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Early Mortality in a Multinational Systemic Sclerosis Inception Cohort

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

Methods. **We quantified mortality as standardized mortality ratio (SMR), years of life lost, and percentage mortality in the first decade of disease. The inception cohort comprised subjects recruited within 4 years of disease onset. For comparison, we used a prevalent cohort, which included all subjects irrespective of disease duration at recruitment. We determined a single primary cause of death (SSc related or non–SSc related) using a standardized case report form, and we evaluated predictors of mortality using multivariable Cox regression.**

Results. **In the inception cohort of 1,070 subjects, there were 140 deaths (13%) over a median follow-up of 3.0 years (interquartile range 1.0–5.1 years), with a pooled SMR of 4.06 (95% confidence interval [95% CI] 3.39–4.85), up to 22.4 years of life lost in women and up to 26.0 years of life lost in men, and mortality in the diffuse disease subtype of 24.2% at 8 years. In the prevalent cohort of 3,218 subjects, the pooled SMR was lower at 3.39 (95% CI 3.06–3.71). In the inception cohort, 62.1% of the primary causes of death were SSc related. Malignancy, sepsis, cerebrovascular disease, and ischemic heart disease were the most common non–SSc-related causes of death. Predictors of early mortality included male sex, older age at disease onset, diffuse disease subtype, 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.**

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 showed a 10-year survival rate as low as 50% (5), while more recent studies, including a study from the European League Against Rheumatism Scleroderma Trial and Research (EUSTAR) registry (6), have shown survival rates of 90% at 5 years and 84% at 10 years.

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Two major methodologic concerns in these studies of "prevalent" cohorts, including the EUSTAR registry, are underestimation of mortality due to left truncation, which occurs when early deaths are not captured, and survivor bias, which occurs from oversampling of individuals who have survived initial disease and who are therefore likely to have better overall outcomes. Studies of "inception" cohorts, in which 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, little has been reported on risk factors for, and causes of death in, incident SSc.

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

SUBJECTS AND METHODS

Subjects and cohorts. We included subjects from the Australian Scleroderma Cohort Study (ASCS), the Canadian Scleroderma Research Group (CSRG) cohort study, and the Madrid University Hospital 12 de Octubre Scleroderma Cohort Study. The Australian Scleroderma Cohort and CSRG cohort are multicenter cohorts, while the Madrid cohort is a single-center cohort. A list of investigators in the CSRG and the Australian Scleroderma Interest Group is provided in Appendix A.

Ethics approval was obtained from the human research ethics committees of each of the participating sites. Subjects in these cohorts fulfilled the American College of Rheumatology preliminary criteria for SSc (7) and provided written informed consent to participate at recruitment. No specific treatment algorithm was used in the 3 cohorts, and subjects were followed up at least once a year. We included adult (age ≥18 years) SSc subjects who had at least 1 follow-up visit in the ASCS between January 2007 and March 2014, in the CSRG cohort study between January 2005 and March 2014, and in the Madrid 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's phenomenon symptom attributable to SSc. This inception cohort is referred to hereafter as the "4-year inception cohort." The prevalent cohort included all registered subjects, regardless of disease duration at cohort entry. Accordingly, the prevalent cohort included all subjects in the inception cohort. However, we undertook extra analyses in which we removed inception cohort subjects from the prevalent cohort; the remaining subjects in the prevalent cohort are referred to hereafter as the "noninception cohort." We also undertook extra analyses using the definition of subjects recruited for the inception cohort within 1 year of onset of the first non–Raynaud's phenomenon symptom, referred to hereafter as the "1-year inception cohort."

Mortality data. Survival status was ascertained up until the end of April 2014 based on the records in the databases and telephone tracing of subjects for whom no data had been entered in the database for ≥24 months. A subject was determined to be lost to follow-up when no data had been entered for ≥24 months and at least 2 attempts to contact the subject had failed.

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

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

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

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 in a similar manner; the expected number of deaths was stratified by 10-year age groups and sex. The mortality rates of the general population were obtained from the Australian Bureau of Statistics, Statistics Canada, and the Spanish National Statistics Institute, and the most recent available data at the time of data analysis were from December 2012. We calculated the SMRs of the 3 national cohorts from the start date of each cohort (January 2007 for Australia, January 2005 for Canada, and January 2000 for Spain) to December 2012. The SMRs of the inception and prevalent cohorts of each country were calculated and compared. We undertook extra SMR analyses for the noninception cohort and the 1-year inception cohort; in these analyses, the noninception cohort included only subjects with disease duration of >4 years at recruitment. In relation to subjects lost to follow-up, we performed 2 sensitivity analyses to recalculate SMR, one of which assumed that all such subjects were alive at the end of the study and the other of which assumed that all such subjects were dead at the end of the study.

Calculation of life expectancy and years of life lost. Life expectancy for the study population as well as for the general population of each country was calculated according to sex using a period-abridged life table as described by Chiang (10) and Newell (11) with 5-year age intervals up to the interval of ≥85 years. The calculations used the same data as those used above for SMR calculations. Years of life lost was calculated as life expectancy at the time of birth in the general population minus life expectancy at the time of birth in the study population.

Causes of death. A standardized death case report form (see Supplementary Forms, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract) 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 related or non–SSc related) and all other SSc organ involvement that contributed to death. SSc involvement of each organ was defined using standard uniform

Table 1. Baseline characteristics of the subjects in the study*

Characteristic	Australian cohort		Canadian cohort		Spanish cohort		Combined cohorts	
	Inception (n = 389)	Prevalent (n = 1,411)	Inception (n = 484)	Prevalent (n = 1,465)	Inception (n = 197)	Prevalent (n = 342)	Inception (n = 1,070)	Prevalent (n = 3,218)
Female sex, no. (%)	318 (81.7)	1,277 (90.5)	391 (80.8)	1,258 (85.9)	173 (87.8)	295 (86.3)	882 (82.4)	2,780 (86.4)
Age at disease onset, years†	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, years	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, median (IQR) years	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, median (IQR) years	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, years	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, years	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, no. (%)								
Limited	232 (59.6)	993 (70.4)	255 (52.7)‡	856 (58.4)‡	135 (68.5)	237 (69.3)	622 (58.1)	2,086 (64.8)
Diffuse	156 (40.1)	371 (26.3)	213 (44.0)‡	531 (36.2)‡	62 (42.3)	104 (30.4)	431 (40.3)	1,006 (31.3)
Autoantibodies, no./total no. (%)§								
Anticentromere	136/364 (37.4)	593/1,278 (46.4)	104/352 (29.6)	401/1,164 (34.5)	83/196 (42.3)	140/334 (41.9)	323/912 (35.4)	1,134/2,776 (40.9)
Anti–Scl-70	67/358 (18.7)	181/1,252 (14.5)	64/352 (18.2)	177/1,164 (15.2)	53/196 (27.0)	90/335 (26.9)	184/906 (20.3)	448/2,751 (16.3)
Anti–RNAP III	40/211 (19.0)	89/698 (12.8)	62/236 (26.3)	143/811 (17.6)	–	–	102/447 (22.8)	232/1,509 (15.4)
SSc-associated disease manifestations, no. (%)¶								
PAH	34 (8.7)	152 (10.8)	17 (3.5)	61 (4.2)	7 (3.6)	27 (7.9)	58 (5.4)	240 (7.5)
ILD	96 (24.7)	311 (22.0)	110 (22.7)	301 (20.5)	58 (29.4)	107 (31.3)	264 (24.7)	719 (22.3)
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)
Myocardial involvement	25 (6.4)	96 (6.8)	7 (1.4)	69 (4.7)	13 (6.6)	19 (5.6)	45 (4.2)	184 (5.7)
Pericardial effusion	16 (4.1)	83 (5.9)	189 (39.0)	640 (43.7)	16 (8.1)	36 (10.5)	221 (20.7)	759 (23.6)
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)	1,139 (77.7)	133 (67.5)	252 (73.7)	684 (63.9)	2,157 (67.0)
Digital ulcer	156 (40.1)	639 (45.3)	225 (46.5)	834 (56.9)	74 (37.6)	159 (46.5)	455 (42.5)	1,632 (50.7)
Comorbidities, no. (%)¶								
IHD	21 (5.4)	128 (9.1)	19 (3.9)	75 (5.1)	–	–	40 (3.7)	203 (6.3)
CVD	11 (2.8)	62 (4.4)	22 (4.5)	75 (5.1)	–	–	33 (3.1)	137 (4.3)
Diabetes mellitus	28 (7.2)	94 (6.7)	34 (7.0)	110 (7.5)	11 (5.6)	19 (5.6)	73 (6.8)	223 (6.9)
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)

* Except where indicated otherwise, values are the mean ± SD. IQR = interquartile range; anti–RNAP III = anti–RNA polymerase III; SSc = systemic sclerosis; PAH = pulmonary arterial hypertension; ILD = interstitial lung disease; IHD = ischemic heart disease; CVD = cerebrovascular disease.
† Defined as the date of the first non–Raynaud's phenomenon symptom.
‡ Disease subtype data were missing for 3.3% of subjects in the Canadian inception cohort and for 4.2% of subjects in the Canadian prevalent cohort.
§ Total number represents all subjects for whom autoantibody records were available and who were tested for the presence of a particular autoantibody.
¶ Ever present during follow-up.

definitions (see Supplementary Forms, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract).

Statistical analysis. Data are presented as the mean ± SD for continuous variables, the median and interquartile range for non-normally distributed continuous variables, and the number and percent for categorical variables. Baseline characteristics were compared between subjects who were alive and those who had died. Normally distributed continuous variables were compared using Student's *t*-test with unequal variances, and non-normally distributed continuous variables were compared using Kruskal-Wallis and Mann-Whitney U tests. Differences in frequency were determined using a chi-square test and Fisher's exact test.

Meta-analysis was performed to pool the incident and prevalent SMRs of the 3 national cohorts; the "weight" of each cohort was calculated based on sample size. Pooling was conducted on the ln(SMR), and statistical heterogeneity was assessed using the I^2 statistic. Since there was heterogeneity, we used a random-effects model to estimate a pooled ln(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 end point was death from any cause 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's phenomenon symptom until death or the last follow-up visit. We also performed extra Kaplan-Meier survival analysis for the 1-year inception cohort.

Univariable and multivariable Cox proportional hazards models were used to determine variables associated with mortality. Age, sex, disease duration, disease subtypes, antibody positivity, organ involvement, and comorbidities were included in the univariable Cox proportional hazards model. Variables with significance in the univariable analysis were then included in the multivariable Cox proportional hazards regression analysis, in which we ensured that the assumption of proportional hazards was valid.

Two-tailed *P* values less than or equal to 0.05 were considered significant. All statistical analyses were performed using Stata statistical software, release 13.1 (StataCorp).

RESULTS

Characteristics of the subjects. A total of 1,070 subjects (389 Australian, 484 Canadian, and 197 Spanish) were in the combined inception cohort. A total of 3,218 subjects (1,411 Australian, 1,465 Canadian, and 342 Spanish) were in the combined prevalent cohort. Baseline demographics, clinical characteristics, organ involvement, and major comorbidities in the 3 individual national cohorts and the combined cohorts are summarized in Table 1.

There were 140 deaths (36 Australian, 67 Canadian, and 37 Spanish) in the combined inception cohort and 440 deaths (157 Australian, 213 Canadian, and 70 Spanish) in the combined prevalent cohort. In the combined inception cohort, compared with subjects who were alive until the end of follow-up, those who died were significantly older at disease onset (mean ± SD 58.8 ± 13.5 years versus 50.8 ± 13.6 years; $P < 0.0001$) and recruitment and were more likely to be men (30.0% versus 15.4%; $P < 0.0001$). More of those who died had diffuse disease (54.3% versus 38.1%; $P < 0.0001$) and anti–RNA polymerase III (anti–RNAP III) antibodies (36.5% versus 20.2%; $P = 0.005$), while more who were alive had limited disease (60.8% versus 42.9%; $P < 0.0001$) and anticentromere antibodies (36.8% versus 25.8%; $P = 0.018$). In the combined inception cohort, subjects who died had more organ complications, including pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), myocardial involvement, pericardial effusion, and renal crisis, while the frequency of gut involvement in the 2 groups was similar. There were also significant differences between the 2 groups in frequency of comorbidities, including ischemic heart disease (see Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract). In the combined prevalent cohort, the characteristics of subjects who had died and of those who were alive at the end of the study were similar to those of the corresponding subjects in the combined inception cohort, with the notable exception that in the combined prevalent cohort, those who died also had more frequent digital ulcers, cerebrovascular disease, and malignancy (see Supplementary Table 1).

SMR, life expectancy, and years of life lost. Because of the time limitation of matched general population data, in the analyses of SMR and years of life lost we included 942 subjects (339 Australian, 420 Canadian, and 183 Spanish) in the combined inception cohorts and 2,872 subjects (1,252 Australian, 1,325 Canadian, and 295 Spanish) in the combined prevalent cohorts. Among them, 113 subjects (42 Australian, 62 Canadian, and 9 Spanish) in the combined inception cohorts and 430 subjects (196 Australian, 214 Canadian, and 20 Spanish) in the combined prevalent 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 those in the corresponding prevalent cohorts, while the age- and sex-adjusted SMR in the inception cohort from Spain (3.2 [95% CI 2.3–4.2]) was lower than that in the corresponding prevalent cohort. Regardless of cohort type (inception versus prevalent), the crude (unadjusted for age) and age-adjusted SMRs for men were higher than for women in all nations. In men, SMRs in inception cohorts were consistently higher than in prevalent cohorts in all nations (Table 2).

Pooled SMR. The pooled age- and sex-adjusted SMR of the 3 inception cohorts was higher at 4.06 (95% CI 3.39–4.85; $I^2 = 76.4\%$; *P* for heterogeneity between studies = 0.014) than that of the 3 prevalent cohorts, which was 3.39 (95% CI 3.06–3.71; $I^2 = 84.9\%$; *P* for heterogeneity between studies = 0.001) (Figure 1). In

Table 2. Measures of mortality 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 = 1,252)	Inception (n = 420)	Prevalent (n = 1,325)	Inception (n = 183)	Prevalent (n = 295)
Number of deaths	27	110	58	182	30	58
Number of subjects lost 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 SMR						
Women	2.9	3.8	4.4	4.2	3.7	4.6
Men	9.6	6.5	7.9	7.7	27.1	22.8
Age-adjusted SMR (95% CI)						
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)
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)
Years of life lost						
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, %						
Overall	84	95	80	94	77	86
Women	87	97	85	96	80	88
Men	74	88	65	88	50	75

* SMR = standardized mortality ratio; 95% CI = 95% confidence interval.

extra SMR analyses, the pooled SMR of the noninception cohorts was even lower at 3.20 (95% CI 2.86–3.58; $I^2 = 90.2\%$; P for heterogeneity between studies < 0.0001).

SMR sensitivity analyses. In SMR sensitivity analyses, assuming that all subjects lost to follow-up were alive or assuming that they were dead, the pooled SMR for the inception cohorts was higher than the pooled SMR for the prevalent cohorts (see Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract).

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 3 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 that of the corresponding prevalent cohort, the crude SMR in either men or women was higher in all 3 national 1-year inception cohorts than in the

Figure 1. Pooled standardized mortality ratio (SMR) of the 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 horizontal lines represent the 95% confidence intervals (95% CIs) for the point estimates in each cohort. The diamond represents the pooled SMR. The pooled SMR of inception cohorts was higher than that of prevalent cohorts.

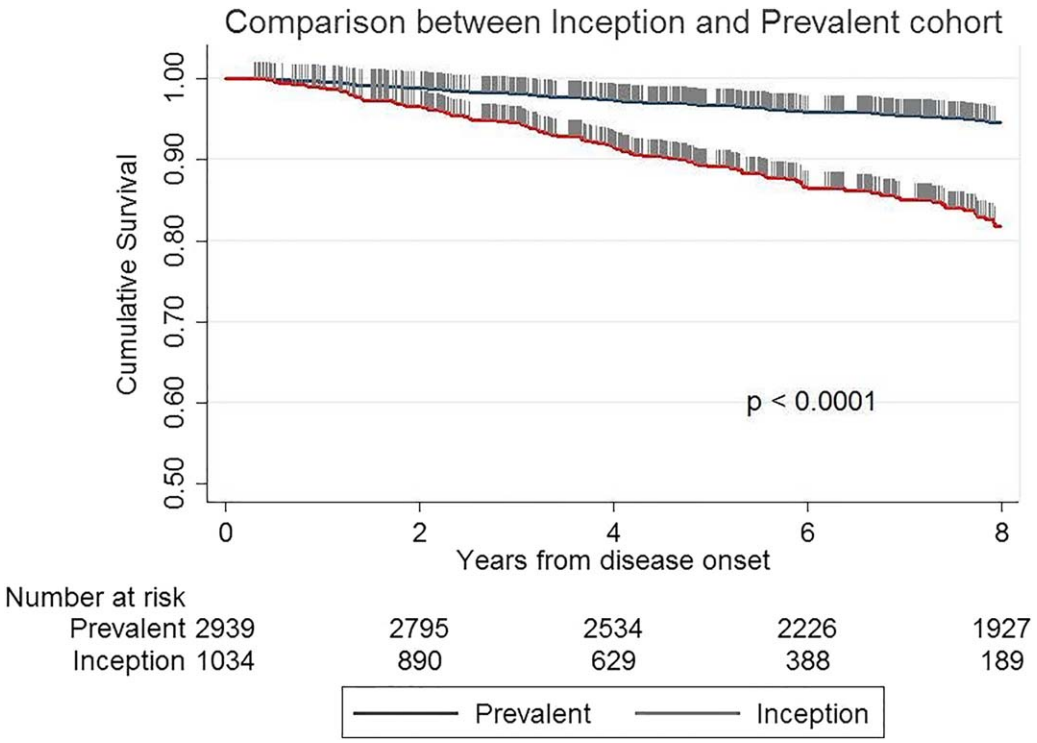

Figure 2. Kaplan-Meier analysis of overall survival in the first decade following disease onset in the combined inception cohort and combined prevalent cohort. The survival of the combined inception cohort was significantly lower than that of the combined prevalent cohort (99.0%, 94.8%, 88.9%, and 81.3% versus 99.5%, 98.0%, 96.7%, and 94.6% at 1, 3, 5, and 8 years, respectively; $P < 0.0001$ by log rank test).

corresponding prevalent cohorts (see Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract).

Life expectancy and years of life lost. The life expectancy at birth of the Australian general population from 2007 to 2012 was 84.4 years for women and 79.9 years for men. The life expectancy of the Australian SSc study population within the same 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. There were 11.3 years of life lost in the inception cohort and 11.9 years of life lost in the prevalent cohort for women, and there were 25.8 years of life lost in the inception cohort and 17.2 years of life lost in the prevalent cohort for men. The findings were similar for the Canadian cohort and for men in the Spanish cohort (Table 2). For women in the Spanish cohort, years of life lost in the inception cohort were much lower than in the prevalent cohort (15.2 years of life lost versus 20.9 years of life lost).

Survival analysis. Overall survival in the first decade of disease in the combined inception cohort was lower than that in the combined prevalent cohort at 1, 3, 5, and 8 years (99.0%, 94.8%, 88.9%, and 81.3%, respectively, versus 99.5%, 98.0%, 96.7%, and 94.6%, respectively; $P < 0.0001$) (Figure 2) and lower than that in the combined noninception cohort (100%, 100%, 99.8%, and 98.8%, respectively; $P < 0.0001$) (see Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract), and this difference was greater for men than for women (see Supplementary Figure 2, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract) and for diffuse disease subtype than for limited disease subtype (see Supplementary Figure 3, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract). Kaplan-Meier analysis revealed lower survival in men than in women and lower survival in those with the diffuse disease subtype than in those with the limited disease subtype (both $P < 0.0001$), regardless of cohort type (combined inception cohort or combined prevalent cohort) (see Supplementary Figures 2 and 3).

We performed an extra survival analysis for the 1-year combined inception cohort. Survival of subjects in the 1-year combined inception cohort at 1, 3, 5, and 8 years (95.2%, 85.2%, 78.0%, and 70.8%, respectively) decreased further compared with survival of subjects in the 4-year combined inception cohort and combined prevalent cohort. Kaplan-Meier analysis

Table 3. Causes of SSc-related deaths in the combined inception cohort and combined prevalent cohort*

Organ system/ etiology	Combined inception cohort		Combined prevalent cohort	
	Principal cause (n = 87)	Contributing cause (n = 140)	Principal cause (n = 244)	Contributing cause (n = 440)
Heart and lung	48 (55.2)	25 (17.9)	173 (70.9)	111 (25.2)
PAH	22 (25.3)	9 (6.4)	88 (36.1)	49 (11.1)
ILD	18 (20.7)	16 (11.4)	53 (21.7)	62 (14.1)
PAH and ILD	8 (9.2)	–	32 (13.1)	–
Myocardial involvement	13 (14.9)	8 (5.7)	22 (9.0)	15 (3.4)
Gut involvement	12 (13.8)	16 (11.4)	24 (9.8)	44 (10.0)
Renal crisis	12 (13.8)	6 (4.3)	17 (7.0)	10 (2.3)
Pericardial effusion	1 (1.1)	4 (2.9)	4 (1.6)	11 (2.5)
Sepsis	1 (1.1)	11 (7.9)	4 (1.6)	41 (9.3)

* Each combined cohort included the corresponding Australian, Canadian, and Spanish cohorts. Values are the number (%) of subjects. SSc = systemic sclerosis; PAH = pulmonary arterial hypertension; ILD = interstitial lung disease.

revealed that the survival of subjects in the 1-year combined inception cohort was significantly lower than that in the corresponding combined noninception cohort (100%, 99.4%, 98.1%, and 96.1%, respectively) ($P < 0.0001$) (see Supplementary Figure 4, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract).

Causes of death. Among the 140 deaths in the combined inception cohort, 62.1% of the principal causes were SSc related and 24.3% were non–SSc related. We were unable to determine causes of death for 13.6% of subjects. The most common principal cause of SSc-related death (55.2%) 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%) (Table 3). Malignancy (38.2%), sepsis (14.7%), cerebrovascular disease (11.8%), and ischemic heart disease (8.8%) were the most common non–SSc-related primary causes (Table 4). Regardless of the primary cause, SSc organ involvement contributed to 50.1% of deaths (Table 3). Causes of death in the 3 individual national inception cohorts were similar (see Supplementary Tables 4 and 5, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract).

Among the 440 deaths in the combined prevalent cohort, proportionally fewer principal causes were SSc related (55.5%), and more were non–SSc related (33.6%), compared with principal causes of death in the combined inception cohort. We were unable to determine causes of death for 10.9% of subjects. The most common principal cause of SSc-related death was also heart–lung involvement, accounting for proportionally more deaths than in the combined inception cohort (70.9% versus 55.2%), including PAH (36.1% versus 25.3%), ILD (21.7% versus 20.7%), and PAH combined with ILD (13.1% versus 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 combined inception cohort. As with the combined inception cohort, malignancy was the most common non–SSc-related primary cause in the combined prevalent cohort (37.1%), with ischemic heart disease and sepsis accounting for 12.2% and 9.5%, respectively, of non–SSc-related deaths (Table 4). Causes of death in the 3 individual national prevalent cohorts were similar (see

Table 4. Principal causes of non-SSc-related deaths in the combined inception cohort and combined prevalent cohort*

Organ system/etiology	Combined inception cohort (n = 34)	Combined prevalent cohort (n = 148)
Malignancy	13 (38.2)	55 (37.2)
Sepsis	5 (14.7)	14 (9.5)
CVD	4 (11.8)	7 (4.7)
IHD	3 (8.8)	18 (12.2)
Liver disease	2 (5.9)	3 (2.0)
Postoperative complications	1 (2.9)	9 (6.1)
Trauma	1 (2.9)	8 (5.4)
Sudden death	1 (2.9)	4 (2.7)
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 (18.2)

* Each combined cohort included the corresponding Australian, Canadian, and Spanish cohorts. Values are the number (%) of subjects. SSc = systemic sclerosis; CVD = cerebrovascular disease; IHD = ischemic heart disease; COPD = chronic obstructive pulmonary disease.

Table 5. Multivariable predictors of mortality in the combined inception cohort and combined prevalent cohort*

Variable	Combined inception cohort		Combined prevalent cohort	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Male sex	2.28 (1.42–3.65)	0.001	1.72 (1.27–2.33)	0.001
Age at disease onset, years†	1.05 (1.03–1.07)	0.000	1.05 (1.04–1.06)	<0.0001
Diffuse disease subtype	1.83 (1.14–2.92)	0.002	1.40 (1.07–1.83)	0.013
Disease duration at recruitment, years	0.59 (0.47–0.74)	<0.0001	0.71 (0.68–0.74)	<0.0001
Anticentromere antibody‡	–	–	0.71 (0.53–0.94)	0.019
Anti–Scl-70 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

* Each combined cohort included the corresponding Australian, Canadian, and Spanish cohorts. HR = hazard ratio; 95% CI = 95% confidence interval; PAH = pulmonary arterial hypertension; ILD = interstitial lung disease; IHD = ischemic heart disease; CVD = cerebrovascular disease.
† Defined as the date of the first non–Raynaud's phenomenon symptom.
‡ Not included in the multivariable model in the inception cohort because not statistically significant in univariable hazards regression analyses.

Supplementary Tables 5 and 6, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract).

Predictors of mortality. In the combined inception cohort, univariable hazards analyses showed that subjects with male sex, older age at disease onset, diffuse disease subtype, PAH, renal crisis, myocardial involvement, and ischemic heart disease/cerebrovascular disease had a higher risk of death (all $P < 0.05$), while subjects with longer disease duration at recruitment had a lower risk of death ($P = 0.001$). Anticentromere positivity, anti–Scl-70 positivity, ILD, gut involvement, and malignancy were not found to be significant predictors of mortality (see Supplementary Table 7, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract). Multivariable hazards regression analysis showed that male sex, older age at disease onset, diffuse disease subtype, PAH, and renal crisis were independent predictors of risk, and longer disease duration at recruitment was an independent protective factor. PAH conferred the highest risk (hazard ratio [HR] 2.35 [95% CI 1.29–4.29]; $P = 0.006$) (Table 5).

In the combined prevalent cohort, univariable hazards analyses showed that subjects with male sex, older age at disease onset, diffuse disease subtype, anti–Scl-70 positivity, PAH, ILD, myocardial involvement, renal crisis, ischemic heart disease/cerebrovascular disease, and malignancy had a higher risk of death, while subjects with longer disease duration at recruitment and anticentromere positivity had a lower risk of death (see Supplementary Table 7, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract). Finally, multivariable hazards regression analysis showed that male sex, older age at disease onset, diffuse disease subtype, PAH, and ILD were independent predictors of death, and longer disease duration at recruitment and anticentromere positivity were independent protective factors. PAH conferred the highest risk (HR 2.50 [95% CI 1.83–3.42]; $P < 0.0001$) (Table 5).

DISCUSSION

In this largest study to date of mortality and causes of death in an inception cohort of subjects with SSc, we have reported a very high pooled SMR of 4.06 (95% CI 3.39–4.85), up to 22.4 years of life lost in women and up to 26.0 years of life lost 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 SMRs were even higher, at 8.1 (95% CI 4.3–12.0) for the Australian cohort, 9.4 (95% CI 6.1–12.8) for the Canadian cohort, and 3.9 (95% CI 2.4–5.4) for the Spanish cohort. The values for Australian and Canadian 1-year inception cohorts are much higher than those for the corresponding prevalent cohorts and higher than those reported from some previous studies (12–16), and they highlight the phenomenon of survivor bias, which leads to underestimation of the true burden of mortality in prevalent cohorts of subjects with SSc. This bias arises in large part because SSc has a substantial burden of early mortality with many deaths occurring within 5 years of disease onset, particularly in men and in the diffuse disease subtype. The protective effect against mortality of longer disease duration at recruitment that we found in our multivariable hazards regression analyses

further highlights the burden of mortality in the early stage of disease.

In our study, the pooled SMR for the prevalent cohort (3.39) is similar to that reported from a meta-analysis of 9 prevalent cohort studies from the 1960s to the 2000s (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 showing 5-year survival ranging from 68% to 88% (18–22), the major strength of the present study is the large sample size achieved by pooling 3 cohorts, which enabled us to compare the mortality of a combined inception cohort with that of 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 those of the respective prevalent cohorts. In Spanish subjects, the age- and sex-adjusted SMR of the prevalent cohort was higher than that of the inception cohort, but this may have been due to the overall short duration of disease at recruitment in both of the Spanish cohorts as well as the difference in the age structure of the Spanish cohort compared with the Australian and Canadian cohorts as demonstrated by crude SMRs (see Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract).

The SMRs for men were higher than for women in each of the cohorts. The difference in mortality for men in inception cohorts versus prevalent cohorts was more substantial than that 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 sex was a strong independent predictor of death in the combined inception cohort. Our univariable comparisons showed more diffuse disease, myocardial involvement, renal crisis, digital ulcers, and ischemic heart disease in men than in women (see Supplementary Table 8, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract), and most of these factors were associated with risk of death according to our univariable hazards regression analyses. A recent published model by Domsic et al also showed that male sex was an independent predictor of mortality in incident disease in patients with the diffuse subtype of SSc (23). Therefore, for male patients, especially those with diffuse disease, close monitoring and active treatment are important (24,25).

Organ involvement is another important factor associated with prognosis. In our combined inception cohort, SSc-related causes of death accounted for 62.1% of all deaths, which was higher than that in the combined prevalent cohort (55.5%) and published EUSTAR data (55%) (6). Although the proportion of SSc-related deaths has been reported to be decreasing from 1972 to 2002 (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% of deaths in the combined inception cohort (25.3% from PAH only and 9.2% from the combination of PAH and ILD). Although advanced PAH therapies have been used more widely in recent years, and the survival of subjects with SSc-associated PAH has improved compared with historical control data, the mortality of subjects with PAH is still high (27,28). In our analyses, the survival of subjects with PAH at 1, 3, 5, and 8 years was 100%, 88.0%, 71.0%, and 53.1%, respectively, in the combined inception cohort, which was significantly lower than that of subjects without PAH (98.0%, 95.0%, 90.5%, and 83.1%, respectively) (see Supplementary Figure 5, http://onlinelibrary.wiley.com/doi/10.1002/art.40027/abstract). In addition to being the leading cause of death, PAH was also identified as the strongest independent risk factor for mortality in both our combined inception cohort and combined prevalent cohort, as some other models showed (14,28). These results confirm that PAH is still the SSc-related complication with the greatest impact on survival.

ILD accounted for a higher proportion of deaths in the combined prevalent cohort than in the combined inception cohort (34.8% versus 29.9% for principal cause of death, and 14.1% versus 11.4% for contributing cause of death, when deaths due to ILD and PAH together with ILD were included). Hazards regression analyses showed that ILD was an independent risk factor for mortality in the combined prevalent cohort but not in the combined inception cohort. Collectively, these results point to ILD as a risk factor for poor long-term survival rather than early death.

In our combined inception cohort, 24.3% of deaths were non–SSc related. A higher proportion of deaths were non–SSc related in the combined prevalent cohort (33.6%), which reminds us that these long-term complications become particularly important later in the disease course. Ischemic heart disease and cerebrovascular disease were major causes of non–SSc-related deaths both in the inception cohort and in the prevalent cohort. A study from the ASCS showed 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 were general population controls (29), which suggests that the high prevalence of ischemic heart disease may be partly related to SSc itself rather than just to traditional atherosclerosis risk factors. Furthermore, a study by Dave et al has shown that SSc patients with ischemic heart disease have higher in-hospital mortality than do controls, systemic lupus erythematosus patients with ischemic heart

disease, and rheumatoid arthritis patients with ischemic heart disease (30). Although not all studies have shown a similarly increased frequency of ischemic heart disease and in-hospital mortality, there is need for better understanding, prevention, and management of atherosclerosis in SSc patients, especially those with longer disease duration.

Malignancy was one of the most common non–SSc-related causes of death both in the combined inception cohort and in the combined prevalent cohort. While a close temporal association has been reported between the onset of SSc and diagnosis of malignancy in patients with anti–RNAP III (31), further studies are needed to determine whether there is an increased risk of malignancy in SSc overall, and, if so, whether this is attributable to the disease itself, to immunosuppressive therapy, or to 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 a higher proportion of deaths in the combined inception cohort (14.7%) than in the combined prevalent cohort (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 subjects who died within 1 year of recruitment and 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 $\geq$2 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 in the whole combined prevalent cohort. Furthermore, while most data regarding cause of death were collected prospectively in each cohort, in order to standardize results, our death case report form was completed retrospectively (although verified against source documents) for all subjects 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 due to the lack of accurate data on the indication for, and duration of, treatment. Also, anti–RNAP III positivity was not included in the hazards regression model as this variable was not available for all subjects. 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 its other goals, the International Systemic Sclerosis Inception Cohort study, initiated in 2012, aims to quantify early mortality in SSc and the potential effect of treatment.

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

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.

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ROLE OF THE STUDY SPONSORS

Actelion Australia, Bayer, CSL Biotherapies, GlaxoSmithKline Australia, and Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Actelion Australia, Bayer, CSL Biotherapies, GlaxoSmithKline Australia, and Pfizer.

REFERENCES

1. Denton CP. Systemic sclerosis: from pathogenesis to targeted therapy. Clin Exp Rheumatol 2015;33 Suppl 92:S3–7.
2. Stern EP, Denton CP. The pathogenesis of systemic sclerosis. Rheum Dis Clin North Am 2015;41:367–82.
3. Gu YS, Kong J, Cheema GS, Keen CL, Wick G, Gershwin ME. The immunobiology of systemic sclerosis. Semin Arthritis Rheum 2008;38:132–60.
4. Asano Y, Sato S. Vasculopathy in scleroderma. Semin Immunopathol 2015;37:489–500.
5. Bennett R, Bluestone R, Holt PJ, Bywaters EG. Survival in scleroderma. Ann Rheum Dis 1971;30:581–8.
6. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809–15.
7. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
8. Andersen PK, Borgan O, Gill RD, Keiding N. Statistical models based on counting processes. New York: Springer-Verlag; 1993. p. 322.
9. Mok CC, Kwok CL, Ho LY, Chan PT, Yip SF. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. Arthritis Rheum 2011;63:1182–9.

10. Chiang CL. The life table and its construction. In: Introduction to stochastic processes in biostatistics. New York: John Wiley & Sons; 1968. p. 189–214.
11. Newell C. Methods and models in demography. Chichester (UK): John Wiley & Sons; 1994. p. 63–81.
12. Sampaio-Barros PD, Bortoluzzo AB, Marangoni RG, Rocha LF, del Rio AP, Samara AM, et al. Survival, causes of death, and prognostic factors in systemic sclerosis: analysis of 947 Brazilian patients. J Rheumatol 2012;39:1971–8.
13. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66:1625–35.
14. Joven BE, Almodovar R, Carmona L, Carreira PE. Survival, causes of death, and risk factors associated with mortality in Spanish systemic sclerosis patients: results from a single university hospital. Semin Arthritis Rheum 2010;39:285–93.
15. Hoffmann-Vold AM, Molberg Ø, Midtvedt Ø, Garen T, Gran JT. Survival and causes of death in an unselected and complete cohort of Norwegian patients with systemic sclerosis. J Rheumatol 2013;40:1127–33.
16. Vettori S, Cuomo G, Abignano G, Iudici M, Valentini G. Survival and death causes in 251 systemic sclerosis patients from a single Italian center. Reumatismo 2010;62:202–9. In Italian.
17. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2012;51:1017–26.
18. Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). Br J Rheumatol 1998;37:750–5.
19. Bulpitt KJ, Clements PJ, Lachenbruch PA, Paulus HE, Peter JB, Agopian MS, et al. Early undifferentiated connective tissue disease. Part III. Outcome and prognostic indicators in early scleroderma (systemic sclerosis). Ann Intern Med 1993;118:602–9.
20. Jacobsen S, Ullman S, Shen GQ, Wiik A, Halberg P. Influence of clinical features, serum antinuclear antibodies, and lung function on survival of patients with systemic sclerosis. J Rheumatol 2001;28:2454–9.
21. Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. Arthritis Rheum 1999;42:2660–5.
22. Bryan C, Howard Y, Brennan P, Black C, Silman A. Survival following the onset of scleroderma: results from a retrospective inception cohort study of the UK patient population. Br J Rheumatol 1996;35:1122–6.
23. Domsic RT, Nihtyanova SI, Wisniewski SR, Fine MJ, Lucas M, Kwoh CK, et al. Derivation and external validation of a prediction rule for five-year mortality in patients with early diffuse cutaneous systemic sclerosis. Arthritis Rheumatol 2016;68:993–1003.
24. Strickland G, Pauling J, Cavill C, Shaddick G, McHugh N. Mortality in systemic sclerosis: a single centre study from the UK. Clin Rheumatol 2013;32:1533–9.
25. Fransen J, Popa-Diaconu D, Hesselstrand R, Carreira P, Valentini G, Beretta L, et al. Clinical prediction of 5-year survival in systemic sclerosis: validation of a simple prognostic model in EUSTAR centres. Ann Rheum Dis 2011;70:1788–92.
26. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. Ann Rheum Dis 2007;66:940–4.
27. Williams MH, Das C, Handler CE, Akram MR, Davar J, Denton CP, et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. Heart 2006;92:926–32.
28. Lefevre G, Dauchet L, Hachulla E, Montani D, Sobanski V, Lambert M, et al. Survival and prognostic factors in systemic sclerosis–associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum 2013;65:2412–23.
29. Ngian GS, Sahhar J, Proudman SM, Stevens W, Wicks IP, van Doornum S. Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis. Ann Rheum Dis 2012;71:1980–3.
30. Dave AJ, Fiorentino D, Lingala B, Krishnan E, Chung L. Atherosclerotic cardiovascular disease in hospitalized patients with systemic sclerosis: higher mortality than patients with lupus and rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66:323–7.
31. Nikpour M, Hissaria P, Byron J, Sahhar J, Micallef M, Paspaliaris W, et al. Prevalence, correlates and clinical usefulness of antibodies to RNA polymerase III in systemic sclerosis: a cross-sectional analysis of data from an Australian cohort. Arthritis Res Ther 2011;13:R211.

APPENDIX A: CANADIAN SCLERODERMA RESEARCH GROUP AND AUSTRALIAN SCLERODERMA INTEREST GROUP INVESTIGATORS

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