio (HR) of 2.35 (1.29-4.29) ($p=0.006$) (Table 4).

In the prevalent$_{combined}$ cohort, univariable hazards analyses showed that male gender, older age at disease onset, diffuse disease subtype, subjects with anti-Scl70 antibody, PAH, ILD, myocardial involvement, renal crisis, IHD/CVD and malignancy carried a higher risk of death, whereas subjects with longer disease duration at recruitment and anti-centromere antibody had a lower risk of death (Supplementary Table 7). Finally, multivariable hazards regression analysis showed that male gender, older age at disease onset, diffuse disease subtype, PAH and ILD were independent predictors of death, and longer disease duration at recruitment and anti-centromere



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antibody were independent protective factors. Among the risk factors, PAH had the highest HR of 2.50 (1.83-3.42) ($p$<0.0001) (Table 4).

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**DISCUSSION**

In this largest study to date of mortality and causes of death in an inception SSc cohort, we have reported a very high pooled SMR of 4.06 (95% CI 3.39 – 4.85), up to 22.4 YLL in women and 26.0 YLL in men, and mortality in men of 34.2% and in the diffuse disease subtype of 24.2% at 8 years. When we limited the definition of the inception cohort to those recruited within 1 year of disease onset, the SMR was even higher at 8.1 (4.3-12.0) for the Australian cohort, 9.4 (6.1-12.8) for the Canadian cohort, and 3.9 (2.4-5.4) for the Spanish cohort. These figures are much higher than those for the corresponding prevalent cohort and some previous studies (12-16), and highlight the phenomenon of survivor bias, which leads to underestimation of the true burden of mortality in SSc of prevalent cohorts. This bias arises in large part because SSc has a substantial burden of early mortality with many deaths occurring within five years of disease onset, particularly in men and in the diffuse disease subtype. The protective effect of longer disease duration at recruitment for mortality in our multivariable hazards regression analyses further highlights the burden of mortality in the early disease stage.

In our study, the pooled SMR (3.39) for the prevalent cohort is similar to that reported in a meta-analysis of 9 prevalent cohort studies from the 1960's to the 2000's (SMR=3.53) (17). Therefore, although the proportion of deaths attributable to each cause may have changed over time, SSc still carries a large burden of mortality.

Although there are several small mortality studies in incident SSc, wherein 5-year survival ranges



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from 68 to 88% (18-22), the major strength of the present study is the large sample size achieved by pooling three cohorts, enabling us to compare the mortality of a combined inception cohort with a combined prevalent cohort.

As hypothesized, our results showed that the age and sex adjusted SMRs of Australian and Canadian inception cohorts were higher than the respective prevalent cohorts. In Spanish patients, the age and sex adjusted SMR in the prevalent cohort was higher than the inception cohort, but this may be due to the overall short duration of disease at recruitment in both inception and prevalent Spanish cohorts and also the difference in the age structure of the Spanish cohort compared with the Australian and Canadian cohorts as demonstrated by crude SMRs (Supplementary Table 3).

The SMRs for men were higher than for women in each of the cohorts. The difference in mortality of men in inception versus prevalent cohorts was more substantial than for women, which suggests faster disease progression and more deaths in the early stages of disease in men. The hazards regression analysis also revealed that male gender was a strong independent predictor of death in the inception$_{combined}$ cohort. Our univariable comparisons showed more diffuse disease, myocardial involvement, renal crisis, digital ulcers, and IHD in men than women (Supplementary Table 8), and most of these factors were associated with risk of death according to our univariable hazards regression analyses. A recent published model by Domsic RT et al. also showed that male gender was an independent predictor for mortality in incident disease in patients with diffuse subtype SSc (23). Therefore, for male patients, especially for those with diffuse disease, close monitoring and active treatment is important (24,25).

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Organ involvement is another important factor associated with prognosis. In our inception$_{combined}$ cohort, SSc related causes of death accounted for 62.1% of all deaths, which was higher than that of the prevalent$_{combined}$ cohort (55.5%) and published EUSTAR data (55%) (6). Although the proportion of SSc related deaths has been reported to be decreasing over the past decades (26), our results suggest that SSc related causes remain the major contributors to early mortality in this disease.

PAH was the leading SSc related cause of death, accounting for 34.5% (25.3% from PAH only and 9.2% from combination of PAH and ILD) of deaths in the inception$_{combined}$ cohort. Although advanced PAH therapies have been used more widely in recent years, and the survival of SSc-associated PAH has improved compared with historical control data, the mortality of patients with PAH is still high (27,28). In our analyses, the 1, 3, 5 and 8-year survival of patients with PAH was 100%, 88.0%, 71.0% and 53.1% respectively in the inception$_{combined}$ cohort, which was significantly lower than patients without PAH (98.0%, 95.0%, 90.5%, and 83.1% respectively) (Supplementary Figure 5). In addition to being the leading cause of death, PAH was also identified as the strongest independent risk factor for mortality in both our inception$_{combined}$ and prevalent$_{combined}$ cohorts, as some other models showed (14,28). These results confirm that PAH is still the SSc related complication with the highest impact on survival.

ILD accounted for a higher proportion of deaths in the prevalent$_{combined}$ cohort than the inception$_{combined}$ cohort (34.8% *vs* 29.9% for principal cause, and 14.1% *vs* 11.4% for contributing cause of death). Hazards regression analyses showed that ILD was an independent risk factor for mortality in the prevalent$_{combined}$ cohort but not in the inception$_{combined}$ cohort. Collectively, these results point to ILD as a risk factor for poor long-term survival rather than early death.

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In our inception$_{combined}$ cohort, 24.2% of deaths were non-SSc related. Compared with the inception$_{combined}$ cohort, non-SSc related death accounted for a higher proportion of deaths in the prevalent$_{combined}$ cohort (33.6%), which reminds us that these long term complications become particularly important later in the disease course. IHD and CVD were major causes of non-SSc related deaths in both inception and prevalent cohorts. A study from the ASCS reported that after adjusting for age, sex and traditional risk factors for atherosclerosis, SSc patients were 3.2 times more likely to have coronary heart disease than general population controls (29), which suggests that the high prevalence of IHD may be partly related to SSc itself, rather than just traditional atherosclerosis risk factors. Furthermore, a study from Dave et al. has shown that SSc patients with IHD have higher in-hospital mortality than controls, SLE, and RA with IHD (30). Although not all studies have shown a similarly increased frequency of IHD and in-hospital mortality, there is a need for a better understanding, prevention and management of atherosclerosis in SSc patients, especially in patients with longer disease duration.

Malignancy was one of the most common non-SSc related causes of death in both the inception$_{combined}$ and prevalent$_{combined}$ cohorts. While the close temporal association between the onset of SSc and diagnosis of malignancy in patients who have anti-RNAPIII antibody has been reported (31), further studies are needed to determine whether there is an increased risk of malignancy in SSc overall and whether this is attributable to the disease itself, to immunosuppressive therapy, or other factors.

Sepsis was also one of the major non-SSc related causes of death, which is consistent with mortality data from the EUSTAR registry and several other studies (6,9,24). Sepsis accounted for


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a higher proportion of death in the inception$_{combined}$ cohort than the prevalent$_{combined}$ cohort (14.7% *vs* 9.5%), possibly due to more use of immunosuppressive therapy early in the disease course when there is greater inflammatory disease activity.

The present study has some limitations. It is possible that some patients who died within one year of recruitment, whose death was not known to the treating doctors, were incorrectly classified as 'alive' because the criterion we used for tracing was 'lost to follow-up for 2 or more years'. Despite considerable efforts to determine the cause of death in all subjects, we were unable to confirm this in 10.9% of the deceased. Furthermore, while most data regarding cause of death were collected prospectively in each cohort, in order to standardize results, our death CRF was completed retrospectively, albeit verified against source documents, for all patients who had died.

Another limitation is that we have refrained from including treatment in our analyses due to the potential bias in observational studies evaluating treatment effects and lack of accurate data on the indication for, and duration of treatment. Also, anti-RNAP III antibody was not included in the hazards regression model as this variable was not available for all patients. A large-scale prospective inception cohort study will more accurately quantify early mortality and evaluate the impact of treatment on mortality in SSc, through collection of all relevant data. Among other goals, the International Systemic Sclerosis Inception Cohort (INSYNC) study, founded in 2012, aims to quantify early mortality in SSc and the potential effect of treatment.

In conclusion, mortality in Australian, Canadian and Spanish SSc patients is substantial. Cardiopulmonary disease is still the most common cause of SSc-related death. Malignancy, sepsis

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and atherosclerotic disease are the most common non-SSc related causes. Our results suggest that prevalent cohorts underestimate mortality in SSc by failing to capture early deaths, particularly in men and those with diffuse disease. Collectively, these findings provide a compelling rationale for establishing a large prospective multinational inception cohort of patients with SSc to more accurately quantify early mortality in this disease.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Nikpour had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

YH, MN: study design, data collection, data analysis, interpretation of results, and preparation of manuscript.

MH (Hudson), MB, PC, WS, SP: study design, data collection, interpretation of results, and preparation of manuscript.

CR, ST, LC, BJ, MH (Huq): data collection, data analysis, interpretation of results, and preparation of manuscript.

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**Table 1** – Baseline characteristics

| | Australian Cohort | | Canadian Cohort | | Spanish Cohort | | Combined Cohort[§] | |
|---|---|---|---|---|---|---|---|---|
| | **Inception** | **Prevalent** | **Inception** | **Prevalent** | **Inception** | **Prevalent** | **Inception** | **Prevalent** |
| **Characteristic** | n=389 | n=1411 | n= 484 | n=1465 | n=197 | n=342 | n=1070 | n=3218 |
| **Gender - female** | 318(81.8) | 1277(87.0) | 391(80.8) | 1258(85.9) | 173(87.8) | 295(86.3) | 882(82.4) | 2780(86.4) |
| **Age at disease onset*** | 52.1±13.3 | 46.2±14.2 | 52.0±12.7 | 45.6±13.7 | 50.2±17.1 | 46.0 ±16.6 | 51.7±13.8 | 45.9±14.2 |
| **Age at recruitment**** | 54.1±13.2 | 57.6±12.5 | 53.5±12.6 | 55.5±12.2 | 51.4±17.1 | 52.3±15.7 | 53.3±13.8 | 56.1±12.8 |
| **Disease duration at recruitment**** | 1.8(0.9-2.8) | 10.9(4.1-21.7) | 1.9(1.1-2.9) | 7.4(2.9-15.3) | 1.1(0.4-2.4) | 3.3(0.9-9.6) | 1.7(0.9-2.8) | 7.0(2.7-15.2) |
| **Duration of follow-up**** | 2.9 (1.0-4.5) | 3.0(1.0-5.0) | 3.0(0.9-5.0) | 3.1 (1.0-5.2) | 4.4(1.3-8.2) | 4(1.4-7.7) | 3.0(1.0-5.1) | 3.1(1.0-5.2) |
| **Number of deaths** | 36 | 157 | 67 | 213 | 37 | 70 | 140 | 440 |
| **Age at death**** | 65.6±11.7 | 68.0±10.4 | 60.4±13.8 | 63.8±12.3 | 65.8±13.5 | 63.7±13.4 | 63.1±13.4 | 65.2±12.0 |
| **Disease duration at death**** | 3.5±1.9 | 16.0±12.1 | 4.4±2.6 | 14.1±10.5 | 4.7±3.7 | 11.2±9.8 | 4.2±2.8 | 14.3±11.0 |
| **Disease subtype** | | | | | | | | |
| Limited | 232(59.8) | 993(72.8) | 255(52.7)[†] | 856(59.1)[†] | 135(68.5) | 237(69.5) | 622(58.2) | 2086(66.1) |
| Diffuse | 156(40.2) | 371(27.2) | 213(44.0)[†] | 531(36.7)[†] | 62(31.5) | 104(30.5) | 431 (40.3) | 1006(31.9) |
| **Autoantibodies***** | | | | | | | | |
| Anti-Centromere | 136(37.4)/364[#] | 593(46.4)/1278[#] | 104(29.6)/352[#] | 401(34.5)/1164[#] | 83(31.5)/196[#] | 140(41.9)/334[#] | 323(35.4)/912[#] | 1134(40.9)/2776[#] |
| Anti-Scl70 | 67(18.7)/358[#] | 181(14.5)/1252[#] | 64(18.2)/352[#] | 177(15.2)/1164[#] | 53(27.0)/196[#] | 90(26.9)/335[#] | 184(20.3)/906[#] | 448(16.3)/2751[#] |
| Anti-RNAP III | 40(19.0)/211[#] | 89(12.8)/698[#] | 62(26.3)/236[#] | 143(17.63)/811[#] | - | - | 102(22.8)/447[#] | 232(15.4)/1509[#] |
| **SSc associated disease manifestations[∞]** | | | | | | | | |
| PAH | 34(8.7) | 152(10.8) | 17(3.5) | 61(4.16) | 7(3.6) | 27(7.9) | 58(5.4) | 240(7.5) |
| ILD | 96(24.7) | 311(22.0) | 110(22.7) | 301(20.6) | 58(29.4) | 107(31.6) | 264(24.7) | 719(22.4) |
| PAH and ILD | 10(2.6) | 48(3.4) | 3(0.6) | 19(1.3) | 2(1.0) | 11(3.2) | 15(1.4) | 78(2.4) |



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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Myocardial involvement | 25(6.4) | 96(6.8) | 7(1.5) | 69(4.7) | 13(6.8) | 19(5.7) | 45(4.2) | 184(5.7) |
| Pericardial effusion | 16(4.2) | 83(6.2) | 189(39.1) | 640(43.7) | 16(8.3) | 36(10.8) | 221(21.0) | 759(24.2) |
| Renal crisis | 15(3.9) | 37(2.6) | 35(7.2) | 72(4.9) | 12(6.1) | 19(5.6) | 62(5.8) | 128(4.0) |
| Gut involvement | 213(54.8) | 766(54.3) | 338(69.8) | 1139(77.8) | 133(67.5) | 252(73.9) | 684(63.9) | 2157(67.0) |
| Digit ulcer | 156(40.1) | 639(45.3) | 225(46.5) | 834(56.9) | 74(37.6) | 159(46.6) | 455(42.5) | 1632(50.7) |
| **Comorbidities∞** | | | | | | | | |
| IHD | 21(5.4) | 128(9.1) | 19(3.9) | 75(5.1) | - | - | 40(4.6) | 203(7.1) |
| CVD | 11(2.83) | 62(4.4) | 22(4.6) | 75(5.1) | - | - | 33(3.8) | 137(4.8) |
| Diabetes | 28(7.2) | 94(6.7) | 34(7.0) | 110(7.5) | 11(5.6) | 19(5.6) | 73(6.8) | 223(6.8) |
| Malignancy | 46(11.8) | 242(17.2) | 40(8.3) | 143(9.8) | 22(11.2) | 32(9.4) | 108(10.1) | 417(13.0) |

Data are presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for abnormally distributed continuous variables and numbers (percentages) for categorical variables.

* Years; disease onset defined as the date of first non-Raynaud's symptoms

** Years

*** For antibodies, data are presented as positive numbers (percentages)/total numbers of patients who have the antibody records

∞ Present ever during follow-up

§ The combination of the Australian, Canadian and Spanish inception or prevalent cohorts

† There were 3.3% and 4.2% missing data for the disease subtype variable in the Canadian inception and prevalent cohorts, respectively

# The second number is the 'denominator' and denotes the total number of patients in whom a particular autoantibody was tested

Abbreviations: RNAP III=RNA polymerase III; PAH=pulmonary arterial hypertension; ILD=interstitial lung disease; IHD=ischemic heart disease; CVD=cerebrovascular disease.



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**Table 2** – Measures of mortality (SMR, YLL and survival) in each of the Australian, Canadian and Spanish inception and prevalent cohorts

| | Australian cohort 01/2007-12/2012 | | Canadian cohort 01/2005-12/2012 | | Spanish cohort 01/2000-12/2012 | |
|---|---|---|---|---|---|---|
| | **Inception** n=339 | **Prevalent** n=1252 | **Inception** n=420 | **Prevalent** n=1325 | **Inception** n=183 | **Prevalent** n=295 |
| **Number of deaths** | 27 | 110 | 58 | 182 | 30 | 58 |
| **Number of loss to follow-up** | 42 | 196 | 62 | 214 | 9 | 20 |
| **Age and sex adjusted SMR (95%CI)** | **3.4(2.3-4.5)** | **2.8(2.4-3.3)** | **5.1(4.0-6.2)** | **3.8(3.3-4.2)** | **3.2(2.3-4.2)** | **4.2(3.3-5.0)** |
| Crude Women | 2.9 | 3.8 | 4.4 | 4.2 | 3.7 | 4.6 |
| Crude Men | 9.6 | 6.5 | 7.9 | 7.7 | 27.1 | 22.8 |
| Age adjusted Women | 2.4(1.2-3.5) | 2.6(2.1-3.1) | 4.4(3.1-5.7) | 3.4(2.9-4.0) | 2.8(1.7–3.9) | 3.8(2.7–4.9) |
| Age adjusted Men | 9.1(3.7-14.5) | 4.2(2.4-5.9) | 8.6(4.4-12.9) | 5.9(4.1-7.8) | 9.3(1.9–16.8) | 7.9(3.0–12.8) |
| **YLL (years)** | | | | | | |
| Women | 11.3 | 11.9 | 22.4 | 19.4 | 15.2 | 20.9 |
| Men | 25.8 | 17.2 | 19.2 | 16.7 | 26.0 | 23.9 |
| **% survival in the first decade of disease** | **84%** | **95%** | **80%** | **94%** | **77%** | **86%** |
| Women | 87% | 97% | 85% | 96% | 80% | 88% |
| Men | 74% | 88% | 65% | 88% | 50% | 75% |

Abbreviations: SMR=standardised mortality ratio; YLL=years of life lost

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**Table 3** – Causes of deaths in the inception$_{combined}$ and prevalent$_{combined}$ cohorts

| | Causes of SSc related death | | | | | Causesof Non-SSc related death | |
|---|---|---|---|---|---|---|---|
| | Inception$_{Combined}$§ | | Prevalent$_{Combined}$§ | | | Inception$_{Combined}$§ | Prevalent$_{Combined}$§ |
| | Principal cause | Contributing cause | Principal cause | Contributing cause | | Principal cause | Principal cause |
| | n=87 | n=140 | n=244 | n=440 | | n=34 | n=148 |
| **Organ system** | n(%) | n(%) | n(%) | n(%) | **Organ system** | n(%) | n(%) |
| **Heart and Lung** | 48(55.2) | 25(17.9) | 173(70.9) | 111(25.2) | **Malignancy** | 13(38.2) | 55(37.1) |
| PAH | 22(25.3) | 9(6.4) | 88(36.1) | 49(11.1) | **Sepsis** | 5(14.7) | 14(9.5) |
| ILD | 18(20.7) | 16(11.4) | 53(21.7) | 62(14.1) | **CVD** | 4(11.8) | 7(4.7) |
| PAH and ILD | 8(9.2) | - | 32(13.1) | - | **IHD** | 3(8.8) | 18(12.2) |
| **Myocardial involvement** | 13(14.9) | 8(5.7) | 22(9.0) | 15(3.4) | **Liver disease** | 2(5.9) | 3(2.0) |
| **Gut involvement** | 12(13.8) | 16(11.4) | 24(9.8) | 44(10.0) | **Post operative complications** | 1(2.9) | 9(6.1) |
| **Renal crisis** | 12(13.8) | 6(4.3) | 17(7.0) | 10(2.3) | **Trauma** | 1(2.9) | 8(5.4) |
| **Pericardial effusion** | 1(1.1) | 4(2.9) | 4(1.6) | 11(2.5) | **Sudden death** | 1(2.9) | 4(2.7) |
| **Sepsis** | 1(1.1) | 11(7.9) | 4(1.6) | 41(9.3) | **Renal failure** | 1(2.9) | 1(0.7) |
| | | | | | **Asthma/COPD/ emphysema** | 0(0) | 6(4.1) |
| | | | | | **Peripheral vascular disease** | 0(0) | 2(1.4) |
| | | | | | **Pulmonary embolism** | 0(0) | 1(0.7) |
| | | | | | **Arrhythmia** | 0(0) | 1(0.7) |
| | | | | | **Drug related** | 0(0) | 1(0.7) |
| | | | | | **Other** | 3(8.8) | 18(12.1) |

§ The combination of the Australian, Canadian and Spanish inception or prevalent cohorts

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**Table 4** – Multivariable predictors of mortality in the inception$_{combined}$ and prevalent$_{combined}$ cohorts

| | Inception$_{combined}$ cohort§ | | | Prevalent$_{combined}$ cohort§ | | |
|---|---|---|---|---|---|---|
| **Variable** | Hazard ratio | 95% CI | p | Hazard ratio | 95% CI | p |
| **Gender-Male** | 2.28 | 1.42-3.65 | 0.001 | 1.72 | 1.27-2.33 | 0.001 |
| **Age at disease onset*** | 1.05 | 1.03-1.07 | 0.000 | 1.05 | 1.04-1.06 | <0.0001 |
| **Diffuse subtype** | 1.83 | 1.14-2.92 | 0.002 | 1.40 | 1.07-1.83 | 0.013 |
| **Disease duration at recruitment**** | 0.59 | 0.47-0.74 | <0.0001 | 0.71 | 0.68-0.74 | <0.0001 |
| **Anti-Centromere antibody** | - | - | - | 0.71 | 0.53-0.94 | 0.019 |
| **Anti-Scl70 antibody#** | - | - | - | 0.95 | 0.67-1.35 | 0.774 |
| **PAH** | 2.35 | 1.29-4.29 | 0.006 | 2.50 | 1.83-3.42 | <0.0001 |
| **ILD#** | - | - | - | 1.31 | 1.01-1.70 | 0.040 |
| **Myocardial involvement** | 0.99 | 0.44-2.23 | 0.977 | 1.18 | 0.83-1.69 | 0.363 |
| **Renal crisis** | 1.87 | 1.01-3.48 | 0.048 | 1.33 | 0.86-2.07 | 0.205 |
| **IHD and/or CVD** | 1.54 | 0.86-2.76 | 0.145 | 1.28 | 0.96-1.72 | 0.094 |
| **Malignancy#** | - | - | - | 0.97 | 0.72-1.30 | 0.832 |

*Years; Disease onset defined as the date of first non-Raynaud's symptoms

** Years

§ The combination of the Australian, Canadian and Spanish inception or prevalent cohorts

#Anti-Scl70 antibody, ILD and Malignancy were not included in multivariable model in the inception cohort because they were not statistically significant in univariable hazards regression analyses.

Abbreviations: PAH=pulmonary arterial hypertension; ILD=interstitial lung disease; IHD=ischemic heart disease; CVD=cerebrovascular disease.

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**FIGURE LEGENDS**

**Figure 1** Pooled SMR of Australian, Canadian and Spanish inception and prevalent cohorts. Each square represents an individual SMR estimate, the size of the square being proportional to the weight given to the SMR. The lines represent the 95% CI for the point estimate in each cohort. The diamond represents the pooled SMR. The pooled SMR of inception cohorts was higher than that of prevalent cohorts.

**Figure 2** Kaplan-Meier analysis of overall survival in the first decade following disease onset in the $\text{inception}_{\text{combined}}$ and $\text{prevalent}_{\text{combined}}$ cohorts. The survival of the $\text{inception}_{\text{combined}}$ cohort was significantly lower than the $\text{prevalent}_{\text{combined}}$ cohort (99.0%, 94.8%, 88.9% and 81.3% *vs* 99.5%, 98.0%, 96.7% and 94.6%, at 1, 3, 5 and 8 years respectively, $p<0.0001$, log rank).

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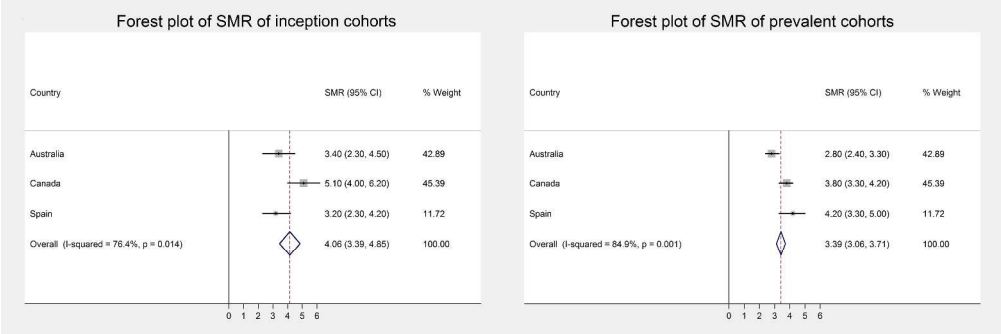



Figure 1 Pooled SMR of Australian, Canadian and Spanish inception and prevalent cohorts. Each square represents an individual SMR estimate, the size of the square being proportional to the weight given to the SMR. The lines represent the 95% CI for the point estimate in each cohort. The diamond represents the pooled SMR. The pooled SMR of inception cohorts was higher than that of prevalent cohorts.

659x220mm (300 x 300 DPI)

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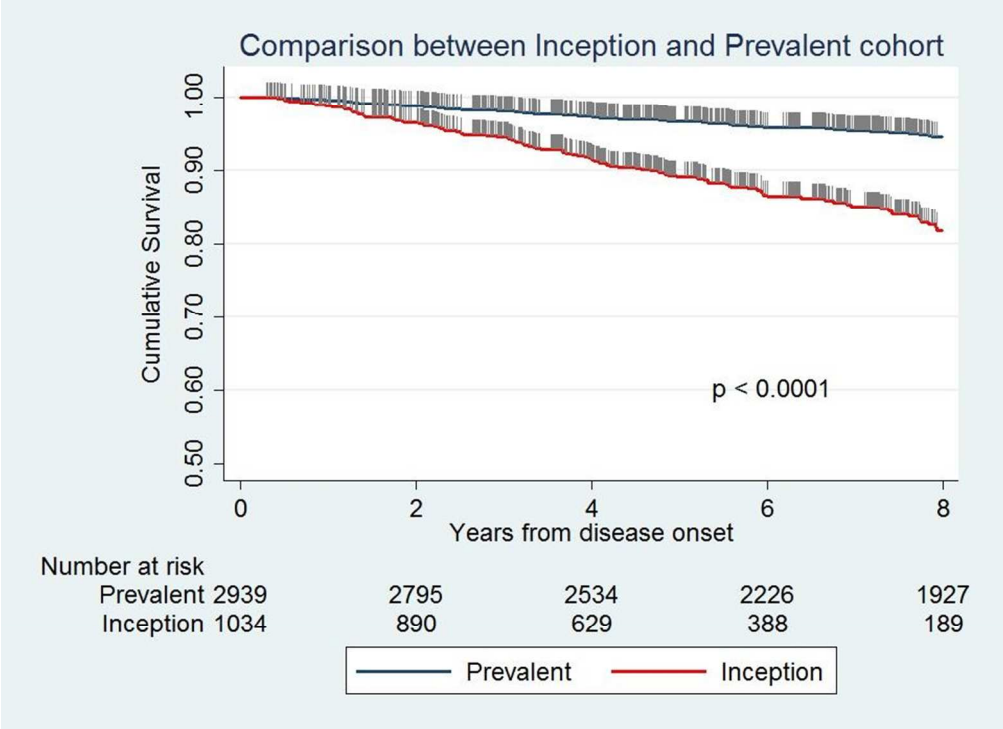



Figure 2 Kaplan-Meier analysis of overall survival in the first decade following disease onset in the inceptioncombined and prevalentcombined cohorts. The survival of the inceptioncombined cohort was significantly lower than the prevalentcombined cohort (99.0%, 94.8%, 88.9% and 81.3% vs 99.5%, 98.0%, 96.7% and 94.6%, at 1, 3, 5 and 8 years respectively, p<0.0001, log rank).

81x59mm (300 x 300 DPI)

Accep



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# Supplementary File

## Death Case Report Form

Patient ID:

Patient initials:

Site:

Reporting doctor's name:

In your opinion is the ***primary*** cause of death in this patient (tick one box only):

1. **Scleroderma-related** ☐

If yes, proceed to Form A and complete Form A ONLY

2. **Non-scleroderma related** ☐

If yes, proceed to Form B and complete Form B ONLY

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**Form A – Primary cause of death scleroderma related**

**What is the primary scleroderma-related organ involvement causing death (tick one box only)?**

Please note we are interested in the organ involvement that led to death rather than the inevitable terminal event. For example, if a patient with severe pulmonary arterial hypertension (PAH) dies of an arrhythmia, the primary scleroderma-related organ involvement causing death is PAH.

Pulmonary arterial hypertension (PAH) ☐

Interstitial lung disease (ILD) ☐

Combined PAH and ILD ☐

Scleroderma myocardial involvement ☐

(Note: this does not include ischemic heart disease)

Scleroderma pericardial involvement with effusion and tamponade ☐

Renal failure due to scleroderma renal crisis ☐

Scleroderma gut involvement ☐

If yes, please specify how this caused death (for example aspiration pneumonia, profound malnutrition due to malabsorption, etc.):

……

Sepsis due to ischemic digit or decubitus ulcer ☐

If yes, please briefly describe events leading to death:



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……

**Please list other <u>scleroderma-related</u> organ involvement that you believe contributed to death (you may tick as many boxes as required).**

*Example*: If a patient with severe gut involvement and significant weight loss/malabsorption dies following presentation with an ischemic foot, the primary cause of death may be sepsis related to ischemic digit, but scleroderma gut involvement would be recorded here.

Pulmonary arterial hypertension (PAH) ☐

Interstitial lung disease (ILD) ☐

Scleroderma myocardial involvement ☐

(Note: this does not include ischemic heart disease)

Scleroderma pericardial involvement with effusion and tamponade ☐

Renal failure following scleroderma renal crisis ☐

Scleroderma gut involvement ☐

Sepsis due to ischemic digit ☐

Sepsis due to scleroderma skin ulcers ☐

Lung infection with underlying PAH and/or ILD ☐

……

**Definitions for scleroderma related organ involvement**

PAH was defined on right heart catheterization with a mean pulmonary artery pressure ≥ 25 mmHg and a pulmonary arterial wedge pressure ≤ 15 mmHg. ILD was defined as the presence of characteristic fibrotic changes on high-resolution computed tomography chest. Scleroderma myocardial involvement was defined on endomyocardial biopsy or as the presence of conduction

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deficits, arrhythmia, right ventricular or left ventricular dysfunction in the absence of other causes. Pericardial effusion was confirmed on echocardiogram. Scleroderma renal crisis was defined as a combination of any two of the following three criteria, which included new onset severe hypertension (≥ 180 mmHg systolic and/or ≥ 100 mmHg diastolic) without an alternate aetiology, microangiopathic hemolytic anemia or rising creatinine. Scleroderma gut involvement was defined as one or more of oesophageal stricture, gastroparesis, gastric antral vascular ectasia (GAVE), bowel dysmotility and pseudo-obstruction. Oesophageal stricture and GAVE were defined on endoscopy. Bowel dysmotility was defined based on barium and nuclear medicine studies, antibiotic response or characteristic symptoms. Pseudo-obstruction was defined as the presence of clinical features suggestive of intestinal obstruction in the absence of an anatomic lesion.

……

**What <u>non-scleroderma</u> comorbidities do you believe contributed to death?**

Ischemic heart disease ☐

Cerebrovascular disease ☐

Peripheral vascular disease ☐

Deep vein thrombosis ☐

Pulmonary embolism ☐

Renal failure <u>not</u> due to scleroderma renal crisis ☐

Diabetes ☐

Asthma or Chronic Obstructive Airways Disease / emphysema ☐

Sepsis ☐

Please state site:

……..

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Gastrointestinal bleeding ☐

Please specify:

……..

Liver disease ☐

Please state type:

……..

Malignancy ☐

Please state type and site:

……..

Drug-related ☐

Please state drug and reaction:

……..

Metabolic Disturbance ☐

Please specify:

……..

Post-operative complication: ☐

……

Trauma ☐

Please state event:

……..

Other ☐

Please state:

……..

If you have additional comments in relation to death and its causes, please add these here:

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……

……

**End of Form A**

If you complete form A do not complete form B for this patient

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**Form B – Primary cause of death non-scleroderma related**

**What is the primary non-scleroderma related cause of death (tick one box only)?**

Please note we are interested in the cause of death rather than the inevitable terminal event. For example, if a patient with acute myocardial infarction dies due to ventricular tachycardia, the cause of death is 'ischemic heart disease' rather than 'arrhythmia' or cardiac arrest.

Ischemic heart disease ☐

Sudden death (presumed cardiac, without known heart disease) ☐

Arrhythmias ☐

Cerebrovascular disease ☐

Peripheral vascular disease ☐

Pulmonary embolism ☐

Renal failure not due to scleroderma renal crisis ☐

Metabolic disturbance ☐

Please specify:

……..

Asthma or Chronic Obstructive Airways Disease / emphysema ☐

Sepsis ☐

Please state site:

……..

Liver disease ☐

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Please state type:

……..

Gastrointestinal bleeding ☐

Please specify:

……..

Malignancy ☐

Please state type and site:

……..

Drug-related ☐

Please state drug and reaction:

……..

Post-operative complication ☐

Please specify:

……..

Trauma ☐

Please state event:

……..

Suicide ☐

Please specify:

……..

Other ☐

Please state:

……..

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**Please list <u>scleroderma-related</u> organ involvement that you believe contributed to death (you may tick as many boxes as required).**

Example: If a patient with moderate but stable ILD develops acute myocardial infarction and dies within days due to cardio-respiratory failure, the primary cause of death is ischemic heart disease but interstitial lung disease would be recorded here.

Pulmonary arterial hypertension (PAH) ☐

Interstitial lung disease (ILD) ☐

Scleroderma myocardial involvement ☐

(Note: this does not include ischemic heart disease)

Scleroderma pericardial involvement with effusion and tamponade ☐

Renal failure due to scleroderma renal crisis ☐

Scleroderma gut involvement ☐

Sepsis due to ischemic digit ☐

Sepsis due to scleroderma skin ulcers ☐

Lung infection with underlying PAH and/or ILD ☐

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**What other <u>non-scleroderma comorbidities</u> do you believe contributed to death (you may tick as many boxes as required)?**

Ischemic heart disease ☐

Cerebrovascular disease ☐

Peripheral vascular disease ☐

Deep vein thrombosis ☐

Pulmonary embolism ☐

Renal failure <u>not</u> due to scleroderma renal crisis ☐

Diabetes ☐

Asthma or Chronic Obstructive Airways Disease / emphysema ☐

Sepsis ☐

Please state site:

……..

Liver disease ☐

Please state type:

……..

Malignancy ☐

Please state type and site:

……..

Drug-related ☐

Please state drug and reaction:

……..

Metabolic Disturbance ☐

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Please specify:

……..

Post-operative complication: ☐

……

Trauma ☐

Please state event:

……..

Other ☐

Please state:

……

If you have additional comments in relation to death and its causes, please add there here:

……

……

**End of Form B**

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**Supplementary Table 1** – Univariable comparison of characteristics of subjects who died and those alive in the inception$_{combined}$ and prevalent$_{combined}$ cohorts

| Characteristic | Inception$_{combined}$ cohort§ n=1070 | | | Prevalent$_{combined}$ cohort§ n=3218 | | |
|---|---|---|---|---|---|---|
| | Alive n=725 | Dead n=140 | *P* | Alive n=2044 | Dead n=440 | *P* |
| **Gender - male** | 112(15.4) | 42(30.0) | <0.0001 | 247(12.1) | 92(20.9) | <0.0001 |
| **Age at disease onset*** | 50.8±13.6 | 58.8±13.5 | <0.0001 | 45.7±14.0 | 51.0±14.9 | <0.0001 |
| **Age at recruitment**** | 52.4±13.6 | 58.8±13.5 | <0.0001 | 55.5±12.6 | 62.1±12.1 | <0.0001 |
| **Disease duration at recruitment**** | 1.8(0.9-2.8) | 1.3(0.6-2.4) | 0.004 | 6.4(2.4-14.5) | 9.2(2.7-17.0) | 0.016 |
| **Duration of follow-up**** | 3.9(1.6-5.8) | 1.5(0.3-3.7) | <0.0001 | 4.0(1.9-5.9) | 2.1(0.9-3.9) | <0.0001 |
| **Disease subtype** | | | | | | |
| Limited | 440(60.8) | 60(42.9) | <0.0001 | 1376(69.0) | 252(57.8) | <0.0001 |
| Diffuse | 276(38.1) | 76(54.3) | <0.0001 | 585(29.3) | 177(40.6) | <0.0001 |
| **Autoantibodies** | | | | | | |
| Anti-Centromere | 229(36.8) | 33(25.8) | 0.018 | 773(43.8) | 140(34.2) | <0.0001 |
| Anti-Scl70 | 134(21.7) | 29(22.8) | 0.775 | 280(16.0) | 76(18.9) | 0.168 |
| Anti-RNAP III | 58(20.2) | 23(36.5) | 0.005 | 127(14.3) | 48(20.5) | 0.019 |
| **Disease manifestations***** | | | | | | |
| PAH | 32(4.4) | 21(15.0) | <0.0001 | 129(6.3) | 88(20) | <0.0001 |
| ILD | 18(25.2) | 47(33.6) | 0.041 | 448(21.9) | 153(34.8) | <0.0001 |
| PAH and ILD | 8(1.1) | 7(5.0) | 0.003 | 40(2.0) | 31(7.0) | <0.0001 |
| Myocardial involvement | 24(3.3) | 16(11.4) | <0.0001 | 97(4.8) | 54(12.3) | <0.0001 |
| Pericardial effusion | 133(18.7) | 40(28.8) | 0.007 | 446(22.6) | 136(31.6) | <0.0001 |
| Renal crisis | 32(4.4) | 23(16.4) | <0.0001 | 69(3.4) | 38(8.6) | <0.0001 |
| Gut involvement | 463(63.9) | 92(65.7) | 0.676 | 1348(66.0) | 309(70.2) | 0.086 |
| Digit ulcer | 307(42.3) | 65(46.4) | 0.372 | 985(48.2) | 250(56.8) | 0.001 |
| **Comorbidities** | | | | | | |
| IHD | 23(4.0) | 12(11.7) | 0.005 | 116(6.41) | 52(14.1) | <0.0001 |
| CVD | 21(3.6) | 7(6.8) | 0.109 | 79(4.4) | 31(8.4) | <0.0001 |
| Diabetes | 49(6.8) | 17(12.1) | 0.020 | 148(7.2) | 39(8.9) | 0.157 |
| Malignancy | 74(10.2) | 20(14.3) | 0.156 | 279(13.7) | 87(19.8) | 0.001 |

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Data are presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for abnormally distributed continuous variables and numbers (percentages) for categorical variables.

* Years; disease onset defined as the date of first non-Raynaud's symptom

** Years

*** Present ever during follow-up

§ The combination of the Australian, Canadian and Spanish inception or prevalent cohorts

Abbreviations: RNAP III=RNA polymerase III; PAH=pulmonary arterial hypertension; ILD=interstitial lung disease; IHD=ischemic heart disease; CVD=cerebrovascular disease

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**Supplementary Table 2** -- Sensitivity analyses for SMR assuming all losses to follow up are (i) alive and (ii) dead

*

| | Australian cohort 01/2007-12/2012 | | Canadian cohort 01/2005-12/2012 | | Spanish cohort 01/2000-12/2012 | | Pooled SMR (95%CI) | |
|---|---|---|---|---|---|---|---|---|
| | Inception n=339 | Prevalent n=1252 | Inception n=420 | Prevalent n=1325 | Inception n=183 | Prevalent n=295 | Inception | Prevalent |
| **Number of deaths** | 27 | 110 | 58 | 182 | 30 | 58 | | |
| **Number of loss to follow-up** | 42 | 196 | 62 | 214 | 9 | 20 | | |
| **Age and sex adjusted SMR (95% CI) assuming all loss alive** | **3.0(2.0–3.9)** | **2.4(2.0–2.8)** | **3.3(2.6-4.1)** | **2.6(2.3-2.9)** | **2.3(1.6–3.0)** | **3.2(2.5–3.9)** | **3.0 (2.5-3.5)** | **2.6(2.3-2.8)** |
| Age adjusted Women | 2.1(1.1–3.1) | 2.3(1.8–2.7) | 2.9(2.0-3.8) | 2.4(2.0-2.8) | 2.0(1.2–2.8) | 3.0(2.1–3.8) | | |
| Age adjusted Men | 7.2(2.9–11.4) | 3.4(2.0–4.8) | 5.4(2.8-8.1) | 3.8(2.6-5.0) | 5.1(1.0–9.3) | 4.8(1.8–7.8) | | |
| **Age and sex adjusted SMR (95% CI) assuming all loss dead** | **7.3(5.6–8.9)** | **6.3(5.6–6.9)** | **10.4(8.8-12.0)** | **8.2(7.5-8.9)** | **4.4(3.3–5.5)** | **5.6(4.6–6.6)** | **7.0(4.3-11.5)** | **6.7(5.3-8.4)** |
| Age adjusted Women | 6.5(4.6–8.4) | 6.2(5.4–7.0) | 9.5(7.6-11.5) | 7.7(6.8-8.5) | 3.8(2.5–5.1) | 5.0(3.8–6.3) | | |
| Age adjusted Men | 11.6(5.5-17.7) | 6.6(4.4–8.8) | 15.1(9.5-20.7) | 11.4(8.8-14.0) | 12.4(3.8–21.1) | 11.1(5.3–16.9) | | |



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**Supplementary Table 3** – SMR in each of the Australian, Canadian and Spanish 1-year inception and the prevalent cohorts

| | Australian cohort 01/2007-12/2012 | | Canadian cohort 01/2005-12/2012 | | Spanish cohort 01/2000-12/2012 | |
|---|---|---|---|---|---|---|
| | **1y-Inception** n=110 | **Prevalent** n=1252 | **1y-Inception** n=112 | **Prevalent** n=1325 | **1y-Inception** n=91 | **Prevalent** n=295 |
| **Number of deaths** | 14 | 110 | 23 | 182 | 19 | 58 |
| **Number of loss to follow-up** | 9 | 196 | 17 | 214 | 3 | 20 |
| **Age and sex adjusted SMR(95%CI)** | **8.1(4.3–12.0)** | **2.8(2.4-3.3)** | **9.4(6.1-12.8)** | **3.8(3.3-4.2)** | **3.9(2.4–5.4)** | **4.2(3.3–5.0)** |
| Crude Women | 8.1 | 3.8 | 9.4 | 4.2 | 5.4 | 4.6 |
| Crude Men | 12.3 | 6.5 | 15.4 | 7.7 | 40.8 | 22.8 |
| Age-adjusted Women | 7.6(2.9–12.2) | 2.6(2.1–3.1) | 8.5(4.5-12.5) | 3.4(2.9-4.0) | 3.5(1.7–5.3) | 3.8(2.7–4.9) |
| Age-adjusted Men | 10.1(0.2–20.7) | 4.2(2.4–5.9) | 13.7(2.7-24.7) | 5.9(4.1-7.8) | 7.1(0.1–14.1) | 7.9(3.0–12.8) |

Abbreviations: SMR=standardised mortality ratio

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**Supplementary Table 4** - Causes of SSc related deaths in each of the inception cohorts

| | Australian Cohort | | Canadian Cohort | | Spanish Cohort | |
|---|---|---|---|---|---|---|
| | **Principal Cause** | **Contributing cause** | **Principal Cause** | **Contributing cause** | **Principal cause** | **Contributing cause** |
| | n=23 | n=36 | n=40 | n=67 | n=24 | n=37 |
| **Organ system** | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) |
| **Heart and Lung** | 16(69.6) | 6(16.7) | 20(50.0) | 11(16.4) | 12(50.0) | 8(21.6) |
| PAH | 7(30.4) | 6(16.7) | 12(30.0) | 2(3.0) | 3(12.5) | 1(2.7) |
| ILD | 5(21.7) | 0(0) | 5(12.5) | 9(13.4) | 8(33.3) | 7(18.9) |
| PAH and ILD | 4(17.4) | - | 3(7.5) | - | 1(4.2) | - |
| **Gut involvement** | 3(13.0) | 2(5.6) | 6(15.0) | 6(9.0) | 3(12.5) | 8(21.6) |
| **Sepsis** | 0(0) | 4(11.1) | 0(0) | 2(3.0) | 1(4.2) | 5(13.5) |
| **Myocardial involvement** | 1(4.3) | 0(0) | 6(15.0) | 3(4.5) | 6(25.0) | 5(13.5) |
| **Renal crisis** | 3(13.0) | 0(0) | 7(17.5) | 4(6.0) | 2(8.3) | 2(5.4) |
| **Pericardial effusion** | 0(0) | 0(0) | 1(2.5) | 2(3.0) | 0(0) | 2(5.4) |

Abbreviations: PAH= pulmonary arterial hypertension; ILD= interstitial lung disease.

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**Supplementary Table 5** - Causes of SSc-related deaths in each of the prevalent cohorts

| | Australian Cohort | | Canadian Cohort | | Spanish Cohort | |
|---|---|---|---|---|---|---|
| | **Principal** | **Contributing** | **Principal** | **Contributing** | **Principal** | **Contributing** |
| **Organ system** | **Cause** n=84 n(%) | **cause** n=157 n(%) | **Cause** n=109 n(%) | **cause** n=213 n(%) | **cause** n=51 n(%) | **cause** n=70 n(%) |
| **Heart and Lung** | 72(85.7) | 44(28.0) | 67(61.5) | 55(25.8) | 34(66.7) | 12(17.1) |
| PAH | 40(47.6) | 24(15.3) | 34(31.2) | 22(10.3) | 14(27.5) | 3(4.3) |
| ILD | 18(21.4) | 20(12.7) | 22(20.2) | 33(15.5) | 13(25.5) | 9(12.9) |
| PAH and ILD | 14(16.7) | - | 11(10.1) | - | 7(13.7) | - |
| **Gut involvement** | 5(6.0) | 14(8.9) | 15(13.8) | 17(8.0) | 4(7.8) | 13(18.6) |
| **Sepsis** | 1(1.2) | 22(14.0) | 2(1.8) | 6(2.8) | 1(2.0) | 13(18.6) |
| **Myocardial involvement** | 2(2.4) | 0(0) | 10(9.2) | 7(3.3) | 10(19.6) | 8(11.4) |
| **Pericardial effusion** | 0(0) | 3(1.9) | 4(3.7) | 5(2.3) | 0(0) | 3(4.3) |
| **Renal crisis** | 4(4.8) | 1(0.6) | 11(10.1) | 6(2.7) | 2(3.9) | 3(4.3) |

Abbreviations: PAH= pulmonary arterial hypertension; ILD= interstitial lung disease.

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**Supplementary Table 6** - Causes of non-SSc related deaths in each of the inception and prevalent cohorts

| | Inception Cohorts | | | Prevalent Cohorts | | |
|---|---|---|---|---|---|---|
| | **Australian Cohort** | **Canadian Cohort** | **Spanish Cohort** | **Australian Cohort** | **Canadian Cohort** | **Spanish Cohort** |
| **Organ system** | n=10<br>n (%) | n=11<br>n (%) | n=13<br>n (%) | n=60<br>n (%) | n=69<br>n (%) | n=19<br>n (%) |
| **Malignancy** | 5(50.0) | 4(36.4) | 4(30.8) | 27(45.0) | 23(33.3) | 5(26.3) |
| **Sepsis** | 1(10.0) | 0(0) | 4(30.8) | 4(6.7) | 5(7.2) | 5(26.3) |
| **CVD** | 2(20.0) | 2(18.2) | 0(0) | 5(8.3) | 2(2.9) | 0(0) |
| **IHD** | 1(10.0) | 1(9.1) | 1(7.7) | 8(13.3) | 9(13.0) | 1(5.3) |
| **Liver disease** | 0(0) | 2(18.2) | 0(0) | 0(0) | 2(2.9) | 1(5.3) |
| **Post operative complications** | 1(10.0) | 0(0) | 0(0) | 3(5.0) | 4(5.8) | 2(10.5) |
| **Trauma** | 0(0) | 0(0) | 1(7.7) | 3(5.0) | 3(4.3) | 2(10.6) |
| **Sudden death** | 0(0) | 0(0) | 1(7.7) | 1(1.7) | 2(2.9) | 1(5.3) |
| **Renal failure** | 0(0) | 1(9.1) | 0(0) | 0(0) | 1(1.4) | 0(0) |
| **Asthma/COPD/emphysema** | 0(0) | 0(0) | 0(0) | 2(3.3) | 4(5.8) | 0(0) |
| **Peripheral vascular disease** | 0(0) | 0(0) | 0(0) | 0(0) | 2(2.9) | 0(0) |
| **Pulmonary embolism** | 0(0) | 0(0) | 0(0) | 0(0) | 1(1.4) | 0(0) |
| **Arrhythmia** | 0(0) | 0(0) | 0(0) | 0(0) | 1(1.4) | 0(0) |
| **Drug related** | 0(0) | 0(0) | 0(0) | 0(0) | 1(1.4) | 0(0) |
| **Other** | 0(0) | 1(9.1) | 2(15.4) | 7(11.7) | 9(13.0) | 2(10.5) |

Abbreviations: CVD=cerebrovascular disease**;** IHD=ischemic heart disease; COPD=chronic obstructive airways disease.

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**Supplementary Table 7** – univariable predictors of mortality in the inception$_{combined}$ and prevalent$_{combined}$ cohorts

| | Inception$_{combined}$ cohort§ | | | Prevalent$_{combined}$ cohort§ | | |
|---|---|---|---|---|---|---|
| **Variable** | Hazard ratio | 95% CI | p | Hazard ratio | 95% CI | p |
| **Gender-Male** | 2.41 | 1.66-3.49 | 0.000 | 2.30 | 1.80-2.92 | 0.000 |
| **Age at disease onset*** | 1.05 | 1.03-1.06 | 0.000 | 1.08 | 1.07-1.09 | 0.000 |
| **Diffuse subtype** | 1.99 | 1.41-2.81 | 0.000 | 1.90 | 1.56-2.33 | 0.000 |
| **Disease duration at recruitment**** | 0.80 | 0.70-0.91 | 0.001 | 0.75 | 0.73-0.77 | 0.000 |
| **Anti-Centromere antibody** | 0.72 | 0.41-1.03 | 0.053 | 0.67 | 0.54-0.82 | 0.000 |
| **Anti-Scl70 antibody** | 1.08 | 0.71-1.64 | 0.727 | 1.50 | 1.16-1.95 | 0.002 |
| **PAH** | 3.18 | 1.98-5.11 | 0.000 | 2.19 | 1.71-2.80 | 0.000 |
| **ILD** | 1.34 | 0.94-1.92 | 0.108 | 1.79 | 1.46-2.19 | 0.000 |
| **Myocardial involvement** | 2.83 | 1.66-4.85 | 0.000 | 1.94 | 1.44-2.60 | 0.000 |
| **Pericardial effusion** | 1.17 | 0.80-1.71 | 0.409 | 1.18 | 0.95-1.45 | 0.131 |
| **Renal crisis** | 3.06 | 1.92-4.88 | 0.000 | 2.67 | 1.90-3.76 | 0.000 |
| **Gut involvement** | 0.79 | 0.55-1.23 | 0.191 | 0.95 | 0.76-1.18 | 0.632 |
| **Digital ulcer** | 0.87 | 0.62-1.22 | 0.427 | 0.94 | 0.77-1.14 | 0.508 |
| **IHD and/or CVD** | 2.10 | 1.24-3.56 | 0.006 | 1.55 | 1.19-2.02 | 0.001 |
| **Diabetes** | 1.01 | 1.00-1.02 | 0.051 | 1.00 | 1.00-1.01 | 0.054 |
| **Malignancy** | 1.37 | 0.85-2.20 | 0.195 | 1.29 | 1.01-1.64 | 0.038 |

*Years; Disease onset defined as the date of first non-Raynaud's symptoms

** Years

§ The combination of the Australian, Canadian and Spanish inception or prevalent cohorts

Abbreviations: PAH=pulmonary arterial hypertension; ILD=interstitial lung disease; IHD=ischemic heart disease; CVD=cerebrovascular disease..

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**Supplementary Table 8** - Univariable comparison of characteristics of male and female subjects in the inception$_{combined}$ and prevalent$_{combined}$ cohorts

| Characteristic | Inception$_{combined}$ cohort$^{\$}$ n=1070 | | *p* | Prevalent$_{combined}$ cohort$^{\$}$ n=3218 | | *p* |
|---|---|---|---|---|---|---|
| | **Male** n=188 | **Female** n=882 | | **Male** n=438 | **Female** n=2780 | |
| **Age at disease onset*** | 51.6±13.8 | 51.7±13.9 | 0.945 | 47.0±14.2 | 45.8±14.2 | 0.095 |
| **Age at recruitment**** | 53.4±13.7 | 53.3±13.8 | 0.971 | 55.2±13.3 | 56.1±12.8 | 0.132 |
| **Disease duration at recruitment**** | 1.7(0.8-2.8) | 1.7(0.9-2.8) | 0.709 | 5.1(2.0-12.2) | 7.6(2.8-15.5) | <0.0001 |
| **Duration of follow-up**** | 2.2(0.7-4.1) | 3.1(1.0-5.3) | 0.0005 | 2.5(0.7-4.4) | 3.2(1.0-5.3) | <0.0001 |
| **Disease subtype** | | | | | | |
| Limited | 70 (37.2) | 552(62.7) | <0.0001 | 202(47.0) | 1884(69.2) | <0.0001 |
| Diffuse | 115(61.2) | 316(35.9) | <0.0001 | 224(52.1) | 782(28.7) | <0.0001 |
| **Auto antibodies** | | | | | | |
| Anti-Centromere | 32(21.1) | 291(38.3) | <0.0001 | 77(20.8) | 1057(44.0) | <0.0001 |
| Anti-Scl70 | 40(26.0) | 144(19.2) | 0.055 | 87(23.5) | 361(15.2) | <0.0001 |
| Anti-RNAP III | 16(21.6) | 86(23.1) | 0.788 | 38(19.1) | 194(14.8) | 0.118 |
| **Disease manifestations***** | | | | | | |
| PAH | 9(4.8) | 49(5.6) | 0.673 | 28(6.4) | 212(7.6) | 0.361 |
| ILD | 55(29.3) | 209(23.7) | 0.108 | 120(27.5) | 599(21.6) | 0.005 |
| PAH and ILD | 1(0.5) | 12(1.4) | 0.346 | 8(1.8) | 59(2.1) | 0.687 |
| Myocardial involvement | 16(8.5) | 29(3.3) | 0.001 | 42(9.6) | 142(5.1) | <0.0001 |
| Pericardial effusion | 46(24.6) | 175(20.2) | 0.181 | 100(23.6) | 659(24.3) | 0.766 |
| Renal crisis | 19(10.1) | 43(4.9) | 0.005 | 26(6.0) | 102(3.7) | 0.023 |
| Gut involvement | 113(60.1) | 571(64.7) | 0.230 | 278(63.6) | 1879(67.6) | 0.100 |
| Digit ulcer | 106(56.4) | 349(39.6) | <0.0001 | 269(61.6) | 1363(49.0) | <0.0001 |
| **Comorbidities** | | | | | | |
| IHD | 16(9.8) | 24(3.4) | 0.001 | 46(11.8) | 157(6.3) | <0.0001 |
| CVD | 3(1.8) | 30(4.2) | 0.323 | 13(3.3) | 124(5.0) | 0.353 |
| Diabetes | 16(8.5) | 57(6.5) | 0.486 | 36(8.2) | 187(6.7) | 0.449 |
| Malignancy | 18(9.6) | 90(10.2) | 0.795 | 58(13.2) | 359(12.9) | 0.849 |

Data are presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for abnormally distributed continuous variables and numbers (percentages) for categorical variables.

*years; disease onset defined as the date of first non-Raynaud's symptom

** years



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*** present ever during follow-up

§ The combination of the Australian, Canadian and Spanish incident or prevalent cohorts

Abbreviations: RNAP III=RNA polymerase III; PAH=pulmonary arterial hypertension; ILD=interstitial lung disease; IHD=ischemic heart disease; CVD=cerebrovascular disease.

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**FIGURE LEGEND**

**Supplementary Figure 1 -** Kaplan-Meier analysis of survival in the inception$_{combined}$ and 'non-inception$_{combined}$' cohorts. The survival of the inception$_{combined}$ cohort was significantly lower than the 'non-inception$_{combined}$' cohort (99.0%, 94.8%, 88.9% and 81.3% *vs* 100%, 100%, 99.8% and 98.8%, at 1, 3, 5 and 8 years, respectively) ($p$<0.0001, log rank).

**Supplementary Figure 2 -** Kaplan-Meier analysis of survival in the inception$_{combined}$ and prevalent$_{combined}$ cohorts according to gender. Male subjects had significantly shorter survival than female subjects both in the inception and prevalent cohorts ($p$<0.0001, log rank). However, this difference was more substantial in the inception cohort than in the prevalent cohort. The 1, 3, 5, and 8-year survival in the inception$_{combined}$ cohort was 97.0%, 89.4%, 80.8% and 65.8% respectively in male *vs* 98.1%, 95.0%, 91.5% and 85.0% respectively in female subjects, while in the prevalent$_{combined}$ cohort the 1, 3, 5 and 8-year survival was 99.4%, 95.6%, 92.1% and 86.8% respectively in male *vs* 99.8%, 98.7%, 97.3% and 95.8% respectively in female subjects.

**Supplementary Figure 3 -** Kaplan-Meier analysis of survival in the inception$_{combined}$ and prevalent$_{combined}$ cohorts according to disease subtype. The survival of patients with diffuse disease was significantly shorter than for those with limited disease, both in the inception and prevalent cohorts ($p$<0.0001, log rank). However, this difference was more substantial in the inception cohort than the prevalent cohort. The 1, 3, 5 and 8-year survival in the inception$_{combined}$ cohort was 98.4%, 92.1%, 85.5% and 75.8% respectively in the diffuse subtype *vs* 99.0%, 92.1%, 91.6%, and 85.8% respectively in the limited subtype of disease, whereas in the prevalent$_{combined}$ cohort 1, 3, 5 and 8-



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year survival was 99.2%, 96.8%, 94.3% and 90.7% respectively in the diffuse subtype *vs* 99.7%, 98.9%, 97.8% and 96.3% respectively in the limited subtype of SSc.

**Supplementary Figure 4 -** Kaplan-Meier analysis of survival in the 1-year inception$_{combined}$ and the corresponding 'non-inception$_{combined}$' cohorts. The survival of the 1-year inception$_{combined}$ cohort was significantly lower than the 'non-inception$_{combined}$' cohort (95.2%, 85.2%, 78.0% and 70.8% *vs* 100%, 99.4%, 98.1% and 96.1%, at 1, 3, 5 and 8 years, respectively) ($p$<0.0001, log rank).

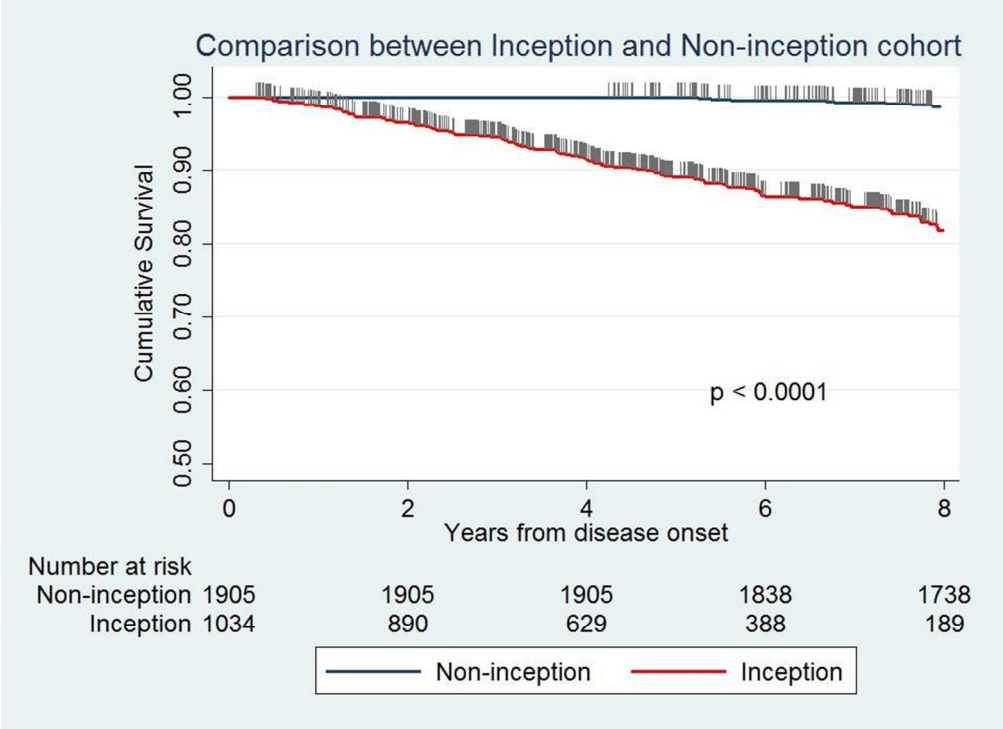
**Supplementary Figure 5 -** Kaplan-Meier analysis of survival in the inception$_{combined}$ and prevalent$_{combined}$ cohorts according to PAH. Subjects with PAH had significantly shorter survival than subjects without PAH both in the inception and prevalent cohorts. However, the magnitude of this difference was more substantial in the inception cohort than the prevalent cohort. The 1, 3,5 and 8-year survival in the inception$_{combined}$ cohort was 100%, 88.0% 71.0% and 53.1% respectively in the PAH group *vs* 98.0%, 95.0%, 90.5% and 83.1% respectively in the non-PAH group (P<0.0001, log rank), and in the prevalent$_{combined}$ cohort, 1, 3, 5 and 8-year survival was 100%, 96.8%, 93.9% and 90.1% respectively in the PAH group *vs* 99.6%, 98.2%, 97.0% and 95.0% respectively in the non-PAH group (P=0.001, log rank).

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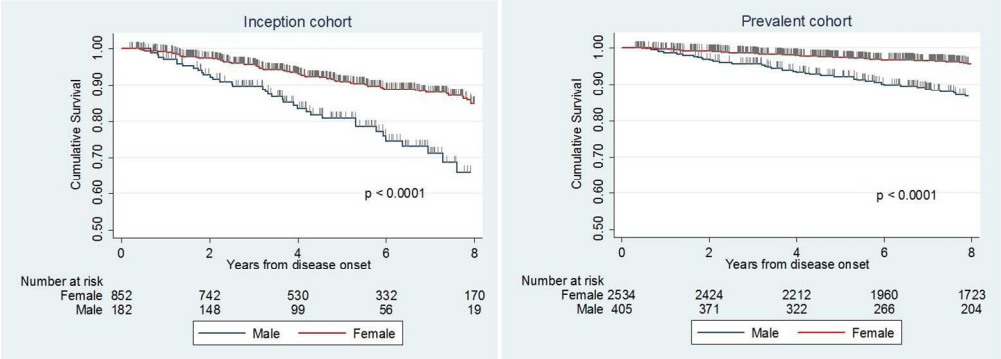

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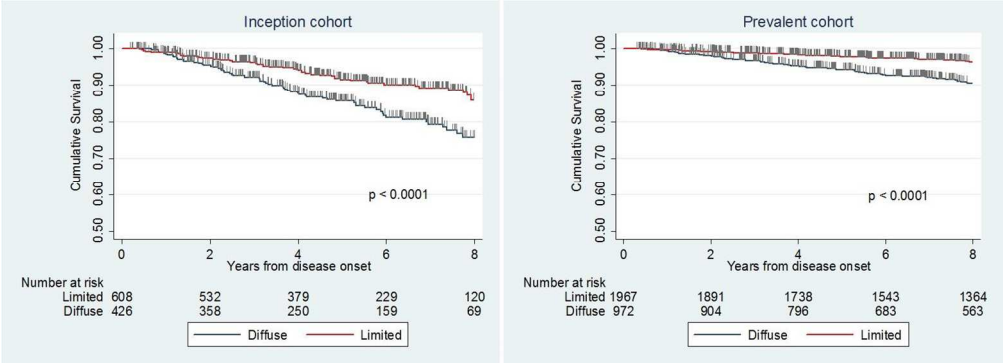

Supplementary Figure 2 - Kaplan-Meier analysis of survival in the inceptioncombined and prevalentcombined cohorts according to gender. Male subjects had significantly shorter survival than female subjects both in the inception and prevalent cohorts (p<0.0001, log rank). However, this difference was more substantial in the inception cohort than in the prevalent cohort. The 1, 3, 5, and 8-year survival in the inceptioncombined cohort was 97.0%, 89.4%, 80.8% and 65.8% respectively in male vs 98.1%, 95.0%, 91.5% and 85.0% respectively in female subjects, while in the prevalentcombined cohort the 1, 3, 5 and 8-year survival was 99.4%, 95.6%, 92.1% and 87% respectively in male vs 99.8%, 98.7%, 97.3% and 95.8% respectively in female subjects.

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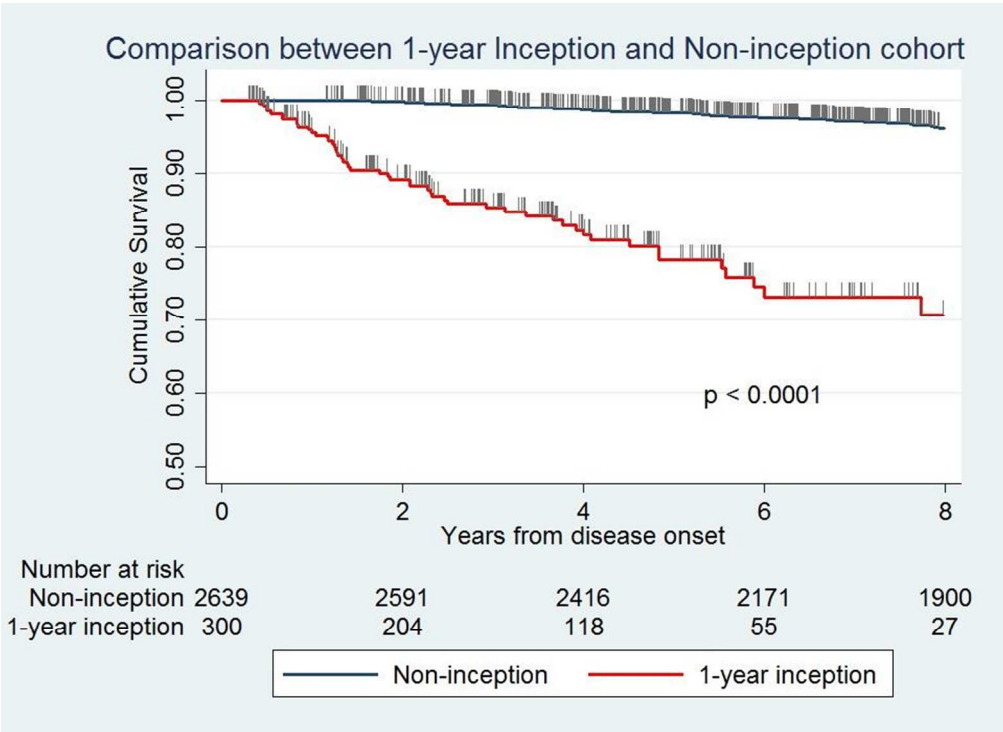

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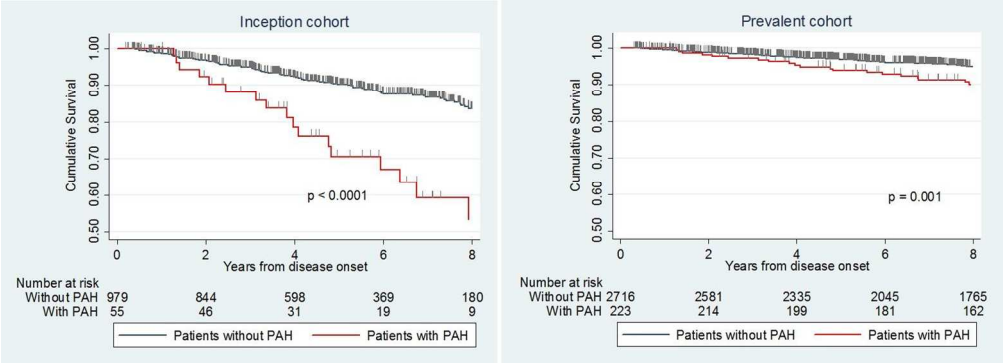

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Supplementary Figure 5 - Kaplan-Meier analysis of survival in the inceptioncombined and prevalentcombined cohorts according to PAH. Subjects with PAH had significantly shorter survival than subjects without PAH both in the inception and prevalent cohorts. However, the magnitude of this difference was more substantial in the inception cohort than the prevalent cohort. The 1, 3,5 and 8-year survival in the inceptioncombined cohort was 100%, 88.0% 71.0% and 53.1% respectively in the PAH group vs 98.0%, 95.0%, 90.5% and 83.1% respectively in the non-PAH group (P<0.0001, log rank), and in the prevalentcombined cohort, 1, 3, 5 and 8-year survival was 100%, 96.8%, 93.9% and 90.1% respectively in the PAH group vs 99.6%, 98.2%, 97.0% and 95.0% respectively in the non-PAH group (P=0.001, log rank).

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