RHEUMATOLOGY

Rheumatology 2012;51:1017–1026
doi:10.1093/rheumatology/ker269
Advance Access publication 7 September 2011

Original article

Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies

Muriel Elhai[1], Christophe Meune[2], Jérôme Avouac[1], André Kahan[1] and Yannick Allanore[1]

Abstract

Objective. SSc is known as the most severe connective tissue disorder, and to be associated with a high mortality risk. Some improvements in therapy for SSc have been achieved in recent years and some preliminary data have suggested an improvement in patient survival. Thus, we set out to determine whether mortality rate in SSc patients has decreased over the past 40 years through a meta-analysis of cohort studies.

Methods. We performed a systematic review and a meta-analysis of literature in MEDLINE and Embase databases from January 1960 to June 2010. All cohort studies reporting on SSc mortality were analysed. We then calculated pooled standardized mortality ratios (SMRs) of SSc mortality and calculated their changes over time using meta-regression analysis.

Results. Nine studies were included, corresponding to a total of 2691 SSc patients. The pooled SMR was 3.53 [95% CI 3.03, 4.11, $P < 0.0001$; $I^2 = 93\%$, P(het) = 0.001]. Mid-cohort year ranged from 1977 to 1995 (before 1980: two studies; 1980–90: five studies; and after 1990: two studies): adjusted meta-regression analysis did not show significant change in SMR over time ($P = 0.523$). Among 732 deaths, heart involvement was the most frequent cause of deaths (29%) followed by lung involvement.

Conclusion. Our results confirm that SSc is a devastating condition as reflected by a pooled SMR of 3.5. Additionally, SMR has not significantly changed over the past 40 years. Further studies are needed to assess the effect of the most recent available therapies on mortality in SSc.

Key words: systemic sclerosis, mortality, death, meta-analysis.

Introduction

Among the many different immune-mediated rheumatic diseases, SSc stands out as a severely incapacitating and life-threatening disease [1–13]. Its pathogenesis is complex and remains incompletely known [14]. Several poor prognosis factors were identified: diffuse cutaneous subtype, presence of main organ (lung, heart and kidney) involvement, anti-Scl70 antibody, increased ESR and anaemia [1, 3, 7–10, 12–13, 15–22]. The most recent studies have suggested that SSc-related deaths are mainly caused by lung involvement (pulmonary fibrosis and pulmonary hypertension) and primary heart involvement, whereas non-SSc causes include infections, malignancies and atherosclerosis [1, 5, 8, 9, 11, 17, 21].

Therapeutics options in SSc were previously supportive of organ involvement; some drugs emerged recently as preventive of organ failure, i.e. angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers [14]. In addition, the management of SSc patients, including the accurate detection of SSc-associated organ involvement, has improved as a result of various national/international organization guidelines [23]. Nevertheless, their impact on mortality remains unclear.

Investigations on mortality have reported an increase in SSc mortality rates since 1980, which was hypothesized by the authors as reflecting an increasing incidence of

[1]Rheumatology A Department and [2]Cardiology Department, Paris Descartes University, Cochin Hospital, APHP, Paris, France.

Submitted 3 March 2011; revised version accepted 28 June 2011.

Correspondence to: Yannick Allanore, Service Rhumatologie A, Hôpital Cochin, 27 rue du faubourg St Jacques, 75014 Paris, France. E-mail: yannick.allanore@cch.aphp.fr

SSc [24–26]. Conversely, other observational studies, referring to historical cohorts, have suggested an improvement in the overall survival over time with reduced mortality and higher survival rates in the contemporary cohorts as compared with the older ones [8, 16, 27–30]. Improved survival in SSc, if confirmed, may be the reflection of improved survival in the general population, the consequence of preventive and therapeutics advances in the management of SSc, or both. Knowing whether SSc survival has improved less than, equal to or more than that in the general population during past decades is crucial clinical information, as yet not known. The standardized mortality ratio (SMR), which is the ratio between the observed number of deaths in a cohort to the expected number of deaths of a comparable age- and sex-matched population, is an accurate tool to assess mortality rate and its changes over time. Consequently, using this tool, we conducted a systematic review and meta-analysis of cohort studies to investigate whether mortality rate in SSc patients has changed over the past 40 years.

Materials and methods

The Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines were followed [31]. Eligible studies were cohort studies or case–control studies with SSc diagnosed according to ACR criteria [32] or LeRoy's criteria [33]. We searched MEDLINE and Embase databases between January 1960 and June 2010 using the terms (systemic, scleroderma or systemic sclerosis) [MesH] AND (death or mortality). In addition, reference lists of the papers initially detected were searched by hand to identify additional relevant reports. In order to identify recent studies not yet published, we also searched in European League against Rheumatism (EULAR)/ACR congress abstract archives of 2009 and 2010. No language restriction was applied. We also contacted authors of one study to obtain raw data. Eligibility of references retrieved by the search was assessed independently by two of the authors (Y.A. and M.E.) and disagreements resolved at each step. We only selected studies that reported either SMR or enough data to calculate it (observed deaths in SSc patients as well as expected deaths from the general population of the same community and of same gender and age distribution). Studies were excluded if they did not report enough data to calculate SMR, i.e. if they did not report age- and sex-specific mortality rates in the general population (of the same community) at the same period or age and sex distribution of the study population. Data were extracted separately by two of the authors (M.E. and C.M.) from the selected studies using a predefined standardized form.

Quality assessment of individual studies was performed independently by two of the authors (M.E. and J.A.) using the Newcastle–Ottawa Scale [34]. This scale, specific for cohort studies, uses a star rating system (range: 0–9 stars) scoring three aspects of the study: selection of groups, comparability and ascertainment of the outcome of interest. Follow-up was judged as adequate if there were $<5\%$ of patients lost to follow-up. Comparability, i.e. control of the confounding factors, was assessed for the primary outcome (death). Studies were excluded if either one of the two authors found that there was insufficient information to appraise their quality or study quality was judged insufficient by one of the two assessors. Disagreements were resolved by consensus among all authors.

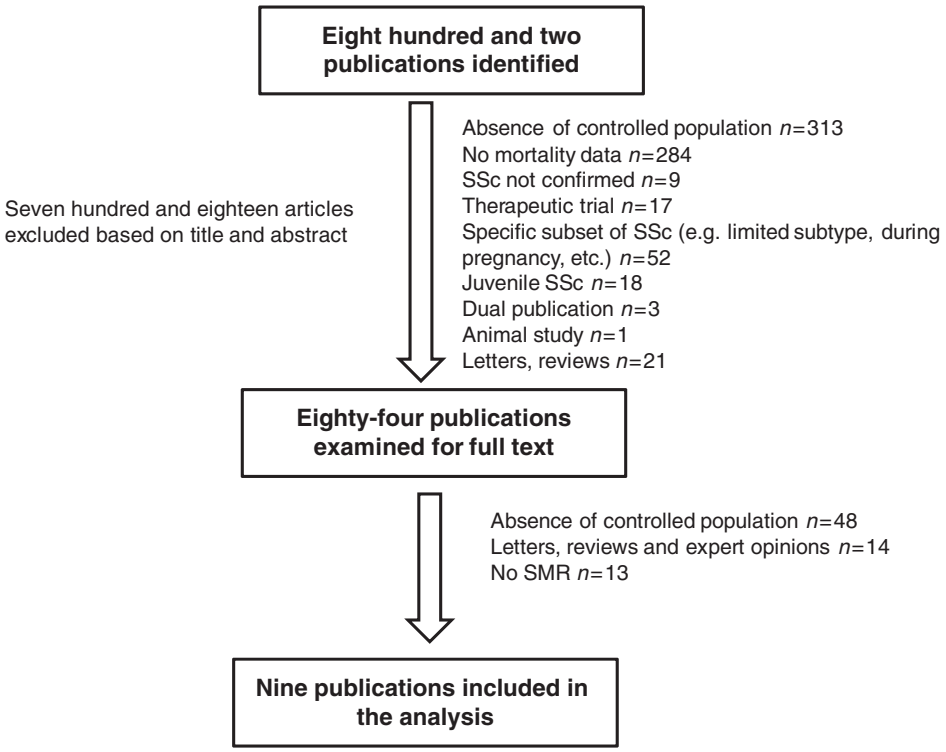
Statistical analysis

SMRs were either extracted, when reported, or calculated as the ratio between observed and expected numbers of deaths in age/sex-adjusted population. Although the SMR is the measure of interest, statistical analysis is conducted on its natural logarithm, the log-SMR, because this has a sampling distribution more closely approximated by a normal distribution. In addition, log-SMR should be encouraged in combination of studies that do not have the same reference population [35]. Then we performed meta-analyses of log-SMR. The standard error of log-SMR was estimated by $1/\sqrt{O}$ with O being the observed number of deaths [35]. Statistical heterogeneity was assessed using the I^2 statistic ($I^2 \geqslant 50\%$ corresponding to substantial heterogeneity and $I^2 \geqslant 75\%$ to considerable heterogeneity). In case of heterogeneity, we used a random effects model to estimate a combined log-SMR, which we then back-transformed. Publication bias was assessed using a funnel plot and Begg's test of the correlation between effect sizes and their variances. To assess change in SMR over the past four decades, we predefined three periods, of almost the same duration, based on the mid-time follow-up of patients in the selected studies, i.e. the mid-cohort year, as follows: before 1980, 1980–90 and after 1990, as used in a previous study [36]. The mid-cohort was calculated as the median year between the starting year of inclusion period and the ending year of the follow-up period. We performed indirect comparison of the combined SMR across the three periods and used meta-regression analysis to assess changes in log-SMR over time. We also conducted a multiple meta-regression analysis adjusted for relevant covariates using Monte Carlo permutation (5000 random permutations) test for meta-regression as recommended [37]. All analyses were performed using STATA software (STATA 10.1, StataCorp L, College Station, TX, USA).

Results

Among a total of 802 identified references, 718 were excluded on the basis of their title or abstract resulting in 84 articles being examined for the full text. Overall, nine studies were included in the present analysis [1, 4–9, 11, 12, 15] (Fig. 1). No study was excluded based on poor quality. These studies provided a total sample of 2691 patients (women 83%, dcSSc in 26% and lcSSc in 63%). Mean age at enrolment was 50.1 years (range: 47.1–59.8 years), mean age at onset of the disease was 46 years (data available in seven out of nine studies) and mean disease duration was 6 years. Patients were mostly Caucasian [1203 (99%) out of 1217 of available data]. The main characteristics of the studies included in the analysis

Fig. 1 Study flow chart.



are summarized in Table 1. Quality assessment of each study is reported in Table 2. SMRs ranged from 2.69 to 4.69 among studies. All studies demonstrated a significant increase in mortality in SSc patients as compared with the general population (Fig. 2). Funnel plots and Begg's test did not reveal funnel plot asymmetry, making publication bias unlikely (data not shown). The pooled SMR was 3.53 [95% CI 3.03, 4.11; $P < 0.0001$; $I^2 = 93\%$; $P(\text{het}) = 0.001$] (Fig. 2). A total of 732 deaths occurred during a mean follow-up of 7.3 years. Causes of deaths from each study are summarized in Table 3. One hundred and twenty (16%) deaths were of unknown causes. Of 612 deaths, 389 (64%) were considered as related or possibly related to SSc, whereas 223 (36%) deaths were defined as not related to SSc. Cardiac deaths were the most frequent causes of deaths [178 (29%) out of 612 deaths] followed by lung involvement [144 (23%) out of 612 deaths], cancer [98 (16%) out of 612 deaths], kidney involvement [66 (11%) out of 612 deaths], infection [45 (7%) out of 612 deaths] and gastro-intestinal involvement [24 (4%) out of 612].

The mid-cohort year ranged from 1977 to 1995 being before 1980 in two studies (1356 patients), from 1980 to 1990 in five studies (948 patients) and after 1990 in two studies (387 patients). The respective pooled SMRs were 2.87 [95% CI 2.62, 3.16; $P(\text{het}) = 0.889$], 4.30 [95% CI 3.75, 4.93; $P(\text{het}) = 0.786$] and 3.02 [95% CI 2.21, 4.12; $P(\text{het}) = 0.190$], respectively, for these three periods. Meta-regression analysis confirmed that there was no significant change in SMR over time ($P = 0.333$) (Fig. 3). As SMR seemed slightly lower in studies with mid-cohort before 1980, an exploratory analysis was performed: we re-estimated the meta-regression analysis without these two studies. Exclusion of these studies revealed a trend for a decrease in SMR, but this did not reach significance ($P = 0.112$).

In order to rule out some possible biases related to the methodology of the included studies and to the between-study differences in patients characteristics, we performed further meta-regression analyses. All stratified analyses, according to the methodology of the studies, were consistent with persistent increased SMR in SSc and without significant change in SMR over time (retrospective studies, $P = 0.514$; Newcastle–Ottawa scale of 8 stars, $P = 0.106$; Newcastle–Ottawa scale of < 8 stars, $P = 0.948$). We also adjusted our results for additional relevant covariates, i.e. age, gender and the cutaneous form of the disease, using a multiple meta-regression model. The adjusted P-values for selected covariates were $P = 0.312$ for cutaneous form, $P = 0.620$ for age at enrolment and $P = 0.707$ for gender. Using such adjustment, we neither found significant change in SMR over time ($P = 0.523$).

Discussion

The main results of our analysis are (i) the confirmation of the increased risk of mortality in SSc and its magnitude of 250% in comparison with age- and sex-matched general population, (ii) the constancy of SMR over the past four

Table 1 Main characteristics of the nine included studies

Study	Localization	Type of study	Study period	Mid-cohort	No. of patients	Age,[a] years	Female *n* (%)	Disease duration, years	dcSSc, *n* (%)/lc SSc, *n* (%)	Diagnosis criteria	Digital pitting scars or ulcers, *n* (%)	Lung involve.,[d] *n* (%)	Heart involve., *n* (%)	ACA, *n* (%)	Anti-Scl 70, *n* (%)
Jacobsen *et al.* [1]	Denmark	Retrospective cohort study	1960–96	1978	344	55.0	278 (81)	8.6	118 (34)/226 (66)	ACR	214 (62)	88 (26)	NA	NA	NA
Bryan *et al.* [4]	UK	Retrospective cohort study	1982–92	1988	283	46.0	218 (77)	Onset after 1982	130 (46)/153 (54)	ACR	NA	NA	NA	NA	NA
Hesselstrand *et al.* [9]	Sweden	Prospective cohort study	1983–95	1989	249	49.6	178 (71)	4.6	63 (25)/186 (75)	ACR	NA	NA	NA	NA	NA
Geirsson *et al.* [5]	Sweden	Prospective cohort study	1982–95	1988	100	47.2	67 (67)	4.9	34 (34)/66 (66)	ACR	12 (12)	NA	32 (32)	NA	NA
Simeón *et al.* [12]	Spain	Retrospective cohort study	1976–96	1986	79	48.8	68 (86)	4.5	22 (28)/57 (72)	ACR (65)[c] and/or Leroy	NA	35 (44)	15 (19)	25 (32)	15 (19)
Scussel-Lonzetti *et al.* [7]	Montreal (Canada)	Retrospective cohort study	1984–99	1992	309	49.0	266 (86)	8.6	49 (16)/260 (84)	ACR (158)[c] and/or Leroy	79 (26)	34 (11)	28 (9)	135 (44)	37 (12)
Ferri *et al.* [8]	Italy	Retrospective cohort study	1955–99	1977	1012	50.5	897 (89)	5.1	172 (17)/567 (56)[b]	ACR	486 (48)	607 (60)	304 (30)	294 (36)	272 (36)
Arias-Nuñez *et al.* [11]	Spain	Retrospctive cohort study	1988–2006	1995	78	59.8	62 (79.5)	8.3	23 (29.5)/55 (70.5)	Leroy and/or ACR (44)[c]	32 (41)	35 (45)	48 (61)	45 (17)	13 (17)
Abu-Shakra *et al.* [6]	Ontario (Canada)	Mortality database analysis	1979–90	1985	237	47.1	196 (83)	3.8	102 (43)/135 (57)	ACR	NA	91 (38)	21 (9)	NA	NA

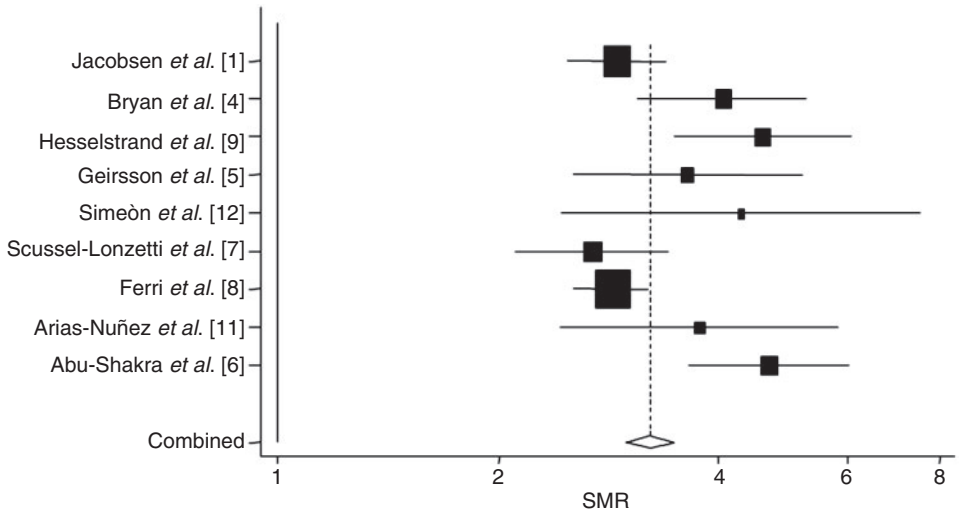
[a]Age: age at enrolment; [b]273 (27%) intermediate cutaneous SSc; [c]number of patients fulfilling ACR criteria; [d]lung involvement includes interstitial lung disease and/or pulmonary hypertension. involve.: involvement; NA: non-available; *n*: number.

Table 2 Quality assessment of the nine included studies

Study	Outcomes	Prospective design	Comparability	Selection bias minimized	NOS, stars	Follow-up, years	Completeness of follow-up
Jacobsen *et al.* [1]	Vital status and causes of death	No	Yes	Yes	8	10.8	Completed
Bryan *et al.*[4]	Vital status and causes of death	No	Yes	Yes	8	6.6	Completed
Hesselstrand *et al.* [9]	Vital status and causes of death	Yes	Yes	Yes	8	5.8	Completed
Geirsson *et al.* [5]	Vital status and causes of death	Yes	Yes	Yes	7	7.7	Completed
Simeón *et al.* [12]	Vital status	No	Yes	Yes	6	6.0	NA
Scussel-Lonzetti *et al.* [7]	Vital status	No	Yes	Yes	7	NA	Completed
Ferri *et al.* [8]	Vital status	No	Yes	Yes	7	7.1	97 (10%) lost to follow-up
Arias-Nuñez *et al.* [11]	Incidence, prevalence, clinical spectrum, survival	No	Yes	Yes	8	6.6	Completed
Abu-Shakra *et al.* [6]	Vital status and cause of death	No	Yes	Yes	7	5.7	17 (7%) lost to follow-up

NOS: Newcastle-Ottawa Scale; NA: non-available.

Fig. 2 Forest plot of SMR for patients with SSc. Each square represents an individual SMR estimate, the size of the square being proportional to the weight given to the study. The lines represent the 95% CI for the point estimate in each study. The diamond represents the combined SMR.



decades and (iii) the confirmation that cardiopulmonary involvement accounts for the majority of SSc-related deaths. Altogether, our results are consistent with the findings that SSc is a devastating condition associated with a high risk of mortality [1–13].

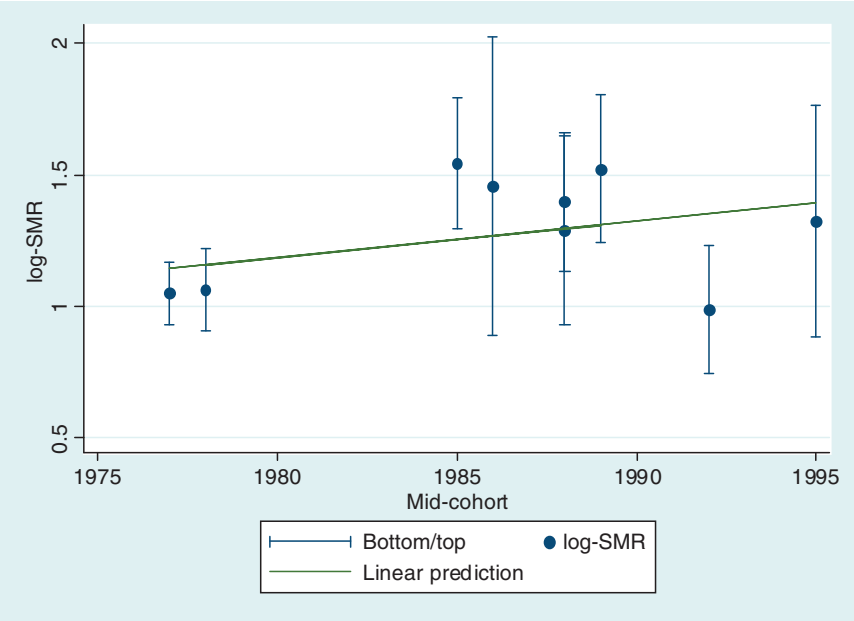
Some observational studies suggested a decrease of mortality risk in SSc [8, 16, 27–30]. Indeed, Ferri *et al*. [8] reported that patients included before 1985 in their cohort have 10-year survival rates of 60.6% as compared with 76.8% in the later subgroup ($P < 0.0001$). Consistently, using comparisons of recent cohorts with historical data, Mayes *et al.* [27] showed, in a large US cohort for the period 1989–91, 77.9 and 55.1% survival rates at 5 and 10 years, respectively, as compared with a 10-year survival of 35% reported by Medsger and Masi [38] in 1971. Such an improvement in the prognosis of SSc patients

Table 3 Number of deaths, SMR and causes of deaths from the nine studies

Study	No. of deaths (%)	SMR (95% CI)	Cause of death assessment	Cause of death unknown, *n*	Related to SSc,[a] *n* (% of known causes)	Non-related to SSc, *n* (% of known causes)	Heart involve.,[b] *n* (% of known causes)	Lung involve.,[c] *n* (% of known causes)	Gastrointestinal involve., *n* (% of known causes)	Renal involve., *n* (% of known causes)	Infection, *n* (% of known causes)	Cancer, *n* (% of known causes)
Jacobsen *et al.* [1]	160 (46)	2.9 (2.5, 3.4)	DC (20), medical records and autopsy (80)	10	41 (27)	109 (73)	41 (27)	18 (12)*	9 (6)	17 (11)	19 (13)	30 (20)
Bryan *et al.*[4]	55 (19)	4.05 (3.03, 5.22)	Medical records, DC	0	34 (62)	21 (38)	16 (29)	15 (27)	3 (5)	5 (9)	4 (7)	1 (2)
Hesselstrand *et al.*[9]	49 (20)	4.59 (3.46, 6.07)	Autopsy (27/49)	0	39 (80)	10 (20)	10 (20)	10 (20)	4 (8)	1 (2)	9 (18)	12 (24)
Geirsson *et al.* [5]	30 (30)	3.5 (m), 3.7 (f) (NA)	NA	0	24 (80)	6 (20)	6 (20)	5 (17)	0	1 (3)	6 (20)	9 (30)
Simeón *et al.* [12]	12 (15)	4.29 (2.22, 7.50)	NA	0	11 (92)	1 (8)	0	4 (33)	0	7 (59)	0	1 (8)
Scussel-Lonzetti *et al.* [7]	66 (21)	2.69 (2.1, 5.4)	DC, medical records, autopsy, questionnaires sent to physicians	0	35 (53)	31 (47)	14 (21)	6 (9)	3 (4)	7 (11)	2 (3)	13 (20)
Ferri *et al.* [8]	279 (55)	2.86 (NA)	DC, medical records, autopsy	109	150 (88)	20 (12)	77 (43)	55 (31)	NA	21 (12)	NA	25 (14)
Arias-Nuñez *et al.* [11]	20 (42)	3.76 (NA)	Medical records, physicians	1	11 (58)	8 (42)	2 (10)	10 (53)	1 (5)	0	3 (16)	1 (5)
Abu-Shakra *et al.* [6]	61 (26)	4.69 (3.6, 6.0)	DC, autopsy, physicians	0	44 (72)	17 (28)	12 (20)	21 (34)	4 (7)	7 (11)	2 (3)	6 (10)

[a]Related to SSc includes all deaths considered as 'related to SSc', 'probably related to SSc' and 'possibly related to SSc'. [b]Heart involvement includes causes related to heart and atherosclerosis. [c]Lung involvement includes interstitial lung disease and/or pulmonary hypertension and one pulmonary embolism (*). involve.: involvement; NA: non-available; m: male; f: female; DC: death certificates; *n*: number.

FIG. 3 Meta-regression of change in SMR (log-scale) with mid-cohort year. The lines represent the 95% CI for the point estimate in each study. Meta-regression analysis showed that there was no significant change in SMR over time ($P = 0.333$).



has also been reported by Steen and Medsger [29] in a single medical centre at the University of Pittsburg: the 10-year survival improved steadily from 54 to 67% between the 1970s and the 1990s. Likewise, Al-Dhaher *et al.* [30] suggested an improvement in the survival for both SSc subtypes over time in Canada [30]. They also compared their contemporary cohort with data from the literature, revealing higher 10-year survival rates in their cohort than in older US and international cohorts [30]. Nevertheless, none of these cohort studies included a matched control group.

Several factors support the possible improvement in the course of SSc over time. One could be related to a larger recruitment of mild-to-moderate clinical variants at tertiary care centres, which better reflect the entire SSc spectrum, whereas a relatively higher percentage of patients with more severe SSc were referred in older studies to tertiary care centres. Changes in the natural history of the disease cannot be ruled out, but a better knowledge of SSc should also be considered, resulting in an earlier diagnosis and better management [28]. The possible contribution of recently available treatments should also be considered (e.g. ACE inhibitors for renal crisis) [29, 39–41].

However, some limitations may influence isolated cohort studies and, to a lesser extent, meta-analyses. Patient demographics, clinical subsets, organ involvement and outcomes may differ across studies. We cannot rule out a possible cohort effect, related to changes affecting people born at the same period. In addition, immortality and missing data biases should be taken into account, since five of these observational studies had a retrospective design [8, 16, 27, 28, 30]. Some factors related to the survival in the general population are also to be considered when interpreting survival data. Since survival in the general population is affected by age and sex, mortality rates in SSc patients must be compared with age/sex-matched population; the SMR, which is the ratio of the observed to expected deaths in age/sex-adjusted cohorts in all included studies, offers this opportunity.

Indeed, our results do not show the same trend as previous observational studies. Our findings are consistent with increases in SSc mortality rates reported by epidemiological studies, although they may also reflect an increasing incidence of the disease [24–26]. For an adequate interpretation, it is important to emphasize that SMR is the ratio of the observed to expected deaths. Therefore, change in SMR over time may be the consequence of change in mortality in the studied population (SSc), change in mortality in the referenced population (general population of same age and gender living in the same community) or both. As mortality has declined in the general population over the past 40 years, a constant SMR over time as we observed should be interpreted as a similar decline in mortality in SSc to the one observed in the general population (and not as the absence of decline in mortality).

Our group performed a similar analysis concerning cardiovascular mortality in RA [36]. As in the present analysis, we found a constant SMR over time, which was interpreted as a similar decrease in cardiovascular mortality

in RA to the one observed in the general population. Likewise, this critical need of comparison with matched general population was also previously highlighted in other reports about RA [42].

In our study, we also re-analysed data after the omission of the oldest studies with mid-cohort before 1980: a trend for a decrease in SMR was noticed but was not significant. Another explanation might be that exposure to the most recent treatments may not have been long enough and the proportion of patients treated by these therapies may be too small to reveal any significant difference over time.

A previous meta-analysis of individual patient data from seven cohorts revealed SMRs ranging between 1.5 and 7.2 over the different cohorts [10]. All cohorts showed significantly high SMRs, which is consistent with our results [10].

The second outcome assessed in our analysis was the causes of the deaths. Deaths were considered as related or possibly related to SSc in 64% of cases. In accordance with previous studies, the majority of deaths were attributed to SSc [17], although they seemed to result from an increase in both the SSc-related mortality and the unrelated mortality [1–4, 6, 7, 16, 17]. In our report, the most frequent cause of mortality was heart involvement followed by lung involvement and cancer. A recent study has shown that lung complications (including both pulmonary fibrosis and pulmonary hypertension) have become the primary cause of SSc-related deaths, replacing SSc renal crisis, whereas the proportion of deaths due to heart disease has not changed significantly over time [29].

Cardiovascular causes of death might not have strictly pertained to primary heart involvement and possibly included atherosclerosis. This may explain these apparent discrepancies. However, the distinction between primary heart involvement and atherosclerosis is sometimes challenging and we assume that the consideration of heart involvement is valid. Heart microvascular involvement is very common in SSc, whereas atherosclerosis and macrovascular coronary lesions do not seem to be increased when compared with age/sex-matched populations [41, 43, 44]. Heart involvement was previously associated with poor prognosis [22, 44] and is known to be one of the leading causes of mortality in patients with SSc [1, 4–9, 11, 15, 44]. In addition, pulmonary hypertension is often associated with both right and, to a lesser extent, left ventricular involvement, consequently cardiac involvement might contribute to death considered as related to pulmonary hypertension (i.e. lung involvement) [45]. Thus, proportion of deaths caused by heart might be underestimated.

In accordance with our results, cancer was previously identified as a major cause of death in SSc [1, 5, 7, 9, 19], with several studies suggesting an increased incidence of cancer in patients with SSc [46, 47]. In our analysis, only 11% of deaths were of renal origin, which is consistent with the improvement in the treatment of renal crisis by the widespread use of ACE inhibitors [29, 39].

Our study should be interpreted within its limitations. First, this meta-analysis might be limited by the small number of studies included. Moreover, there was a significant heterogeneity across the nine included studies. However, we considered this variability in our analysis and analysed the data using an adapted random effects model. Furthermore, to reduce heterogeneity across the studies, we performed stratified analyses according to the recorded quality assessments. These stratified analyses confirmed that SMR remained constant over time. Furthermore, some limitations related to cohort studies may bias our results. Demographical characteristics, clinical subsets and organ involvement may differ across studies. However, to take this bias into account, we performed supplementary meta-regressions testing for the SMR–time relationship adjusted for age, gender and the cutaneous form of the disease, and reported that SMR still did not change over time. Differences between studies concerning antibodies status and organ involvement may also bias our results. However, these factors were not reported in five and three studies (out of a total of nine), respectively, preventing us from entering them in the model. The cause of death was unknown in 120 cases (16% of deaths) [1, 8, 11]. The assignment of the underlying cause of death on death certificates is known to be a relatively unreliable process: SSc may not be mentioned at all as a contributing or proximate cause of death [48, 49]. However, methodological research suggests that this bias is likely to be constant over time [50]. Furthermore, it is not always possible to distinguish SSc-related or unrelated mortality [13]. Moreover, heart causes of death were not limited to SSc-related causes, therefore we cannot exclude that heart causes of death may, in some cases, be non-SSc causes. Cardiovascular risk factors were not reported in the studies preventing us from adjusting causes of deaths for individual rates of risk factors. However, in SSc, some data suggest that microvascular involvement is much prominent and independent of smoking or hypertension. Nevertheless, to avoid these biases, the primary outcome used in our study was the overall mortality rather than SSc-related mortality. Finally, 194 patients were lost to follow-up, but it is unlikely that our results would be changed by this information, since it relates to only 7% of patients.

As fewer patients were included in the most recent studies as compared with the older ones, we can hypothesize that the number of contemporary patients might be too small to reach significance. This underlines the need of large contemporary cohorts, with prospective standardized data collection, to better study outcomes of this rare and heterogeneous disease. Thus, the EULAR Scleroderma Trial and Research (EUSTAR) group database, enabled by the major efforts of multiple medical centres, should allow to study SSc mortality and this evolution over time in a large population of SSc patients [17, 41].

In conclusion, SSc remains a devastating condition associated with a high risk of mortality reflected by a pooled SMR of 3.5. Despite some data suggesting a

decrease in the mortality risk in SSc, SMR has not changed significantly over the past 40 years. Cardiopulmonary involvement appears as a leading cause of mortality in SSc. Further studies are needed to assess the effect of recently available therapies on mortality in SSc.

Rheumatology key messages

- The overall pooled SMR in SSc is 3.53 (95% CI 3.03, 4.11; $P < 0.0001$).
- SMR has not significantly changed over the past 40 years.
- Cardiopulmonary involvement appears to be a leading cause of mortality in SSc.

Disclosure statement: The authors have declared no conflicts of interest.

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