Mortality in systemic sclerosis

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ABSTRACT

Systemic sclerosis is a rare and potentially devastating connective tissue disease. It is highly heterogeneous in terms of clinical presentation, extent and severity of organ involvement, immunologic abnormalities, and clinical course. Although clinical outcomes appear to have improved in recent years, the disease continues to cause substantial excess mortality. In this review, we have systematically collected the published studies addressing the mortality burden in patients with scleroderma in comparison with the general population, as well as studies exploring the most important potential predictors of mortality. Results of these studies are presented and discussed, with emphasis on methodological limitations. Suggestions are made for the design, conduct, and reporting of further research on these themes.

Introduction

Systemic sclerosis (SSc) is a rare and potentially devastating connective tissue disease that affects approximately 20 new patients per million per year and has an estimated prevalence of about 242 to 286 persons per million population in the United States (1, 2). As with many other autoimmune disorders, scleroderma affects women approximately three times as often as men and even more often during the mid- to late-childbearing years. The prevalence and clinical manifestations of scleroderma vary among groups of different racial descent (2). Race-specific prevalence estimates appear to be significantly higher for blacks than for whites. The average age at diagnosis is also significantly younger for blacks than for whites. Compared with white patients, black patients appear to be almost twice as likely to have diffuse disease (2).

The usual hallmarks of SSc are autoimmunity and inflammation, widespread small-vessel vasculopathy affecting multiple vascular beds, and progressive interstitial and vascular fibrosis in the skin as well as in internal organs, with lungs, heart, gastrointestinal tract, and kidneys being the main targets (3, 4). Fibrosis appears to account for much of the morbidity and mortality associated with scleroderma (3, 4). Nevertheless, SSc is a highly heterogeneous disease in clinical presentation, extent and severity of organ involvement, and immunologic abnormalities, and it follows a variable and largely unpredictable course.

Clinical outcomes appear to have improved considerably in the past several years, which may be attributed in part to effective therapies for organ-specific manifestations, in particular for scleroderma renal crisis (5), as well as to advances in general medical care. At the same time, the apparent improvement in survival rates may also reflect the wider recruitment at specialist centers of patients with less severe and earlier disease. Nevertheless, SSc patients continue to carry one of the highest risks of mortality of all connective tissue disorders. Reliable estimates of overall mortality risk, as well as for disease subsets, are essential for design of efficient trials concerning new treatment modalities. Besides, the challenge in deciding when to treat, given the paucity of highly effective disease-modifying therapies and the uncertainty of the benefit-to-toxicity ratio of new and old treatment strategies, highlights the importance of early identification of high-risk patients and appropriate risk stratification.

In the present article, we aim to systematically review reports that have addressed mortality is SSc and the magnitude of risk related to potential clinical and laboratory predictors. Based on this published literature, we attempt to address whether mortality and its predictors are comparable across diverse settings, or whether there is genuine heterogeneity in different countries, ethnicities, and clinical practices. We

also discuss methodological issues raised from survival studies in SSc that represent challenges to reliable identification of high-risk patients and to development of accurate prognostic and predictive assessments.

Review methods

MEDLINE (PubMed; 1966 through May 2008) was searched using the key words: "scleroderma" OR "systemic sclerosis" AND "mortality", OR "death", OR "survival", OR "outcome", OR "predictor", OR "prediction", OR "prognostic factors". Studies that addressed the mortality burden in scleroderma in comparison with the general population, as well as those that explored potential mortality predictors, were retrieved. Eligible studies of predictors were required to address at least one prognostic factor associated with at least one clinical outcome, typically a time-to-event outcome such as overall survival or with clinical manifestations. Searches were restricted to English-language publications. The references of retrieved and review articles were also screened. Duplicate data were counted only once.

Clinical overview

Usually the disease starts from the skin, although visceral involvement may precede cutaneous features (4, 5). Polyarthralgia and Raynaud's phenomenon are early and almost universal clinical manifestations. Subcutaneous edema is common in early stages, but eventually the skin becomes thickened and hidebound, with loss of normal folds. Telangiectasia, pigmentation, and depigmentation are characteristic. Ulceration about the fingertips and subcutaneous calcification are also seen (4, 5). The most reliable clinical sign to the diagnosis of SSc is skin thickening.

Many classification schemes have been developed based on pattern of skin involvement (6-8). Usually SSc is divided (6) into diffuse cutaneous SSc with rapidly progressive fibrosis of the skin, lungs, and other internal organs, and limited cutaneous SSc with skin thickening in areas solely distal to the elbows and knees; organ fibrosis in this subset is limited and slow to progress, yet vascular manifestations prevail (3, 6-8). Other investigators have subdivided the diffuse variant into those with and without truncal involvement and have alluded to differing prognostic implications (7, 9, 10).

The gastrointestinal tract is the most common internal organ involved.

Esophageal dysfunction (gastroesophageal reflux or dysphagia) is frequent and results from abnormalities in motility and later from fibrosis. Fibrosis and atrophy of the gastrointestinal tract cause hypomotility, and malabsorption results from bacterial overgrowth (4, 5).

Pulmonary involvement has emerged as potentially the most serious visceral lesion (4, 5). Diffuse pulmonary fibrosis and pulmonary vascular disease are reflected in restrictive lung physiology and low diffusing capacities. Cardiac abnormalities are common and include pericarditis, heart block, myocardial fibrosis, and right heart failure secondary to pulmonary hypertension. Scleroderma renal crisis, resulting from obstruction of smaller renal blood vessels, is a marker for an unfavorable outcome even though many cases can now be treated effectively with angiotensin-converting enzyme (ACE) inhibitors (4, 5).

Antinuclear antibody tests are nearly always positive, frequently in high titers. Anti-topoisomerase I (anti-Scl-70) antibodies are found in only one-third of patients with diffuse SSc and are correlated with interstitial lung disease. Anti-centromere antibodies (ACA) are seen in more than half of patients with limited SSc. Other disease-specific autoantibodies are less common. They include those directed against RNA polymerases (anti-RNAP I, II, and III) and those against other nucleolar proteins (Th/To, Nor-90, fibrillarin, Pm-Scl, and B23). Associations have been proposed with various patterns of organ involvement, severity, and disease progression (4). Assays for these autoantibodies generally are not commercially available.

Overview of mortality studies: definitions and metrics

Mortality and factors predictive for decreased survival in patients with SSc have been the focus of interest for over 70 years (9-15). The disease definition has changed somewhat over time. American College of Rheumatology (ACR) preliminary criteria were introduced only in 1980 (16), too late for most of the long-term studies reported in the early literature. Although these criteria were designed to establish a standard for definite disease to facilitate comparisons of groups of patients across different centers (16), in clinical practice they have been perceived and used as diagnostic criteria. Yet, the ACR criteria are not sensitive for diagnosing the full spectrum of the disease, particularly the limited variant and SSc sine scleroderma (17, 18). Therefore, recent studies have proposed additional other classification schemes with the inclusion of the intermediate SSc subset (9, 10). The absence of uniform definitions across studies, particularly for disease subtypes, might explain at least part of the variation observed in reported survival rates.

Another difficulty in comparing earlier and recent studies is that the older ones reported mortality rates without considering expected mortality in the background population. It is also sometimes unclear whether the mortality in the general population was estimated correctly and whether caveats have been taken into account for assessing mortality risk in SSc patients. The standardized mortality ratio (SMR) is the typical measure used to assess the relative mortality of patients due to SSc in comparison with the general population. It is estimated by comparing the number of observed deaths with the number of expected deaths, adjusting for age and sex, according to country-specific life tables for the calendar years of follow-up (19).

An international meta-analysis of individual patient data from SSc cohorts recruited from 7 medical centers in the USA, Europe, and Japan was published in 2005 (20). An effort was made to bypass some of the discrepancies observed among different cohorts as well as to standardize definitions and operational procedures across the participating teams. This meta-analysis included 1,645 patients who were enrolled at each participating center

Table I. Standardized mortality ratios in studies including patients with systemic sclerosis.

First author, year of publication (ref.)	Patient accrual	Study design	Country of origin	No. of patients	No. of deaths	SMR
Ioannidis JPA, 2005 (20)	1985-1996*	Meta-analysis of individual patient data	7 medical centers (2 from the USA, 4 from Europe and 1 from Japan)	3,311/1,645 (incident cases)	578	1.5-7.2**
Abu-Shakra M, 1995 (21)	1976-1990	Prospective cohort	Canada	237	NA	4.7
Hesselstrand R, 1998 (24)	1983-1995	Retrospective	Sweden	249	49	4.6
Simeon CP, 2003 (25)	1976-1996	Retrospective inception cohort	Spain	79	12	4.2
Bryan C, 1996 (22)	1982-1992	Retrospective inception cohort	UK	283	55	4.1
Jacobsen S, 1998 (23)	1960-1996	Retrospective	Denmark	344	160	2.9
Scussel-Lonzetti L, 2002 (10)	1984-1999	Prospective cohort	Canada	309	66	2.7
Ferri C, 2002 (9)	1955-1999	Multicenter, retrospective	Italy	1,012	279	NA

NA: not available; SMR: standardized mortality ratio
Some of the teams included in the meta-analysis of individual-level data had previously published team-specific data and these are not shown in the Table. *corresponds to the range of the median year of enrollment per cohort; **corresponds to the range of SMRs for 6 cohorts (Leiden, Athens, Keio, Mayo, Nijmegen, Pittsburgh).

within 6 months of the diagnosis of SSc (incident cases). As shown, SSc undoubtedly confers a high mortality risk as compared with the general population, although the magnitude of this increased mortality rate varies across different settings (Table I). All included patients fulfilled standardized definitions for disease subtype and organ system involvement (20). Therefore, the variability observed in excess mortality among participating centers may imply genuine heterogeneity or may reflect differential impact of biases related to spectrum of disease. At least seven other cohorts from several countries have also published data on SSc patients enrolled in the last 50 years and report a 2.7-fold to 4.7-fold increased risk of death (9, 10, 21-25), as compared with the general population (Table I).

An alternative approach would be to attempt to estimate the proportion of deaths that are due directly to SSc. While this approach might appear to provide in theory a robust estimate of excess mortality, unfortunately the method is limited by difficulties of accurate attribution of the cause of death, especially in population settings. Furthermore, the possible role of inflammation in development of cardiovascular disease adds additional complexity to such attempts and might well confound the cause of death in patients with SSc.

Predictors of mortality

Demographic characteristics

Most studies have demonstrated that male patients have a higher age-adjusted mortality (9, 13, 14, 24, 26, 27) compared with females (Table II), and this difference may be apparent early in the course of the disease (2). One wonders whether this is a real difference, or a reflection of differential spectrum of disease in the identified cases in men versus women. To some extent, it may reflect that women are given a SSc diagnosis even with more subtle manifestations, while for men diagnosis is made mostly in more severe cases, representing a more extreme tip of the diagnostic spectrum. Hospitalization rates may be 4.5 times higher in females than in males, but in-hospital mortality appears to be 25% lower (28). Only two studies found that prognosis was worse in females with more SSc-related deaths in this group of patients (22, 29), whereas another study showed that SMR was not significantly influenced by sex (23).

Older age at diagnosis (10, 11, 13, 14, 25, 27, 30-37) has also been described as a factor associated with decreased survival (Table II), again consistent with the general population. A large study including 706 SSc cases showed that the observed survival was considerably less than the expected survival for a population matched for age, sex, and race (2). The risk of death increased 5% for each 1-year increase in age at diagnosis (hazard ratio: 1.04, 95% CI 1.03-1.05) (2). Proper calculation of the SMR is important in avoiding spurious claims of excess proportional increase in mortality in older patients. At least one study found that SMR was not significantly influenced by age at disease onset (23).

Race-specific mortality estimates for black patients as compared with non-black patients appear to be greater (13, 27, 38), particularly during the first years after diagnosis, but this disadvantage does not widen with longer follow-up (2). Black and other non-Caucasian SSc patients have significantly greater odds of in-hospital death than whites, even after adjustment for markers of socioeconomic status, disease severity, and co-morbidities (39).

Clinical features

The extent of skin sclerosis has been traditionally considered as a useful marker both of current severity and future prognosis. Several studies (9, 23, 24, 37, 40) including the meta-analysis of individual level data (20) indicate that the diffuse variant is a consistent independent predictor of decreased survival (Table II). SMRs are more than 2-fold higher in diffuse SSc (SMR: 6.17) compared with limited SSc (SMR: 2.71) (10). Survival has been reported to be significantly better in patients with skin thickening in upper extremities

proximal to MCP joints without trunk involvement (intermediate variant) than in those with diffuse SSc, but the proposed association is tentative (log-rank p=0.03) (10). A high baseline skin score with no change during follow-up has also been associated with poor survival (41) while striking improvement within 2 years after the initial evaluation has been associated with more favorable outcomes (41, 42). Early rapid progression of skin thickening has also been linked with heart involvement and an increased probability of developing SSc renal crisis over the subsequent 4 years (43).

Overall, the net effect of skin involvement on mortality is difficult to elucidate considering its association with major internal organ manifestations. Renal, pulmonary, and cardiac involvement are important independent adverse predictors, as shown in the meta-analysis (20) and a number of other studies (Table II) (2, 9, 25, 37, 40). Yet, the magnitude of each of these predictors varies across different cohorts (20). Low diffusing capacity for carbon monoxide (Table II) as an indicator of pulmonary disease is a consistent poor prognostic factor (10, 30, 40, 44) while the value of bronchoalveolar lavage cellular profiles appears limited (45). Pulmonary arterial hypertension (PAH) is widely recognized as an important SSc manifestation of both subtypes; the mortality rate for those patients who present PAH may be higher than 20% at two years of follow-up (46-48). Esophageal involvement does not appear to be a prominent risk factor for mortality in SSc and possibly does not affect mortality at all (20). Renal, cardiac, and pulmonary involvement tend to occur together (20) and severe organ manifestations in diffuse SSc patients most often occur early in the disease course (49).

Using this information one can identify a group of patients with relatively favorable prognosis. Patients with limited SSc and no renal, cardiac or pulmonary involvement for 3 years after the disease onset who also have a negative test result for anti-Scl-70 appear to have a subsequent risk of death similar to the general population (20).

Common laboratory findings

There have been three reports suggesting that anemia is an adverse predictor (10, 11, 30) which appears to be independent of any renal effect on blood counts. Similarly, there have been a number of studies suggesting that the erythrocyte sedimentation rate (9-11, 27, 37, 44) as a nonspecific marker of underlying disease activity carries an increased risk of subsequent mortality (Table II) with a rise as modest as 25 mm/h being significant. Leukocytosis, thrombocytosis, hypergammaglobulinemia, low total serum protein level, reduced renal function, abnormal urine sediment, and proteinuria without scleroderma renal crisis (27, 30, 31, 44, 50) have been proposed also as poor predictive factors (Table II). However, it is unclear whether any of these laboratory abnormalities confer truly independent risks beyond demographic and clinical characteristics of the patients. A considerable correlation would be anticipated for several of these laboratory abnormalities among themselves and also with clinical manifestations.

Some studies have proposed the use of models and severity scores to predict mortality in SSc patients (41, 51, 52). A logistic regression model has been proposed to predict accurately the subsequent 5-year mortality experience using only 3 laboratory measurements: elevated erythrocyte sedimentation rate (≥25 mm/h), proteinuria, and low monoxide diffusing capacity (<70% of predicted) (44). However, this was based on a dataset of only 76 deaths, and validation was performed only with internal Monte Carlo cross-validation (leave-one out process), but not external validation. Further study is needed to assess whether organ system or aggregate score is most predictive of survival and more informative in making clinical decisions about individual patients.

Autoantibodies

The meta-analysis of individual level data showed that anti-Scl-70 antibodies increased the baseline risk of death by an additional 1.3-fold (20) and independently of the presence of major organ involvement (Table II). Previous studies had reached conflicting conclusions regarding the potential association of anti-Scl-70 positivity with mortality (32, 53, 54). In addition, pulmonary interstitial fibrosis is a prominent cause of death in SSc patients who are anti-Scl-70 positive (55). Apart of their predictive implications, anti-Scl-70 antibodies have been correlated with the diffuse variant, Raynaud's phenomenon, pulmonary involvement, and less so with cardiac manifestations, distal osteolysis, digital joint deformity, and low prevalence of calcinosis (9, 20, 55, 56). More interestingly, if they are detected in patients with diffuse SSc who have rapid skin thickness progression rate, they may define a clinically distinct subset that is at greatest risk for early and often fatal cardiac and renal involvement (57).

Anti-RNAP antibodies also have been considered to predict poor survival (40). In addition, these antibodies are associated with the diffuse subtype, right heart failure and a high likelihood of developing SSc renal crisis during follow-up (40), whereas ACA antibodies appear to predict a more favorable disease course (Table II) (9, 32). Nevertheless, it is rather difficult to postulate that these autoantibodies are independent predictors of a better prognosis, as adjustment for clinical manifestations was not used in most of these studies.

Changing pattern in causes of death in systemic sclerosis

Data from the Pittsburgh cohort have demonstrated that the 10-year cumulative survival improved significantly from 53% in the 1970s to 67% in the 1990s (58). Similar results were reported in another long-term study of 1,012 Italian SSc patients in whom 10-year survival was 61% before 1985, which improved to 77% in more recent years (9). The most impressive change over time pertains to SSc renal crisis. The frequency of deaths due to renal crisis decreased significantly over the 30-year time period, from 42% to 6% of SSc-related deaths (58). This has been attributed to earlier diagnosis and use of ACE inhibitors. At the same time, the proportion of patients with SSc who died from pulmonary fibrosis

Table II. Proposed predictors of mortality by multivariate models in studies including patients with systemic sclerosis.

First author, year of publication (ref)	Patient accrual	Study design	Country of origin	Enrollment date-eligibility	No. of Patients	Proposed independent adverse predictors
Wynn J, 1985 (14)	NA	NA	NA	NA	64	Older age, presence of an S3 gallop
Altman RD, 1991 (30)	1973-1977	Multicenter	USA	Within 2 years of diagnosis	264	Older age, DL_{CO} ≤50%, Hb ≤11 g/dl, BUN >16 mg/dl, TPR ≤6 gm/dl, FVC <80%
Kaburaki J, 1992 (31)	NA	Retrospective	Japan	NA	86	Older age, male sex, abnormal resting ECG, decreased FVC, pulmonary fibrosis on the chest x-ray, proteinuria, leukopenia, hypergammaglobulinemia
Lee P, 1992 (36)	NA	Prospective cohort	Canada	NA	237	Older age, renal, cardiac, lung involvement
Bulpitt KJ, 1993 (50)	1982-1987	Inception cohort (multicenter)	USA	Only patients with disease diagnosis < 1 year	48	Abnormal cardiopulmonary signs on physical examination, elevated ESR, leukocytosis, thrombocytosis, abnormal urine sediment (pyuria, hematuria)
Hesselstrand R, 1998 (24)	1983-1995	Retrospective	Sweden	Referred patients from hospitals throughout Sweden	249	Male sex, diffuse skin involvement
Bryan C, 1999 (44)	1982-1991	Prospective cohort	UK	Onset of self-reported cutaneous sclerosis after 1982	280	ESR≥ 25 mm/h, proteinuria, DL_{CO} ≤70%
Steen V, 2001 (42)	1972-1997	Prospective cohort	USA	Within 2 years of diagnosis of early (<3 years) diffuse SSc	278	Older age, higher peak skin score, higher frequency of severe organ involvement
Jacobsen S, 2001 (40)	1960-1996	Retrospective	Denmark	Onset of cutaneous sclerosis (only incident cases)	174	Diffuse skin involvement, right heart failure, DL_{CO} <40% SSc renal crisis
Ferri C, 2002 (9)	1955-1999	Multicenter, retrospective	Italy	At diagnosis	1,012	Male sex, diffuse skin involvement, renal, cardiac, lung involvement, ESR ≥25 mm/h,
Scussel-Lonzetti L, 2002 (10)	1984-1999	Prospective cohort	Canada	At diagnosis	309	Older age, skin involvement of the trunk, DL_{CO} ≤70%, ESR ≥25 mm/h, Hb ≤12.5 g/dl
Ruangjutipopan S, 2002 (33)	NA	NA	Thailand	NA	222	Older age, cardiac involvement
Simeon CP, 2003 (25)	1976-1996	Retrospective inception cohort	Spain	Referred patients with an interval of ≤15 years between onset and disease diagnosis	79	Older age, SSc renal crisis, FVC<70%
Mayes MD, 2003 (2)	1989-1991	Retrospective (capture-recapture analysis)	USA	Diagnosis prior to 1/1/1992	706	Male sex, older age, renal, lung, gastrointestinal involvement
Ioannidis JPA, 2005 (20)	1985-1996*	Meta-analysis of individual patient data (multicenter)	7 medical centers	Within 6 months of the first physician diagnosis	3,311/1,645 (incident cases)	Renal, cardiac, lung involvement, anti-topoisomerase I antibodies
Shand L, 2007 (41)	1983-2001	Retrospective	UK	Within 24 months of the first non-Raynaud's manifestation	225	High baseline skin score without improvement during follow-up
Czirjak L, 2008 (37)	1983-2005	Retrospective	Hungary	NA	366	Older age, diffuse skin involvement, renal involvement, increased ESR, coexistence of a malignant disease

BUN: blood urea nitrogen; DL_{CO}: diffusing capacity for carbon monoxide; ECG: electrocardiographic findings; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; Hb: hemoglobin; NA: not available; SSc: systemic sclerosis; TPR: total serum protein level.
Some of the teams included in the meta-analysis of individual-level data had previously published team-specific data and these are not shown in the Table. Duplicate publications were also excluded from this table. Studies from the same center were included only if they explored the predictive ability of different markers.
*corresponds to the range of the median year of enrollment per cohort

increased from 6% to 33% (58). The frequency of pulmonary hypertension, independent of pulmonary fibrosis, also increased significantly during this time period in this cohort (58). Thus, 60% of SSc-related deaths were from both these pulmonary complications combined (58), implying that the lung is the most important organ in excess mortality from SSc.

Methodological limitations of mortality studies in SSc

Interpretation of the results of mortality studies in SSc may be difficult due to methodological limitations. Selection biases appear relatively often and may work in different directions (Table III).

The SMR ideally should be estimated based on all cases diagnosed after thorough and uniform screening of the population of interest for SSc. However, this is impractical. Since SSc is a rather rare disease, expertise at managing these patients inevitably becomes concentrated in a few tertiary referral centers, and it is from such centers that most publications on natural history data emerge. Such centers have the best expertise in managing these patients, and it is possible that the mortality rates in referred cases may be lower than in cases of similar severity that are not referred for expert management. However, there is no study addressing this question directly for SSc and there is debate in the literature on how much specialized centers can improve outcomes for diverse diseases (59, 60).

Second, referral centers are also likely to receive the more severe cases and thus the actual mortality from scleroderma may be overestimated. Third, the initial time-point from which survival is estimated can also affect the results. The onset of the disease may be defined as the start of skin involvement, or alternatively, the onset of Raynaud's phenomenon may be used as the starting point in the course of scleroderma. Depending on the choice of definition of onset, variable time lags may be introduced between the true onset of disease and the first attendance. Additionally, those patients presenting to their doctor with a rampant course, with early diffuse cutaneous and visceral involvement, who are perhaps at greatest risk of death, would not necessarily survive long enough to be included in longitudinal studies. This lag may introduce a selection bias into studies conducted at tertiary referral centers and thus overestimate survival relative to that among the real entire spectrum of patients. Survival may also be falsely increased in retrospective studies that used participants' recalled date of disease onset. Such studies are biased owing to the study cohort being, by definition, a surviving cohort that was selected on the basis that patients had not died before referral.

Some of these biases may also influence the evolution of SMR estimates over time. Spectrum of disease bias (with selection of only the worse cases) may be attenuated over time, if there is more sensitization in the healthcare system about making an earlier diagnosis and asking for expert rheumatologist help earlier. This would lead to decreasing SMR estimates over time. Increasing lead time bias (due to earlier diagnosis) may similarly lead to a spurious seeming prolongation of survival without necessarily better treatment or truly improved outcomes.

There is also a need to differentiate between incident and prevalent cases. Incident cases (new diagnoses) are more representative, since they are followed from the first time the disease is diagnosed. Conversely, in prevalent cases, the diagnosis has occurred some time in the past. Prevalent cases are thus enriched in patients who have already survived long enough to be included in the study. SMR estimates for cohorts of prevalent cases would be underestimated if the time of initiation of follow-up is considered to be the time of retrospective diagnosis; SMR may be either over- or under-estimated if the time of initiation of follow-up is considered to be the time of referral to the study cohort. The international meta-analysis has tried to overcome these limitations by focusing on patients enrolled at each participating center within 6 months of diagnosis (20). Some other studies (10, 30, 44, 55) have also attempted to overcome these shortcomings by concentrating only on

Table III. Some key biases that may affect standardized mortality rates in studies including patients with systemic sclerosis.

Potential biases	Effect on mortality rate
Better management with better outcomes for patients managed in referral centers	Underestimation*
Selective recruitment of more severe cases in referral centers	Overestimation*
Variable time lag from onset of disease to start of follow-up	Over- or underestimation*
Survivorship bias (extremely severe cases die before even being referred)	Underestimation*
Improved sensitization of the referring general healthcare referring system with referral of more mild cases over time	Spuriously diminishing SMR over time
Improved sensitization of the general healthcare referring system with referral of earlier diagnosed cases (increased lead time)	Spuriously diminishing SMR over time
Inappropriate use of control population in the SMR estimation	Overestimation*
Losses to follow-up of people with worse outcomes (including unrecorded deaths)	Underestimation*

SMR: standardized mortality rate; SSc: systemic sclerosis

*as compared with SMRs calculated in theory based on prospective registration of all cases and outcomes under ideal circumstances in a perfectly accurate general population registry with properly chosen population control.

locally referred patients identified early in the disease course.

SMRs would also be biased if the general population (after age and gender adjustment) is not a proper control for SSc patients. Given that we know relatively little about the pathogenesis of SSc, it is not possible to adjust for any other potential confounders. This is probably fair, since there is no strong evidence that other classic predictors of mortality for general populations (*e.g.*, socioeconomic status) are associated also with the risk of SSc.

Additionally, there is a difficulty in some studies of loss to follow-up with incomplete ascertainment of vital status at the end of the follow-up period. This introduces bias if there is a selective difference in the likelihood of death between those with and without follow-up data. The direction of such a bias varies. In some study designs, using population death registers, deaths are ascertained more completely than when patients or their doctors are contacted for follow-up, in which cases deaths are likely to be preferentially missed.

In general, studies of prognostic factors have many limitations both in their design and in their reporting in the literature. There is evidence from independent research fields (*e.g.*, cancer prognosis) that prognostic factor studies are selectively reported in the literature (61) and there is a strong predilection for publishing statistically significant prognostic associations (62), while ignoring non-significant predictors, rendering the reports less than optimally informative. It is difficult to probe the extent of missing, unpublished "negative" data. Given that protocols of prognostic investigations are not available a priori, it is even more difficult to know whether and how selective reporting of outcomes and analyses has operated in prognostic research (63, 64). However, given the existing flexibility in definition of the disease and its subgroups and also the definition of the candidate prognostic factors and the mode of their analysis, selective reporting of outcomes and analyses may be responsible for several spurious prognostic effects.

At a minimum, it is likely that some of the estimates of prognostic effects are inflated compared with the true associations (65). Moreover, there are no standards for reporting results of prognostic studies and important aspects of the design are often missing. Deficiencies in the study design may either inflate or deflate estimated prognostic effects (66). With suboptimal reporting, it becomes even more difficult to probe into the depth of possible bias. The international meta-analysis tried to overcome several of these limitations by ensuring that all data from the participating teams were contributed to the analyses, irrespective of the strength of the observed associations and that consistency of harmonization was enforced in definitions and analyses (20). Nevertheless, even this meta-analysis was retrospective and full standardization was not possible.

Another key issue in the literature of SSc is that several candidate prognostic factors have been probed in small studies and/or without full adjustment for other established predictors of death. Many clinical manifestations, common laboratory tests and autoantibodies are modestly or even highly correlated among themselves. In this situation, it is unclear whether each of these can offer any incremental prognostic information, once a few key features of the disease are known.

The international meta-analysis found that autoantibodies contributed rather limited additional prognostic information beyond what the clinical manifestations would provide alone (20). This project did not evaluate simpler laboratory tests (20), but it is unknown whether these would offer additional prognostic ability in multivariate models. Furthermore, even proper multivariate models do not necessarily provide the most accurate data because the considered predictors may be correlated, leading to multi-collinearity and uncertainty in the derived regression coefficients.

Consideration of time-dependent information concerning some classic clinical manifestations could also improve the prognostic capacity. Finally, more complex modeling with hierarchical regressions may be desirable, to consider more composite correlations and relationships between variables. However, such efforts would require very large databases with carefully collected data concerning all these predictors, and a better understanding of how they may be interrelated with one another, and which one precedes the others. Further external validation of proposed multivariate models is also desirable, especially if derived from limited datasets.

Conclusions

Scleroderma patients continue to experience considerable excess mortality. The relative improvements over the last few decades may reflect better preventive management of some manifestations, in particular renal crisis, as well as general improved medical care for infection and other comorbidities. However, much of the improvement may be spurious, due to differential biases affecting studies in collecting information over several decades, in changing healthcare environments, and increased recognition of patients with disease. Substantial heterogeneity in the mortality risk across diverse settings is obvious, as expected. Involvement of lung, heart, kidney – but not esophagus – and to a lesser extent anti-Scl-70 antibodies are significant predictors of mortality. Although they have been documented to have considerable correlation, these variables also confer independent prognostic information. Pulmonary involvement (both pulmonary arterial hypertension and pulmonary fibrosis) has replaced renal crisis as the primary cause of SSc-related deaths. While a large number of other risk factors for mortality have been reported, the evidence for many is either weak or susceptible to bias, and a few key aspects of the clinical picture may still provide the majority of the prognostic insight. This should not diminish the importance of further research on laboratory and molecular factors. However, this research should ideally be coupled with large-scale collaborative studies that allow for proper validation of proposed prognostic markers for premature death in patients with SSc.

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