Survival, Causes of Death, and Prognostic Factors in Systemic Sclerosis: Analysis of 947 Brazilian Patients

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ABSTRACT. ***Objective.*** To analyze survival, prognostic factors, and causes of death in a large cohort of patients with systemic sclerosis (SSc).

Methods. From 1991 to 2010, 947 patients with SSc were treated at 2 referral university centers in Brazil. Causes of death were considered SSc-related and non-SSc-related. Multiple logistic regression analysis was used to identify prognostic factors. Survival at 5 and 10 years was estimated using the Kaplan-Meier method.

Results. One hundred sixty-eight patients died during the followup. Among the 110 deaths considered related to SSc, there was predominance of lung (48.1%) and heart (24.5%) involvement. Most of the 58 deaths not related to SSc were caused by infection, cardiovascular or cerebrovascular disease, and cancer. Male sex, modified Rodnan skin score (mRSS) > 20, osteoarticular involvement, lung involvement, and renal crisis were the main prognostic factors associated to death. Overall survival rate was 90% for 5 years and 84% for 10 years. Patients presented worse prognosis if they had diffuse SSc (85% vs 92% at 5 yrs, respectively, and 77% vs 87% at 10 yrs, compared to limited SSc), male sex (77% vs 90% at 5 yrs and 64% vs 86% at 10 yrs, compared to female sex), and mRSS > 20 (83% vs 90% at 5 yrs and 66% vs 86% at 10 yrs, compared to mRSS < 20).

Conclusion. Survival was worse in male patients with diffuse SSc, and lung and heart involvement represented the main causes of death in this South American series of patients with SSc. (J Rheumatol First Release Aug 15 2012; doi:10.3899/jrheum.111582)

Key Indexing Terms:

SYSTEMIC SCLEROSIS | SURVIVAL ANALYSIS | PROGNOSIS
CAUSES OF DEATH | LUNG INVOLVEMENT | HEART INVOLVEMENT

Systemic sclerosis (SSc) is a diffuse connective tissue disease characterized predominantly by fibrosis and vascular abnormalities affecting skin and internal organs. Many studies have examined the causes of death and the predictors of poor outcome in SSc[1]. Steen and Medsger, analyzing the Pittsburgh SSc database from 1972–2002, found a significant change in the causes of death in SSc[2]. The frequency of deaths due to scleroderma renal crisis (SRC) decreased over the 30-year period, from 42% to 6% of the SSc-related deaths; whereas lung involvement (pulmonary fibrosis and pulmonary hypertension) is now the main cause of SSc-related deaths[2]. Another study from the same group indicated that the severity of the disease predicted early death; in patients with severe skin (modified Rodnan skin score > 40), lung (forced vital capacity < 55% predicted), heart (severe arrhythmia or congestive heart failure), gastrointestinal (GI; malabsorption, pseudo-obstruction), or kidney involvement, the 9-year cumulative survival was 38%, while it was 78% in patients who had mild organ involvement[3]. A recent study analyzing causes of death and risk factors in a large worldwide series of 5860 patients with SSc prospectively followed in the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) cohort found that 55% of the 234 deaths were attributed directly to SSc [35% to pulmonary fibrosis, 26% to pulmonary arterial hypertension (PAH) and 26% to cardiac causes], and 41% to non-SSc causes (mainly infections, malignancies, and cardiovascular causes). Independent risk factors for mortality included proteinuria, the presence of PAH based on echocardiography, forced vital capacity

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below 80% of normal, diffusing capacity of the lung, patient age at the onset of Raynaud's phenomenon, and the modified Rodnan skin score[4].

Epidemiologic variables associated with a poor prognosis are male sex[5,6,7,8] and older age at onset[5,8,9,10,11,12,13,14,15,16]. Among the clinical variables associated with a worse prognosis are diffuse skin involvement[6,7,12,13,16,17] and internal organ involvement affecting lung[6,7,8,9,10,11,12,13,15,18,19,20,21,22,23,24], kidney[7,8,11,12,14,16,17,20,21], heart[7,11,12,14,17,18,20,21,22,23,24], and GI tract[8]. Laboratory variables include anemia[10,13], increased erythrocyte sedimentation rate (ESR)[7,13,16,18,19], abnormal urine sediment[5,18,19], hypergammaglobulinemia[5], and anti-Scl-70 antibody[20] as factors of poor prognosis.

The series of Tuffanelli and Winkelmann, analyzing 727 patients with SSc, showed a 5-year survival of 70% and a 10-year survival of 59%[25]. This survival gradually improved in the last decades; the best results were associated with a lower percentage of diffuse SSc (dcSSc) and severe organ involvement in the different series. Many studies analyzed longterm survival in SSc. Al-Dhaher, *et al*, in a cohort of 185 patients with SSc in Canada, found a 5-year survival rate of 90% and a 10-year survival rate of 82%[26]. Joven, *et al* observed survival rates of 85%, 75%, and 55% at 5, 10, and 20 years[27] in 204 patients in Spain. Nihtyanova, *et al*, analyzing 520 patients with SSc from the Royal Free Hospital in London, showed that the 5-year survival among patients with dcSSC improved from 69% in a historical cohort (1990–93) to 84% in a contemporary cohort (2000–03), whereas 5-year survival among patients with limited SSc (lcSSc) remained unchanged (93% and 91%, respectively)[28]. Hashimoto, *et al*, analyzing 405 Japanese patients with SSc 1973–2009, found an overall 10-year survival rate of 88%, associated to a significantly higher mortality in the SSc population compared to the general population (standardized mortality ratio 2.76)[29]. A study from Taiwan, analyzing 1479 patients with SSc 2003–07, found a 5-year survival rate of 82.3%; the main risk factors for death were male sex, older age, diagnosis of cancer, and endstage renal disease[30].

A recent systematic review and metaanalysis of cohort studies published from January 1960 to June 2010 showed that SSc is still a very severe disease, reflected by a standardized mortality ratio of 3.5; heart and lung involvement were the main causes of death in a total of 2691 patients[31].

The objective of our study was to report and analyze survival, causes of death, and prognostic factors in a Brazilian series of 947 patients followed at 2 referral university centers.

MATERIALS AND METHODS

Nine hundred forty-seven consecutive patients with SSc treated at the SSc outpatient clinics of the University of São Paulo and University of Campinas between January 1991 and December 2010 were analyzed. These patients lived predominantly in an industrial region of about 20 million inhabitants in the State of São Paulo (southeast Brazil). The 2 universities used the same protocol of investigation for patients with SSc.

All patients fulfilled the American College of Rheumatology classification criteria for SSc[32] and were divided into the subtypes dcSSc and lcSSc, according to LeRoy, *et al*[33]. Patients were also diagnosed as having SSc sine scleroderma according to established criteria[34].

All patients had appointments at least once a year, depending on the severity of their disease. Patients who did not attend a scheduled medical consultation for > 1 year were contacted.

For the patients who did not die at the university hospitals of the University of São Paulo or Campinas, death certificates were requested from the families; if necessary, attending physicians at the time of death were contacted about its specific causes.

Each death was classified as primarily related to SSc or not. The SSc-related causes of death were (1) lung involvement such as interstitial lung disease (ILD), determined by radiograph, high-resolution computed tomography, pulmonary function tests, or hypoxemia requiring oxygen supplementation; (2) lung involvement such as pulmonary hypertension (PH), defined by right heart catheterization with mean pulmonary arterial pressure > 25 mm Hg, or by Doppler echocardiogram with systolic pulmonary artery pressure > 40 mm Hg, not associated to pulmonary fibrosis; (3) ILD + PH: patients with ILD who also presented PH in the followup, and both involvements were considered associated to death; (4) heart involvement such as congestive cardiac failure, arrhythmias, or conduction defects (not attributable to other cardiac conditions) requiring treatment; (5) renal: deaths during the SRC or related to dialysis; (6) GI: severe involvement of the esophagus or small bowel, resulting in malabsorption or malnutrition; and (7) multiorgan failure: severe simultaneous damage from > 1 SSc-related organ involvement, in which it was difficult to determine the primary organ that was the cause of death.

The non-SSc-related causes of death included (1) infection: septicemia as the main cause of death, independent of SSc activity; (2) cardiovascular or cerebrovascular disease: patients who died of myocardial infarction or stroke, or of complications from chronic non-scleroderma atherosclerotic heart disease; (3) cancer: patients who died of cancer, independent of severe organ involvement; (4) sudden death: a sudden death without prior SSc heart disease and without obvious etiology; and (5) other: a variety of common causes of death not related to SSc.

Statistical analysis. Pearson chi-square test (categorical variables), t-test (numeric variables), and log-rank test (survival curve) were used to identify the prognostic factors. Multivariate logistic regression analysis was performed to define predictive factors of death. Survival at 5 and 10 years was estimated using Kaplan-Meier method.

RESULTS

According to the clinical variant, 533 patients (56.4%) presented with limited SSc, 294 (31%) dcSSc, 79 (8.3%) SSc sine scleroderma, and 41 (4.3%) an overlap syndrome. There were 838 (88.5%) female and 109 (11.5%) male patients, as well as 712 (75.2%) whites and 235 (24.8%) African Brazilians (black patients of unmixed ancestry and mulattos, i.e., originating from the mixture of white and black individuals).

Demographic and clinical variables related to the 947 patients with SSc are presented in Table 1.

One hundred sixty-eight patients (17.7% of the whole group) died during the followup; 110 deaths (65.5%) were considered related to SSc. Among those deaths, we found a predominance of lung involvement (48.1%), heart involvement (24.5%), renal crisis (10.9%), and multiorgan failure (9.1%; Table 2). Among the deaths related to lung involve-

Table 1. Clinical, demographic, and immunological data in 947 patients. Data are number (%) unless otherwise indicated.

Characteristic	
Age at disease onset, mean (± SD), yrs	42.6 (14.1)
Disease duration, mean (± SD), yrs	12.9 (8.5)
Followup period, mean (± SD), yrs	9.6 (7.7)
Race	
White	838 (88.5)
African Brazilian	109 (11.5)
Clinical variant	
Limited	712 (75.2)
Diffuse	235 (24.8)
Sine scleroderma	79 (8.3)
mRSS < 20	635 (67.1)
≥ 20	312 (32.9)
Calcinosis	162 (17.1)
Telangiectasia	464 (49.0)
Ulcers	235 (24.8)
Osteoarticular involvement*	452 (47.7)
Esophageal (hypomotility and/or GERD)	897 (94.7)
Interstitial lung disease (ILD)	538 (56.8)
Pulmonary hypertension (PH)	221 (23.3)
ILD + PH	132 (13.9)
Heart	111 (11.7)
Renal crisis	25 (2.6)
Antinuclear antibodies	839 (88.6)
Anticentromere antibody	209 (22.1)
Anti-Scl70	152 (16.1)

* Inflammatory polyarthralgia or polyarthritis. mRSS: modified Rodnan skin score; GERD: gastroesophageal reflux disease.

Table 2. Causes of death. Data are number.

Deaths Related to SSc (n = 110)	
Lung involvement	53 (48.1)
Interstitial lung disease (ILD)	18 (16.3)
Pulmonary hypertension (PH)	18 (16.3)
ILD + PH	17 (15.5)
Heart involvement	27 (24.5)
Congestive cardiac failure	20 (18.2)
Cardiac arrhythmia	7 (6.3)
Scleroderma renal crisis	12 (10.9)
Multiorgan failure	10 (9.2)
Gastrointestinal	5 (4.6)
Unknown	3 (2.7)
Deaths Not Related to SSc (n = 58)	
Septicemia	24 (41.4)
Sudden death	12 (20.7)
Cardiovascular or cerebrovascular	8 (13.8)
Neoplasia	8 (13.8)
Other	6 (10.3)

SSc: systemic sclerosis.

ment, ILD and PH were the causes in 16.3% each; in 15.5% of the cases, both conditions were present and could be considered associated to death. The 5 deaths caused by GI involvement were related to esophageal stenosis (4 patients) and malabsorption syndrome (1 patient). Three other patients died from unknown causes: 2 patients (1 with lcSSc and the other with dcSSc) using intravenous cyclophosphamide were hospitalized with acute severe bleeding and died in 3 days; another patient with dcSSc presented severe pancytopenia while taking azathioprine (with a history of intravenous cyclophosphamide) and died in 5 days; none of these patients were submitted to necroscopic study.

Most of the 58 deaths not related to SSc were associated with infection (septicemia, independent of SSc activity), cardiovascular and cerebrovascular disease (4 with congestive heart failure, 2 with myocardial infarction, 1 with arrhythmia, and 1 with stroke), and cancer (lung in 3 patients, esophagus, colon, stomach, ovary, and breast in 1 patient each; Table 2). Twelve patients (20.7%) with active disease presented sudden death not related to a specific organ involvement; none of these patients were submitted to necroscopic study; and 6 cases presented other causes: autoimmune liver cirrhosis in 2 patients, tuberculosis in another 2 patients (1 with lung tuberculosis and the other with neurotuberculosis), amyloidosis, and polymyositis.

Multivariate logistic regression showed that the variables associated to death were male sex ($p = 0.003$, OR 2.35, 95% CI 1.34–4.12), modified Rodnan skin score (mRSS) > 20 ($p = 0.016$, OR 1.71, 95% CI 1.11–1.65), osteoarticular involvement ($p < 0.001$, OR 4.38, 95% CI 2.72–7.07), lung involvement ($p < 0.001$, OR 4.2, 95% CI 2.7–6.5), and renal crisis ($p < 0.001$, OR 9.96, 95% CI 3.74–26.54).

Overall survival rate was 90% for 5 years and 84% for 10 years (Figure 1). Clinical variants, mRSS > 20, and sex showed significant differences regarding survival. Patients with dcSSc presented worse survival than lcSSc (85% vs 92% at 5 years, respectively, and 77% vs 87% at 10 years; $p < 0.001$; Figure 2). Patients with SSc sine scleroderma presented a 5-year survival of 89%, similar to lcSSc; because patients with SSc sine scleroderma were diagnosed after 2000, we do not have their 10-year survival rates. Male sex was associated with worse survival compared to female sex (77% vs 90% at 5 years and 64% vs 86% at 10 years; $p < 0.001$; Figure 3). Modified RSS > 20 (83% vs 90% at 5 years and 66% vs 86% at 10 years, compared to mRSS < 20; $p < 0.001$) also presented worse prognosis (Figure 4). White patients presented no significant statistical differences in survival when compared to the African Brazilians (90% vs 89% at 5 years and 84% vs 81% at 10 years; $p = 0.786$; Figure 5).

DISCUSSION

Although clinical outcomes appear to have improved in recent years, SSc continues to cause substantial mortality.

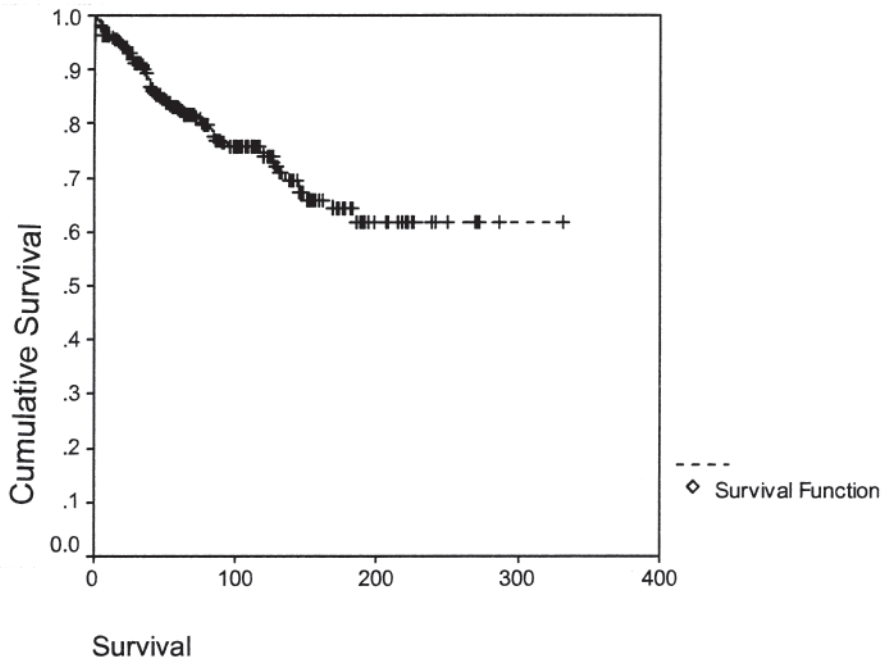

Figure 1. Overall survival.

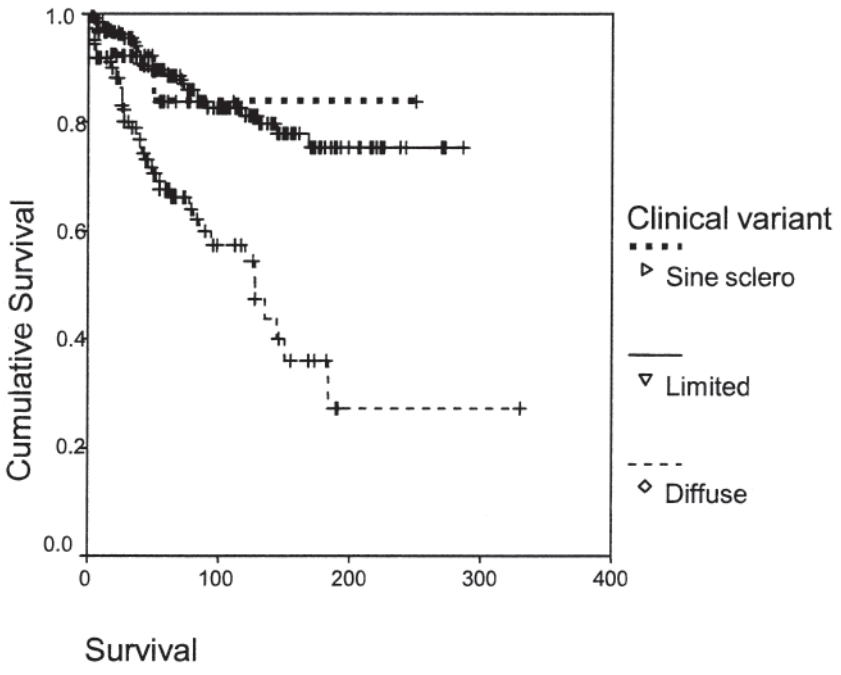

Figure 2. Clinical variants of survival.

Our study confirmed the previous observations showing that lung involvement is now the most frequent cause of death in SSc[2,3,4]. In this series of 947 patients with SSc, treated at the 2 largest SSc centers in Brazil, 48.1% of the deaths were related to lung involvement. ILD and PH were each found in 16.3% of the patients. In 15.5% of the patients (17 cases) there was ILD (affecting at least 20% of the lung area) associated to PH (pulmonary arterial systolic pressure by echocardiogram > 40 mm Hg); as both conditions could be considered associated to death, we decided to specify ILD + PH as the causes of death. A study from the Johns Hopkins SSc cohort has recently shown that ILD associated to PH

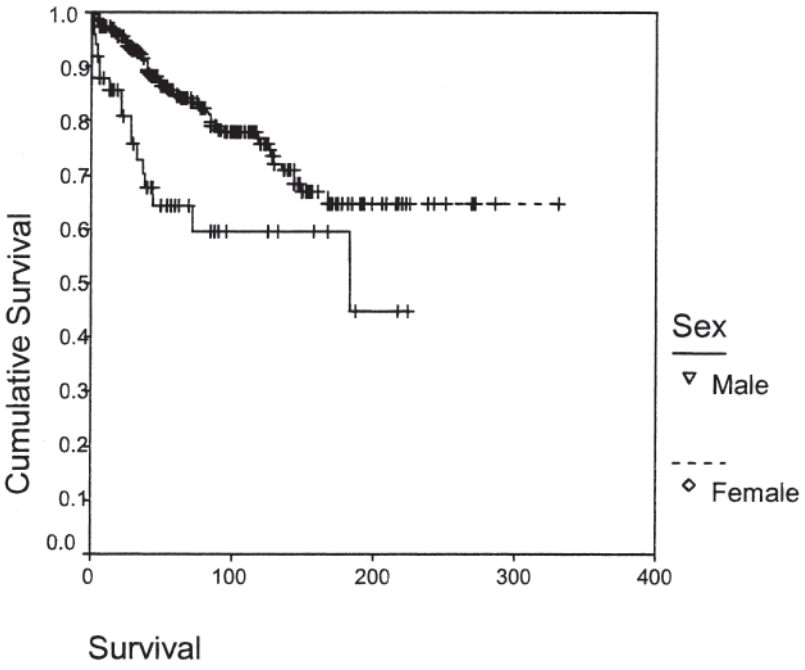

Figure 3. Sex differences and survival.

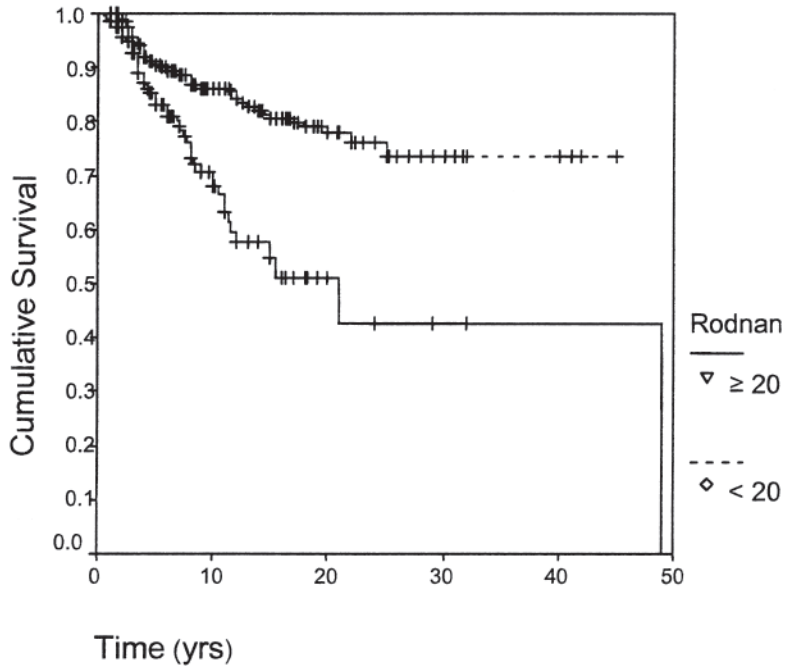

Figure 4. Survival and Rodnan skin score.

has a significantly worse prognosis compared to isolated PAH (1-, 2-, and 3-year survival rates 82%, 46%, and 39% vs 87%, 79%, and 64%, respectively; $p < 0.01$); in a multivariable analysis, ILD-associated PH was associated with a 5-fold increase in risk of death compared with PAH[35].

Steen and Medsger observed that 33% of the SSc-related deaths were related to ILD, as well as that PH, independent of ILD, also represented an important cause of death in SSc[2]. Hachulla, *et al*, analyzing the risk factors for death in a series of 546 French patients with SSc, found that 32.2%

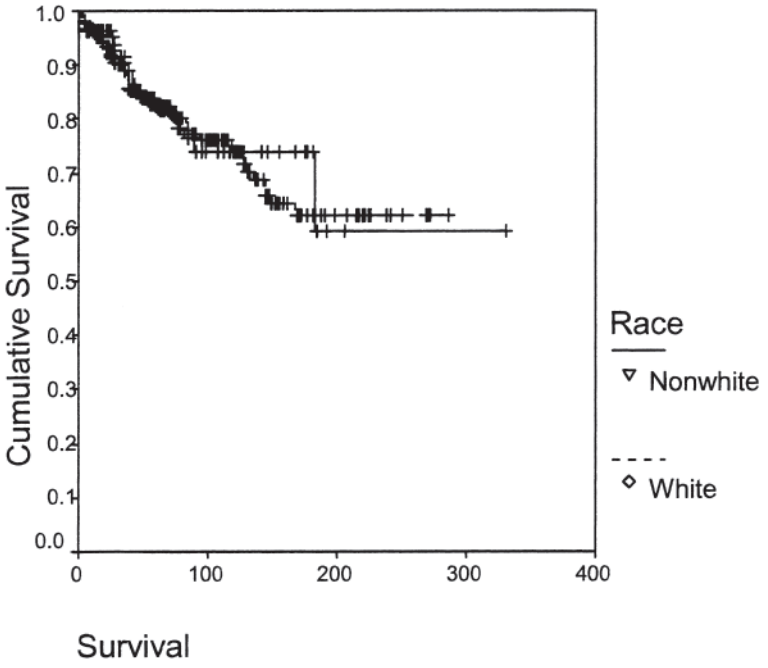

Figure 5. Survival and race.

of the deaths were associated to PH, justifying the yearly echocardiographic screening[24]. The analysis of the large EUSTAR databank showed that lung involvement caused 61% of the deaths, considering 35% for ILD and 26% for PAH[4]. A US study showed that pulmonary fibrosis was the major predictor of poor hospitalization outcomes in patients with SSc[36]. Nihtyanova, *et al* demonstrated that the significant improvement in survival in the last decade in patients with dcSSc was associated with better and more complete ascertainment of lung complications as a result of systematic annual screening[28]. Similar results emphasizing lung involvement as the most frequent cause of death were also observed in SSc series in populations of different ethnicity, published in the last decade in Spain[15], Hungary[16], and Thailand[14].

Heart involvement, especially congestive heart failure and cardiac arrhythmia, represented an important cause of death in our study, causing 24.5% of the SSc-related deaths, in a similar percentage (26%) to that observed in the EUSTAR databank[4]. An Italian study has also emphasized the importance of heart involvement as a significant cause of death in SSc[37]. Steen and Medsger observed no significant changes in heart-related deaths in SSc from 1972 to 2002[2]. Recent studies have emphasized the importance of cardiopulmonary manifestations as prognostic factors in SSc, in adult[24] and juvenile[23] patients. Cardiovascular disease also represents an important cause of death unrelated to SSc.

Renal involvement, especially SRC, was the leading cause of death in SSc for a long time, until the advent of the angiotensin-converting enzyme inhibitor captopril[2]. In the last 3 decades, there was a progressive decrease in the percentage of patients with SRC in SSc. In our series, SRC represented the cause of death in 10.9% of the SSc-related deaths. Corticosteroids have been implicated in the exacerbation of SRC[38]. In our series, only 3 of the 12 patients with SSc who died of SRC had been taking prednisone > 15 mg daily (for treatment of symptomatic pericarditis) in the 3 months before the onset of SRC. Another important cause of death was multiorgan failure (9.1%); some of these patients had dcSSc with SRC and heart and/or pulmonary insufficiency. In fact, visceral involvement (lung, heart, kidney, GI tract, and multiorgan failure) was the main factor responsible for 97.3% of the SSc-related deaths in our study, emphasizing the need to search for the most frequent visceral manifestations systematically.

Although esophageal involvement is present in 60% to 90% of patients with SSc, it is not a frequent cause of death[4]. Because the high frequency of esophageal involvement makes esophageal examination mandatory in patients with SSc, and early use of proton pump inhibitors and prokinetic drugs can be indicated, the progression to severe stenosis and Barrett esophagus, with subsequent malnutrition and death, is probably becoming rarer. Barrett esophagus can represent a risk factor for esophageal adenocarcinoma in SSc[39]. Intestinal involvement is not frequent, and the repeated use of antibiotics in cases of severe diarrhea improved survival and quality of life in these patients with

SSc. Involvement of the GI tract represented 4.6% of SSc-related deaths in our study.

Infection is another important cause of morbidity and mortality in SSc[40]. The increased risk of infections is the result of immune abnormalities and manifestations affecting vital organs associated with the SSc itself and with treatment, particularly in those receiving corticosteroids and immunosuppressive therapy. We considered infection a nonrelated cause of death, independent of SSc activity.

The occurrence of cancer in the context of SSc is predominantly associated with ILD[41]. A recent nationwide population-based cohort study in Denmark, analyzing 2040 patients with SSc for a median followup of 6.4 years, found that SSc was a risk factor for cancer, especially in men [standardized incidence ratio (SIR) 2.2] and particularly smoking- and alcohol-related cancers. These included hematological cancers (SIR 2.5), lung cancer (SIR 1.6), and immune-related cancers (SIR 1.4)[42]. Cancer was responsible for 13.8% of the non-SSc-related deaths in this series, affecting 8 patients. Six different sites (lung, esophagus, stomach, colon, ovary, and breast) were observed; in 2 patients (1 with lung and another with ovary cancer), the neoplasia developed a few years after the use of cyclophosphamide. In our study, only 2 patients with active SSc died of cancer (1 with esophageal and 1 with lung cancer).

Specific autoantibodies such as anti-Scl-70 (with ILD) and anti-RNA-polymerase III (with SRC) are also important prognostic markers for SSc[43]. Various other serum markers are currently being studied. Genetic factors are also prognostic predictors of mortality in SSc. One study, analyzing the HLA class II genotyping in a group of 250 patients with early SSc, found that HLA alleles DRB1*0802 and DQA1*0501 were significant predictors of mortality[44]. Our group has recently found significant good prognosis related to HLA-G in SSc[45].

The overall survival rate in our study was 90% for 5 years and 84% for 10 years. These rates are compatible with studies that have shown an improvement in SSc survival in the last decades[2,3,4,26,27,28,29,30]. The worse results in patients with dcSSc and mRSS > 20 were expected. Patients with SSc sine scleroderma present survival rates similar to patients with lcSSc; it is not clear whether SSc sine scleroderma is a specific clinical variant of SSc or an initial stage of lcSSc.

Studies have shown that clinical and serologic features can be strongly influenced by ethnic background in patients with SSc[46,47,48,49]. African Americans were more likely to present diffuse skin involvement, digital ulcers, and impaired lung function, associated to anti-RNP (anti-U1-RNP and anti-U3-RNP/fibrilarin) compared to North American whites[47,48]. Our study did not show statistical difference in survival rates between Brazilian whites and African Brazilians. The main reason for this finding could be that the African Brazilian population is predominantly mixed; in the demographic census of 2010 in Brazil, 47.7% of the people declared themselves as whites (predominant European ancestry, with Portuguese, Spanish, or Italian origin), 43.6% mestizos (most mixed white/black), 7.6% black (pure origin), 0.7% Asian ancestry (predominantly Japanese), and 0.4% Indians.

Male sex was a significant factor of worse prognosis in our study, with a survival rate of 77% in 5 years and 64% in 10 years. These results confirm that male sex, although affected by SSc in a lower percentage compared to females, represents a factor of bad prognosis[5,6,7,8].

Our study showed that lung and heart involvement are the worst prognostic factors and the main causes of death in this large South American series of patients with SSc, and that survival rates were worse in male patients with dcSSc.

REFERENCES

1. Karassa FB, Ioannidis JPA. Mortality in systemic sclerosis. Clin Exp Rheumatol 2008;26 Suppl 51:S85-93.
2. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66:940-4.
3. Steen VD, Medsger TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000; 43:2437-44.
4. Tyndall AJ, Bannert B, Vonk M, Airó 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.
5. Kaburaki J, Lee CC, Kuwana M, Tojo T, Ikeda Y, Takano M, et al. Initial predictors of survival in patients with systemic sclerosis (scleroderma). Keio J Med 1992;41:141-5.
6. Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. Ann Rheum Dis 1998;57:682-6.
7. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, et al. Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR–GSSSc). Systemic sclerosis: demographic, clinical, and serologic features and survival in 1012 Italian patients. Medicine 2002;81:139-53.
8. Mayes MD, Lacey JV, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003;48:2246-55.
9. Wynn J, Feneberg N, Matzer L, Cortada X, Armstrong W, Dillon JC, et al. Prediction of survival in progressive systemic sclerosis by multivariate analysis of clinical features. Am Heart J 1985; 110:123-7.
10. Altman RD, Medsger TA Jr, Bloch DA, Michel BA. Predictors of survival in systemic sclerosis (scleroderma). Arthritis Rheum 1991;34:403-13.
11. Lee P, Langevitz P, Alderdice CA, Aubrey M, Baer PA, Baron M, et al. Mortality in systemic sclerosis (scleroderma). Q J Med 1992;82:139-48.
12. Steen VD, Medsger TA Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum 2001;44:2828-35.
13. Scussel-Lonzetti L, Joyal F, Raynauld JP, Roussin A, Rich E, Goulet JR, et al. Predicting mortality in systemic sclerosis: Analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. Medicine 2002;81:154-67.

14. Ruangjutipotan S, Kasitanon N, Louthrenoo W, Sukitawut W, Wichainun R. Causes of death and poor survival prognostic factors in Thai patients with systemic sclerosis. J Med Assoc Thai 2002;85:1204-9.
15. Simeon CP, Armadans L, Fonollosa V, Solans R, Selva A, Villar M, et al. Mortality and prognostic factors in Spanish patients with systemic sclerosis. Rheumatology 2003;42:71-5.
16. Czirják L, Kumánowics G, Varjú C, Nagy Z, Pakozdi A, Skekanecz Z, et al. Survival and causes of death in 366 Hungarian patients with systemic sclerosis. Ann Rheum Dis 2008;67:59-63.
17. 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.
18. Bulpitt KJ, Clements PL, Lachenbruch PA, Paulus HE, Peter JB, Agopian MS, et al. Early undifferentiated connective tissue disease: III. Outcome and prognostic indicators in early scleroderma (systemic sclerosis). Ann Intern Med 1993;118:602-9.
19. 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.
20. Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, Medsger TA Jr, Lucas M, Michet CJ, et al. Mortality in systemic sclerosis: An international meta-analysis of individual patient data. Am J Med 2005;118:2-10.
21. Nishioka K, Katayama I, Kondo H, Shinkai H, Ueki H, Tamaki K, et al. Epidemiological analysis of prognosis of 496 Japanese patients with progressive systemic sclerosis (SSc). Scleroderma Research Committee Japan. J Dermatol 1996;23:677-82.
22. Arias-Nuñez MC, Llorca J, Vazquez-Rodrigues TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, et al. Systemic sclerosis in northwestern Spain: A 19-year epidemiologic study. Medicine 2008;87:272-80.
23. Martini G, Vittadello F, Kasapçopur O, Magni Manzoni S, Corona F, Duarte-Salazar C, et al. Factors affecting survival in juvenile systemic sclerosis. Rheumatology 2009;48:119-22.
24. Hachulla E, Carpentier P, Gressin V, Diot E, Allanore Y, Sibilia J, et al. Risk factors for death and the 3-year survival of patients with systemic sclerosis: The French ItinérAIR-Sclérodermie study. Rheumatology 2009;48:304-8.
25. Tuffanelli DL, Winkelmann RK. Systemic scleroderma. A clinical study of 727 cases. Arch Dermatol 1961;84:359-71.
26. Al-Dhaher FF, Pope J, Ouimet JM. Determinants of morbidity and mortality in systemic sclerosis in Canada. Semin Arthritis Rheum 2010;39:269-77.
27. 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.
28. Nihtyanova SI, Tang EC, Coghlan JG, Wells A, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: A retrospective cohort study. Q J Med 2010;103:109-15.
29. Hashimoto A, Tejima S, Tono T, Suzuki M, Tanaka S, Matsui T, et al. Predictors of survival and causes of death in Japanese patients with systemic sclerosis. J Rheumatol 2011;38:1931-9.
30. Kuo CF, See LC, Yu KH, Chou IJ, Tseng WI, Chang HC, et al. Epidemiology and mortality of systemic sclerosis: A nationwide population study in Taiwan. Scand J Rheumatol 2011;40:373-8.
31. 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 2012;51:1017-26.
32. Masi AT, Rodnan GP, Medsger TA Jr, Altman RD, D'Angelo WA, Fries JF, et al. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581-90.
33. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): Classification, subsets and pathogenesis. J Rheumatol 1988; 15:202-5.
34. Poormoghim H, Lucas M, Fertig N, Medsger TA Jr. Systemic sclerosis sine scleroderma: Demographic, clinical, and serologic factors and survival in forty-eight patients. Arthritis Rheum 2000;43:444-51.
35. Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, et al. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: Impact of interstitial lung disease. Arthritis Rheum 2009;60:569-77.
36. Chung L, Krishnan E, Chakravarty EF. Hospitalizations and mortality in systemic sclerosis: Results from the Nationwide Inpatient Sample. Rheumatology 2007;46:1808-13.
37. 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;63:202-9.
38. Steen VD, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 1998;41:1613-9.
39. Wipff J, Coriat R, Masciocchi M, Caramaschi P, Derk CT, Hachulla E, et al. Outcomes of Barrett's oesophagus related to systemic sclerosis: A 3-year EULAR Scleroderma Trials and Research prospective study. Rheumatology 2011;50:1440-4.
40. Alarcon GS. Infections in systemic connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis/ dermatomyositis. Infect Dis Clin North Am 2006;20:849-75.
41. Wooten M. Systemic sclerosis and malignancy: A review of the literature. South Med J 2008;101:59-62.
42. Olesen AB, Svaerke C, Farkas DK, Sorensen HT. Systemic sclerosis and the risk of cancer: A nationwide population-based cohort study. Br J Dermatol 2010;163:800-6.
43. Meyer O. Prognostic markers for systemic sclerosis. Joint Bone Spine 2006;73:490-4.
44. Assassi S, Del Junco D, Sutter K, McNearney TA, Reveille JD, Karnavas A, et al. Clinical and genetic factors predictive of mortality in early systemic sclerosis. Arthritis Rheum 2009;61:1403-11.
45. Wastowski IJ, Sampaio-Barros PD, Amstalden EMI, Palomino GM, Marques-Neto JF, Crispim JC, et al. HLA-G expression in the skin of patients with systemic sclerosis. J Rheumatol 2009;36:1230-4.
46. Kuwana M, Kaburaki J, Arnett FC, Howard RF, Medsger TA Jr, Wright TM. Influence of ethnic background on clinical and serologic features in patients with systemic sclerosis and anti-DNA topoisomerase I antibody. Arthritis Rheum 1999;42:465-74.
47. Reveille JD, Fischbach M, McNearney T, Friedman AW, Aguilar MB, Lisse J, et al. Systemic sclerosis in 3 US ethnic groups: A comparison of clinical, sociodemographic, serologic, and immunogenetic determinants. Semin Arthritis Rheum 2001; 30:332-46.
48. Nietert PJ, Mitchell HC, Bolster MB, Shaftman SR, Tilley BC, Silver RM. Racial variation in clinical and immunological manifestations of systemic sclerosis. J Rheumatol 2006;33:263-8.
49. Nashid M, Khanna PP, Furst DE, Clements PJ, Maranian P, Seibold J, et al. Gender and ethnicity differences in patients with diffuse systemic sclerosis — Analysis from three large randomized clinical trials. Rheumatology 2011;50:335-42.