Determinants of Morbidity and Mortality of Systemic Sclerosis in Canada

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Objectives: To describe the morbidity and mortality in Canadian scleroderma (SSc) patients focusing on gender, SSc type, and organ-specific prognosis in a cohort of patients seen from 1994 to 2004 in a Southwestern Ontario SSc clinic. We also compared this cohort to data from the literature, which showed that mean survival in recent studies has risen to 72 months versus 48 months in earlier studies.

Methods: This was a cohort study of all SSc patients followed at 1 rheumatology center. Data were abstracted by chart review and entered into a database. The demographic and clinical characteristics of SSc patients were compared between those who survived versus those who died over the 10-year follow-up period. Five- and 10-year survival rates were compared between cohort subsets (sex, diffuse/limited disease type, and organ involvement including the following: scleroderma renal crisis, interstitial lung disease (ILD), hypertension, cardiac, gastrointestinal involvement, pulmonary arterial hypertension, and antinuclear antibody positivity).

Results: One hundred eighty-five subjects (158 women), 63% with limited cutaneous SSc, were included. The mean disease duration until last visit or death was 9.1 years (7.9 years in diffuse and 9.8 years in limited). Although more women had either subtype, men were more likely to have diffuse cutaneous SSc (dcSSc) than women (67% of men had dcSSc versus 32% of women, $P = 0.0009$), and to have an earlier mean age of diagnosis (41.3 ± 2.8 years old versus 49.7 ± 1.2 years, $P = 0.006$). Overall mortality was 23%; 22% of men ($n = 6$) and 23% of women ($n = 36$) were deceased. The 5-year survival was 90% (95% for limited and 81% for diffuse) and the 10-year survival was 82% (92% for limited and 65% for diffuse). Deceased persons were more likely to have had dcSSc ($P = 0.03$), cardiac disease ($P < 0.0001$), ILD ($P = 0.006$), gastrointestinal disease ($P = 0.01$), and systemic hypertension ($P = 0.009$). Four of 13 patients with scleroderma renal crisis died. Survival analyses demonstrated that persons with dcSSc ($P = 0.001$), cardiac disease ($P < 0.0001$), and hypertension ($P = 0.01$) had worse survival rates than their counterparts without these disorders. The primary cause of death was ascertained for 33 of the 42 deceased individuals and included the following: pulmonary arterial hypertension ($n = 5$), renal complications ($n = 9$), ILD ($n = 10$), and cardiac complications ($n = 9$). There appears to be a trend toward longer survival of scleroderma patients over the past few decades.

Conclusions: We conclude that cardiac involvement, dcSSc, and hypertension are associated with worse survival, and survival of patients with scleroderma is improving compared with older reports in the literature.

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Systemic sclerosis (SSc, scleroderma) is a chronic connective tissue disease with inflammation and fibrosis of the skin, vascular abnormalities, visceral damage, and production of autoantibodies (1). SSc can be subdivided into limited and diffuse disease. The latter has a greater extent of skin involvement and is more likely to be associated with renal crisis, pulmonary fibrosis, and cardiomyopathy, and thus increased mortality risk and subsequent decreased survival (1-4). Prognosis is worse in SSc than in other rheumatic diseases (5,6) and the risk of mortality is high (4-5 times greater than that of an age- and sex-matched population) (6).[1] Although survival in SSc is still low, it has improved during the past few decades, as demonstrated by a review of the literature that reported the mean survival rate from later studies was significantly higher than that of earlier studies (72 versus 48 months) (5,7,8). Improvements in the disease detection and treatment of SSc-related organ involvement (especially renal disease) have contributed to improved survival (9).

Known predictors of worse survival in SSc include organ involvement, male gender, and earlier age at diagnosis. Diffuse disease and anticentromere antibody negativity have been associated with mortality in some studies, but these may actually be proxy associations for increased organ involvement (9). There is some evidence for worse survival in certain ethnic groups, such as First Nations (Canada's indigenous peoples) and blacks, but it is unknown if this is an effect of genetics and/or socioeconomic status (10,11).

Scleroderma renal crisis (SRC) usually only occurs in diffuse scleroderma, whereas pulmonary arterial hypertension (PAH) occurs approximately equally in limited and diffuse SSc (1). Mortality from SRC has decreased over the past few decades, in part due to the introduction of angiotensin converting enzyme (ACE) inhibitors (12-15). Also, SRC is uncommon so 44% of all SSc deaths have been due to lung disease (interstitial, vascular, or both) (16,17). PAH increases mortality in both limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (17). Patients with dcSSc may have anti-DNA topoisomerase I antibodies (Scl-70) and are at increased risk of death from interstitial lung disease (ILD). Ten-year survival rates were found to be 93% in patients with anticentromere antibody (positive only in lcSSc) and 66% in patients with Scl-70 (18).

We examined the morbidity and mortality of SSc patients at 1 clinic serving patients from southwestern Ontario and compared our observations to previous literature. Our hypotheses were as follows: (1) mortality rates would be lower than in older studies; and (2) patients with dcSSc would suffer from increased mortality due to other organ involvement. Secondary objectives were to compare survival in the following: (1) men and women; (2) various organ involvements; and (3) antinuclear antibody (ANA)-positive status.

[1] The 10-year survival in Canada for the comparable age groups is 98% for men and 95% for women (from Statistics Canada).

MATERIALS AND METHODS

Study Design

This was a cohort study. Demographic and clinical characteristics of SSc patients were compared between those who survived versus those who died during follow-up in a rheumatology SSc practice between 1994 and 2004.

Data Collection

The database was constructed using the medical records of patients with a diagnosis of SSc who met preliminary American College of Rheumatology criteria (19), or who had CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) (20). Patients were categorized as having diffuse or limited disease (20) and demographics including age, gender, and ethnicity were recorded. Clinical factors such as disease duration, organ involvement, smoking, and cancer history were obtained from medical charts. The presence of lung disease was assessed from pulmonary function tests as well as radiological assessments of chest radiographs and computed tomography scans. For the interpretation of the pulmonary function tests, FVC (% predicted forced vital capacity) and DLCO (% predicted of diffusing capacity of carbon monoxide) values were measured. PAH was defined as PAH diagnosed by a specialist, or right heart catheterization evidence of PAH. Renal involvement was defined as elevated creatinine and/or the development of renal crisis (hypertension with microangiopathic hemolysis, and/or raised creatinine levels) and was determined by expert diagnosis. Cardiac involvement was established by the presence of clinical symptoms, electrocardiogram with arrhythmia, left anterior descending blockage, left bundle branch block, ischemia, left ventricular hypertrophy (LVH). Doppler echocardiography results of left ventricular abnormalities, and/or the presence of pericarditis. The presence of other internal organ pathology was obtained from medical records. Missing patient information was retrieved by contacting the patient or family physician. Current vital status was confirmed via contact with the family physician's office. Death summaries were requested if the cause of death was unknown. We analyzed all survival as the difference between date of diagnosis of SSc and death or time of last follow-up (living). Thus, if a patient had 12 years of SSc and then developed PAH and died 2 years later, the time to death would be considered 14 years. Thus, organ involvements that occur late in the disease could look as though survival was long using these methods.

Analysis

Descriptive statistics were used to characterize the cohort and analytical testing was done to determine if disease