Predictors of Survival and Causes of Death in Japanese Patients with Systemic Sclerosis

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ABSTRACT. ***Objective.*** To clarify the mortality rates, causes of death, and contributing clinical factors in Japanese patients with systemic sclerosis (SSc).

Methods. A cohort of 405 patients with SSc, who attended our institution during the period 1973 to 2008, was retrospectively analyzed until the end of 2009. Clinical data were obtained from medical records or autopsy reports.

Results. The 405 patients with SSc consisted of 310 (76.5%) survivors, 86 (21.2%) who died, and 9 who were lost to followup. Diffuse cutaneous SSc and involvement of organs other than the gastrointestinal tract were more frequent in patients who died, and were associated with a worse prognosis according to Kaplan-Meier analysis. Female sex, limited cutaneous SSc, anticentromere antibody (ACA), and overlap with Sjögren's syndrome (SS) were factors favoring a better prognosis, while overlap with myositis contributed to a poor prognosis. The overall 10-year survival rate was 88%. The patients with SSc had a significantly higher mortality than the general population (standardized mortality ratio 2.76), but the patients with ACA or overlapping SS did not. The most common causes of death were unknown ones including sudden death, followed by malignancy and infection. In patients with pulmonary arterial hypertension, sudden death was the most common cause of mortality.

Conclusion. The overall mortality rate of patients with SSc was higher than that of the general population, probably because of poor prognostic factors including organ involvement. These factors should be carefully monitored during followup. (J Rheumatol First Release July 15 2011; doi:10.3899/jrheum.100298)

Key Indexing Terms:
SCLERODERMA SYSTEMIC SCLEROSIS JAPAN MORTALITY CAUSE OF DEATH

Despite the still unknown pathogenesis of systemic sclerosis (SSc), investigators have described its clinical features in detail. On the basis of skin involvement, SSc is classified into diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc). Other than skin, various organ involvements occur in SSc, often resulting in death. Antinuclear antibody is detected in most patients with SSc, suggesting a pathogenesis. Some specific autoantibodies, including anti-Scl-70, anticentromere (ACA), and anti-U1-RNP antibodies, have been demonstrated to be closely associated with organ involvement[1]. Abnormalities of the immune system that produce autoantibodies sometimes cause overlap with other connective tissue diseases (CTD), including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), and myositis (polymyositis or dermatomyositis). Certain clinical factors, including organ involvement, autoantibodies, and overlap with CTD, influence the prognosis of patients with SSc. Indeed, dcSSc and major organ involvement, including that of the lungs, heart, or kidneys, were associated with a poor prognosis in previous reports[2]. Male patients with SSc usually have a worse prognosis than females, but sometimes the influence of sex is limited.

In our study, we analyzed data obtained from longterm followup of Japanese patients with SSc at a single institution, with the aim of identifying predictors of survival and understanding the entire disease course of SSc as well as the causes of death.

MATERIALS AND METHODS

Patients who visited Kitasato University Hospital from 1973 to 2008 with bilateral symmetrical skin thickness, even only with sclerodactyly, were enrolled in our study and in the study by Barnett and Coventry[3]. Although

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some patients with SSc are hard to distinguish from those with mixed connective tissue disease (MCTD), patients who met the Japanese diagnostic criteria for MCTD were excluded[4]. Patients with SSc sine scleroderma also were excluded[5]. The ethics committee of the Kitasato University Hospital approved the study.

There were 376 women and 29 men (total 405). Their antibody profiles and clinical features were obtained from the medical records, including age, sex, disease duration, outcome, organ involvement [skin, gastrointestinal tract (GI), lungs, heart, kidneys, scleroderma renal crisis (SRC), and pulmonary arterial hypertension (PAH)], and overlap with CTD. The organ involvement or overlapping CTD was admitted when it was once continuously revealed during the followup in our institution. But because not all patients were examined for every organ involvement or overlapping CTD, the occurrence of such conditions could be underestimated.

DcSSc was defined on the basis of skin involvement proximal to the elbows and knees, while lcSSc meant skin involvement distal to the elbows and knees or affecting the face at least 2 years after the onset of SSc[6]. GI involvement was defined as gastroesophageal reflux disease, dysphagia, bacterial overgrowth requiring antibiotics, and/or paralytic ileus[7]. Lung involvement was defined as bibasal pulmonary fibrosis detected on chest radiographs or by computed tomography. Heart involvement was defined as a left ventricular ejection fraction < 40% measured by echocardiography, conduction disturbance or arrhythmias requiring therapy, or congestive heart failure. SRC was defined by the occurrence of malignant arterial hypertension (diastolic blood pressure > 120 mm Hg with grade III or IV hypertensive fundoscopic changes according to the Keith-Wagener classification) or rapidly progressive oliguric renal failure without other discernible causes during the course of SSc[8]. SSc can also cause chronic renal disease with an elevated serum creatinine level or proteinuria independently of SRC[9]. Renal involvement was defined as present or past SRC as well as continuous proteinuria or a glomerular filtration rate < 60 ml/min per 1.73 m^2 estimated by the Modification of Diet in Renal Disease study equation for Japanese patients[10,11]. PAH was diagnosed from a mean pulmonary arterial pressure > 25 mm Hg measured directly by right heart catheterization[12], or an estimated pulmonary arterial pressure > 35 mm Hg calculated from the tricuspid flow velocity by Doppler echocardiography[13]. Diagnosis of overlapping CTD was made by the following criteria: SLE or RA were diagnosed according to the 1982 or 1987 criteria of the American College of Rheumatology, respectively[14,15]. SS was diagnosed according to the 1999 Ministry of Health and Welfare's Diagnostic Criteria for SS[16]. Myositis was defined as inflammation of skeletal muscle with a serum creatine kinase (CK) level above the normal institutional range (247 IU/l for men or 170 IU/l for women). Other conditions associated with a high serum CK level were excluded, such as myocardial infarction, muscular dystrophy, circulatory disorders, hypothyroidism, and drug-induced myopathy. Myositis included not only muscle involvement due to SSc, but also polymyositis or dermatomyositis complicated by SSc. Every diagnosis was made retrospectively and confirmed based on the information in medical records.

The onset of SSc was defined by the occurrence of Raynaud's phenomenon and/or joint symptoms ahead of skin sclerosis, as well as the appearance of characteristic symptoms caused by organ involvement[17]. Observation was terminated at the time of death or at the end of 2009. The presumed cause of death was based on information obtained from the medical records or autopsy reports. A clear causal relation or clinical data were necessary to assign a definitive cause of death. Sudden death was defined as death within 24 hours of the onset of acute symptoms without clear signs suggesting a particular disease as the cause[18,19]. Consequently, sudden death was included as an unknown cause of death.

Immunological tests for serum anti-Scl-70 and anti-U1-RNP antibodies were carried out with ELISA kits (TFB Inc., Tokyo, Japan) according to the manufacturer's protocol, or the double immunodiffusion technique was performed according to a standard Ouchterlony protocol, as described[20,21]. Serum ACA was detected with an ELISA kit (Medical & Biological Laboratories Co. Ltd., Nagoya, Japan) or by the indirect immunofluorescence technique based on the characteristic staining of Hep-2 cells[22]. Some patients were excluded because they did not take the above tests. The remaining 352 patients with serum antibody data were analyzed to assess the association between autoantibodies and survival.

Statistics. The between-groups comparisons were made using the Wilcoxon signed-rank test for numerical values or Fisher's exact test for analysis of percentages. Univariable survival analysis covering 30 years after onset was performed by using the Kaplan-Meier method to plot survival curves that were compared with the log-rank test. Similarly, multivariable survival analysis applied Cox's proportional hazard model. Every analysis was conducted with Jmp 5.1 (SAS Institute Japan Ltd., Tokyo, Japan).

The standardized mortality ratio (SMR) is the ratio between the observed death rate of the cohort in our study and the expected death rate in a comparable age-matched and sex-matched Japanese population. Vital statistics for 1990, compiled by the Ministry of Health, Labor, and Welfare, were used for calculation of the SMR. The 95% CI for the SMR was calculated by regarding the observed number of deaths as a Poisson variable and by looking up the related 95% CI in statistical tables. Values are expressed as the median ± SE of the mean (SEM). In all analyses, p values < 0.05 were regarded as significant.

RESULTS

Demographic features. The study covers 6730 person-years of total disease duration for the 405 patients with SSc. General features are presented in Table 1. The 405 patients included 376 women (92.8%) and 29 men (7.2%), who were divided into 310 (76.5%) survivors and 86 patients (21.2%) who died. Nine patients (2.2%) were lost to followup. The number of patients with dcSSc was 132 (32.6%), of whom 53.5% were dead and 27.7% were alive ($p < 0.0001$). The median age at onset of SSc for the 405 patients was 47 years and the median period from onset to the diagnosis of SSc was 2 ± 0.4 years (median ± SEM). The age at onset and the time from onset to diagnosis showed no significant differences between surviving and dead patients. The median duration of disease for all patients was 14 ± 0.6 years and was significantly shorter for patients who died than for survivors (11 ± 1.2 vs 15 ± 0.7 years, respectively; $p = 0.0230$).

Organ involvement (including the GI, lungs, heart, kidneys, SRC, and PAH) was significantly more common in patients who died than in surviving patients. Regarding overlap with CTD, SS was less often found in dead than surviving patients ($p = 0.0018$).

Sera from 352 patients were examined for the presence of anti-Scl-70, anti-U1-RNP, and ACA. Anti-Scl-70 antibody was detected in 82 patients (23.3%), while ACA or anti-U1-RNP antibody was found in 127 (36.1%) or 83 (23.6%) patients, respectively. The prevalence of anti-Scl-70 antibody was significantly higher among patients who died (26 out of 73 dead patients, 35.6%) than among surviving patients (56 out of 279 surviving patients, 20.1%; $p = 0.0078$). Conversely, the prevalence of ACA was significantly higher among surviving patients (116 out of 279, 41.6%) than among dead patients (11 out of 73, 15.1%; $p < 0.0001$).

Survival analysis. Figure 1 shows 30-year survival curves for patients with SSc determined using the Kaplan-Meier method. Pairs of survival curves with significant differences and the survival rates of subgroups at 10, 20, or 30 years after the

Table 1. General demographic features of 405 patients with systemic sclerosis (SSc). Values are median ± SE of the mean. Nine patients who were lost to followup were excluded from survival or standardized mortality ratio analyses.

Characteristic	All Patients	Surviving Patients, n (%)	Dead Patients, n (%)	p
No. patients	405	310 (76.5)	86 (21.2)	—
Men, n (%)	29 (7.2)	19 (6.1)	9 (10.5)	0.1616
dcSSc, n (%)	132 (32.6)	86 (27.7)	46 (53.5)	< 0.0001
Age at onset, yrs (range)	47 ± 0.7 (5–78)	47 ± 1.6 (5–78)	47 ± 0.8 (9–73)	0.9029
Onset to diagnosis, yrs (range)	2 ± 0.4 (0–44)	2 ± 0.5 (0–44)	3 ± 0.7 (0–35)	0.6290
Disease duration, yrs (range)	14 ± 0.6 (1–59)	15 ± 0.7 (1–59)	11 ± 1.2 (1–57)	0.0230
Organ involvement				
GI tract	187	137 (44.2)	49 (57.0)	0.0356
Lung	204	125 (40.3)	75 (87.2)	< 0.0001
Heart	79	35 (11.3)	43 (50.0)	< 0.0001
Kidney	60	34 (11.0)	25 (29.1)	0.0001
Scleroderma renal crisis	13	6 (1.9)	7 (8.1)	0.0100
Pulmonary arterial hypertension	65	36 (11.6)	27 (31.4)	< 0.0001
Overlap of connective tissue disease				
Systemic lupus erythematosus	21	18 (5.8)	3 (3.5)	0.5870
Rheumatoid arthritis	19	15 (4.8)	4 (4.7)	1.0000
Sjögren's syndrome	51	48 (15.5)	3 (3.5)	0.0018
Myositis	22	13 (4.2)	8 (9.3)	0.0970

DcSSc: diffuse cutaneous systemic sclerosis; GI: gastrointestinal.

onset of SSc are shown in Figures 1A-J and Table 2. Subgroup analysis revealed that the presence of organ involvement, except for GI involvement, was significantly associated with a worse prognosis. Accordingly, these factors were significantly associated with worse survival: male sex; dcSSc; involvement of lungs, heart, or kidneys; SRC; PAH; or myositis. The presence of ACA or SS was associated with better survival. Patients with SRC had the worst survival (Table 2). Other factors, including anti-Scl-70 antibody or anti-U1-RNP antibody, had no correlation with survival in this analysis. On the other hand, multivariable survival analysis using Cox's proportional hazard model for factors including clinical features and overlapping CTD revealed that lung involvement (RR 2.21, $p < 0.0001$) followed by heart (RR 1.77, $p < 0.0001$) and kidneys (RR 1.35, $p < 0.0171$) were significant factors in worse survival rates.

Among the 86 patients who died, the range of age at death was 15–82 years. Figure 2 shows the distribution of age at death, indicating that many patients died in their fifties (n = 34, 39.5%), followed by those who died in their sixties and seventies. The median age at death was 58 ± 1.3 years (median ± SEM), and it was not related to sex or the type of skin involvement.

SMR. SMR was calculated to compare mortality among different populations, especially relative to the general population. As shown in Table 3, SMR was computed for all patients, and each subgroup or cause of death. The overall risk of death was nearly treble that of the general population (SMR 2.76; 95% CI 2.18–3.35). Interestingly, only subgroups of patients with SSc who had ACA or overlapping CTD such as SLE, RA, or SS did not have significantly higher mortality, while most of the subgroups (especially those with organ involvement) had a significantly higher SMR compared with the general population. The SMR for patients with SSc who had myositis was highest. With respect to the SMR analysis for each cause of death, death from pneumonia (infectious and interstitial) was significantly more frequent for patients with SSc than for the general population (SMR 9.11; 95% CI 4.34–13.88).

Cause of death. The presumed causes of death for 86 patients, including 25 whose cause of death was confirmed by autopsy (autopsy rate: 29.1%), are shown in Table 4. For about a quarter of the deaths, the cause was unknown (n = 23, 26.7%), including 16 sudden deaths (18.6%). The next most common causes were malignancy (n = 19, 22.1%), followed by infection (n = 14, 16.3%) and heart failure (n = 8, 9.3%). We found no deaths from stroke.

Of note, sudden death did not occur in patients with ACA, and was rare in patients with GI involvement (OR 0.27, $p = 0.0270$). In contrast, half of the patients with sudden death had PAH, as did 27 (31.4%) of all who died. In patients with PAH the most common cause of death was sudden death (n = 8, 29.6%), followed by heart failure (n = 5, 18.5%). Although PAH had no significant correlation with a particular cause of death, PAH was significantly associated with the union of the groups of sudden death and death from heart failure (OR 4.1, $p = 0.0086$). Lung involvement had no significant correlation with the causes of death including unknown, malignancy, pneumonia (infectious or interstitial), and heart failure. No significant association was found among causes of death and clinical factors including the patient's sex, type of skin involvement, and age at death (data not shown).

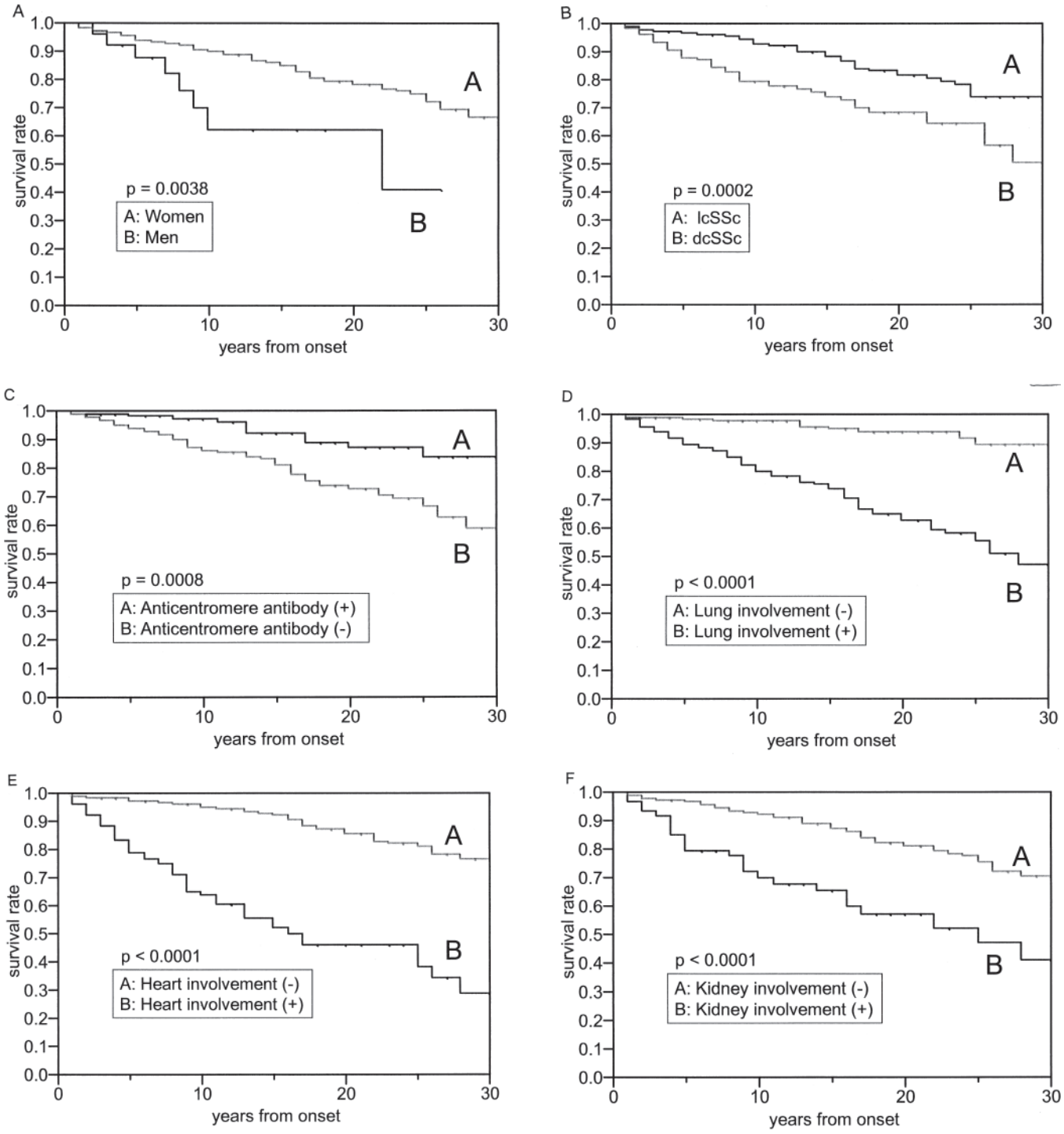

Figure 1. Kaplan-Meier survival curves of patients with systemic sclerosis (SSc) and results of the log-rank test. Horizontal axis represents the duration from the onset of SSc. A. Females showed significantly better survival than males ($p = 0.0038$). The longest disease duration in male patients was 26 years. B. Patients with limited cutaneous SSc showed significantly better survival than those with diffuse cutaneous SSc ($p = 0.0002$). C. Patients with anticentromere antibody had significantly better survival than those without it ($p = 0.0008$). D-H. Patients with involvement of the lungs, heart, kidneys, scleroderma renal crisis, or pulmonary arterial hypertension (PAH) had significantly worse survival than those without such factors ($p < 0.0001$; $p = 0.0002$ only for PAH). I. Patients showing overlap with myositis had significantly worse survival than those without overlap ($p = 0.0005$). The longest disease duration in patients with myositis was 27 years. J. Patients with Sjögren's syndrome had significantly better survival rates than those without it ($p = 0.0240$).

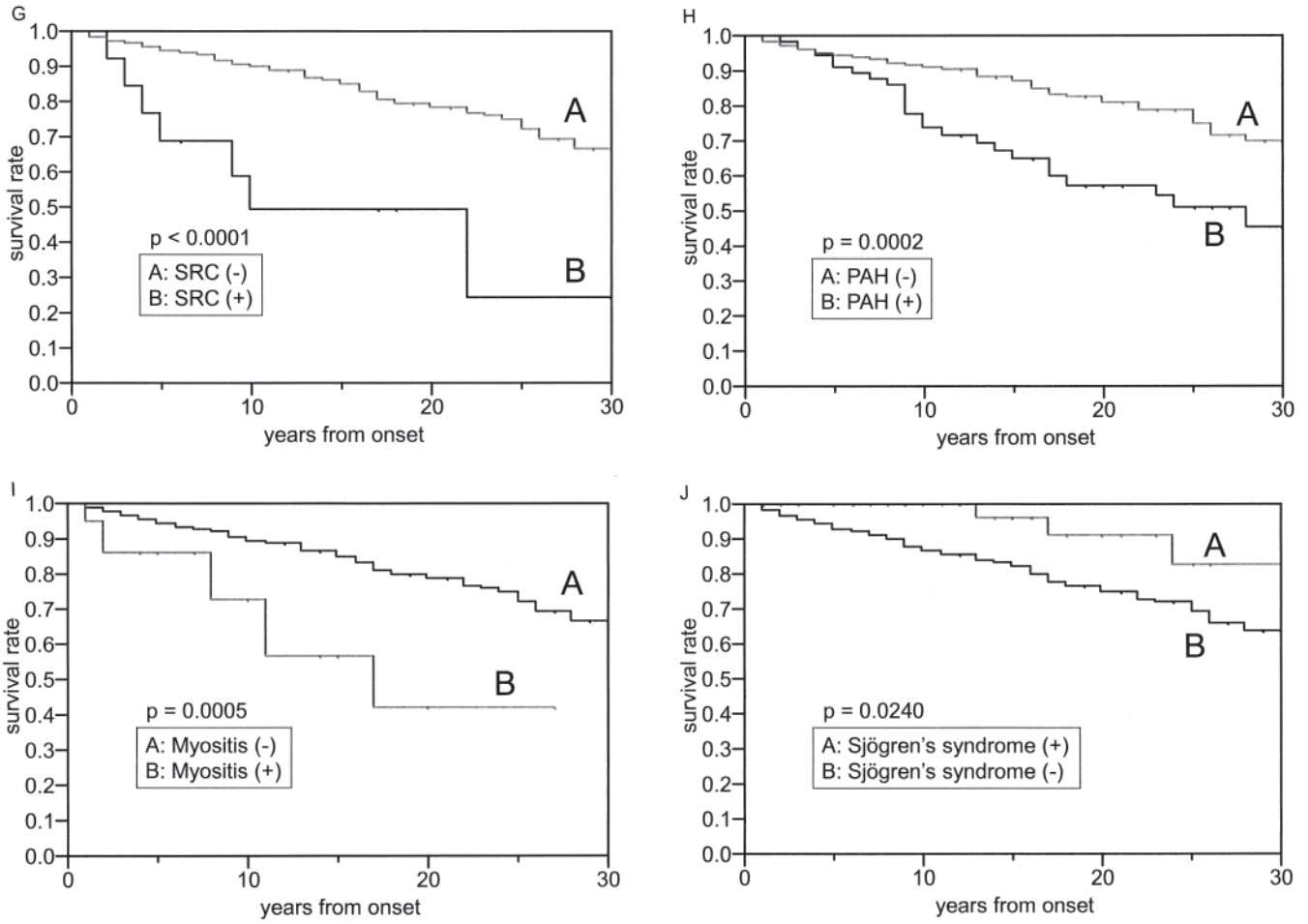

Figure 1. Continued

DISCUSSION

In our study, we investigated the prognosis of patients with SSc in association with clinical factors and the detailed causes of death in order to understand the varied progress of SSc. Since effective therapy for dermal sclerosis or most organ involvements in patients with SSc has still not been established, clinical studies of organ involvement and prognosis are necessary, not only to understand the pathogenesis of SSc, but also to determine the best treatment and to reassure patients. Demographic and survival analyses were conducted to identify clinical factors contributing to the prognosis of patients with SSc. The demographic analysis compared the number of surviving and dead patients with or without specific factors using Fisher's exact test, while survival was analyzed using the Kaplan-Meier method with the log-rank test for univariable analysis and by the Cox's proportional hazard model for multivariable analysis.

First, patients with SSc were confirmed by SMR analysis to have a significantly higher mortality rate than the general population. The SMR of patients with SSc ranges from 1 to 4 among reports[23,24,25,26,27], while it was 2.76 in our study. With regard to individual risk factors for the prognosis of SSc, male sex and dcSSc show a correlation with a worse prognosis[2,17,25,28,29,30,31,32]. In our study, male sex was found to contribute to a poor prognosis according to Kaplan-Meier analysis, while dcSSc contributed on both demographic and Kaplan-Meier analysis. Similarly, we demonstrated that most organ involvement, including that of the lungs, heart, and kidneys, and SRC and PAH, was associated with a poor prognosis, as shown in previous reports[2,26,27,30,31,32,33,34,35]. Our previous study demonstrated that male sex was significantly associated with lung involvement or higher age at onset of SSc. DcSSc was associated with involvement of most organs[1]. These findings might account for the worse prognosis of male patients with SSc or dcSSc. However, it was difficult to unravel the complicated interrelationships among various factors and to precisely identify independent risk factors affecting the prognosis.

Patients who were positive for ACA demonstrated a significantly better prognosis than those without it, in accord with previous reports[31,33,34,36]. On the other hand, the prognosis for patients with SSc who show overlap with other CTD is still not well established. We found a significantly better prognosis for patients with SSc who showed overlap with SS than for

Table 2. Survival rates of each group at 10, 20, and 30 years after the onset of systemic sclerosis (SSc), estimated by the Kaplan-Meier method.

Group	10 Years	20 Years	30 Years
All patients	0.880	0.774	0.681
Women	0.887	0.787	0.698
Men	0.725	0.526	0.381
lcSSc	0.913	0.833	0.761
dcSSc	0.811	0.658	0.534
ACA (+)	0.948	0.898	0.851
ACA (–)	0.856	0.733	0.628
Lung involvement (+)	0.798	0.637	0.509
Lung involvement (–)	0.968	0.937	0.907
Heart involvement (+)	0.673	0.453	0.305
Heart involvement (–)	0.931	0.866	0.807
Kidney involvement (+)	0.739	0.546	0.403
Kidney involvement (–)	0.904	0.817	0.739
SRC (+)	0.609	0.371	0.226
SRC (–)	0.887	0.787	0.699
PAH (+)	0.775	0.601	0.466
PAH (–)	0.900	0.810	0.730
SS (+)	0.961	0.923	0.886
SS (–)	0.869	0.755	0.656
Myositis (+)	0.683	0.467	0.319
Myositis (–)	0.888	0.788	0.699

lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ACA: anticentromere antibodies; SRC: scleroderma renal crisis; PAH: pulmonary arterial hypertension; SS: Sjögren's syndrome.

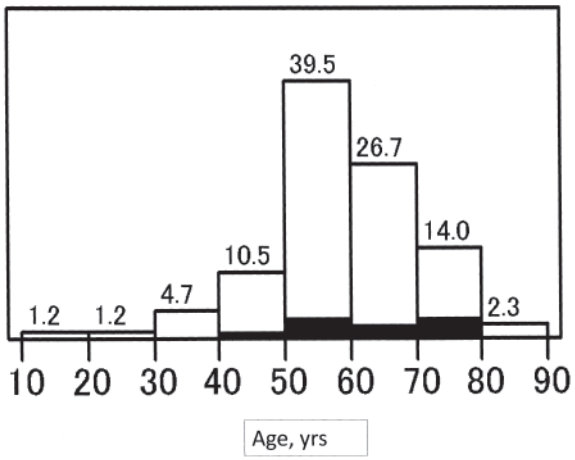

Figure 2. Age of death for 86 patients with systemic sclerosis. The horizontal axis denotes age and each division on the scale represents 1 decade. Numbers on the bars indicate the percentage of the population in that decade. Shaded areas represent male patients.

those who did not, and similarly, a worse prognosis for those with concurrent myositis using the Kaplan-Meier method and the log-rank test. Overlap with SLE or RA did not have a significant influence on the prognosis. An explanation for the better prognosis for patients with SSc who have ACA or SS could be that those patients were not only correlated with lcSSc but also associated with less lung or heart involvement[1]. SMR analysis revealed that patients with SSc who had overlapping myositis had a significantly worse prognosis than the general population, while patients with SSc who had other CTD did not. In our series of patients, there were no sudden

Table 3. Estimated risk of death for each group compared with the general Japanese population.

Group	Standardized Mortality Ratio (95% CI)
All patients	2.76 (2.18–3.35)*
Subgroup	
Male	3.31 (1.15–5.47)*
Female	2.71 (2.10–3.32)*
dcSSc	5.90 (4.20–7.61)*
lcSSc	1.71 (1.18–2.24)*
Onset < 45 yrs	3.99 (2.71–5.28)*
Onset ≥ 45 yrs	2.24 (1.61–2.87)*
Anti Scl-70 antibody (+)	4.57 (2.82–6.33)*
ACA (+)	0.86 (0.35–1.37)
Anti U1-RNP antibody (+)	2.40 (1.14–3.65)*
GI involvement (+)	3.43 (2.47–4.39)*
Lung involvement (+)	5.04 (3.90–6.18)*
Heart involvement (+)	8.01 (5.62–10.40)*
Kidney involvement (+)	4.74 (2.88–6.60)*
PAH (+)	5.67 (3.53–7.81)*
SLE (+)	2.63 (–0.35–5.61)
RA (+)	4.68 (0.09–9.26)
SS (+)	0.81 (–0.11–1.73)
Myositis (+)	10.09 (3.10–17.07)*
Death from	
Malignancy	1.70 (0.94–2.47)
Pneumonia (interstitial or infectious)	9.11 (4.34–13.88)*

* SMR significantly > 1. SMR: standardized mortality ratio; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; ACA: anticentromere antibodies; GI: gastrointestinal; PAH: pulmonary arterial hypertension; SLE: systemic lupus erythematosis; RA: rheumatoid arthritis; SS: Sjögren's syndrome.

Table 4. Causes of death for 86 patients with systemic sclerosis (SSc), including 25 autopsy cases. Numbers in parentheses represent patients with diffuse cutaneous SSc.

Cause of Death	Subgroups	Main Categories
Unknown		23 (11)
Sudden death	16 (8)	
Malignancy		19 (11)
Infection		14 (9)
Pneumonia	10 (6)	
Sepsis	4 (3)	
Heart failure		8 (7)
Interstitial pneumonia		4 (1)
Hepatic failure		4 (0)
Pulmonary embolism		3 (1)
Malnutrition/cachexia		2 (1)
Renal failure		2 (2)
Pulmonary hemorrhage		2 (1)
Gastrointestinal hemorrhage		2 (1)
Thyroid crisis		1 (0)
Thrombotic thrombocytopenic purpura		1 (0)
Coronary embolism		1 (1)

deaths among those with ACA. Considering these findings, we can state that in patients with SSc, ACA positivity and/or overlap with SS are benign signs, as opposed to overlapping myositis, which suggests a poor prognosis.

No significant difference was found for age at onset or period from onset to diagnosis between surviving and nonsurviving patients. In contrast, there have been a number of reports describing an association between late onset and high mortality[25,27,28,30,31,32,33,34,35,37]. However, the results should be adjusted for changes in the corresponding general population because survival usually decreases with aging. Accordingly, we used SMR analysis and found that patients younger than 45 years at onset had a relatively high SMR compared with those with an onset after 45 years (Table 3; SMR 3.99 vs 2.24, respectively). However, the higher SMR in patients with a younger onset should not be overestimated, because SMR analysis of our study was designed to compare mortality between target subjects and the general population, and is not suitable for comparisons between subgroups.

The survival rates of patients with SSc at 10 years in our study (88%) were better than those (71% to 82%) in studies of white populations[25,30,33,38], while our results corresponded to a recent report on Koreans (85.4%)[39]. The difference is attributed to ethnic or regional background, which influences the prevalence of organ involvement. For instance, SRC was associated with the worst survival and was rare in Japanese[1] or Korean[39] patients with SSc. Also, our definition for the onset of SSc, which includes Raynaud's phenomenon and/or joint symptoms ahead of skin sclerosis, may have extended disease duration compared with other studies.

We did not differentiate between SSc-related and SSc-unrelated deaths because they are virtually indistinguishable. First, in almost a quarter of the patients who died, deaths were due to unknown causes despite autopsies. Second, the association between SSc and several causes of death is still unclear. For example, is excess lung cancer in patients with SSc who have interstitial lung disease (ILD) pathophysiologically associated with SSc or only with ILD[40]? Is ischemic heart disease or cerebral infarction not associated with SSc itself, even though vascular involvement has been reported in patients with SSc[41]?

In our study, malignancy, infection, and heart failure were common causes of death in Japanese patients with SSc. These findings agree with previous reports that identified 3 major causes of death, namely heart failure (including PAH), respiratory failure (including ILD and interstitial or infectious pneumonia), and malignancy[25,28,29,30,31,32,33]. SMR analysis demonstrated that patients with SSc have significantly higher risk for death from respiratory failure (interstitial or infectious pneumonia), but it is unclear whether either SSc itself or lung involvement contributes to respiratory failure as a cause of death, because among the patients who died, lung involvement had no significant correlation with respiratory failure. Renal failure (resulting mainly from SRC) was also a common cause of death[23,36,42,43], but not in our study. The causes of death in patients with SSc have changed over time. The appearance of angiotensin-converting enzyme inhibitors could have reduced renal failure due to SRC, resulting in rare deaths from renal disease[43].

A quarter of dead patients in our study died suddenly of unknown causes. Because we found no deaths from stroke, which has not been reported as a frequent cause of death in patients with SSc[23,25,28,29,30,31,32,33,36,42,43], most of the unknown deaths could be associated with heart disease. It is notable that the histological appearance of PAH in patients with SSc was similar to that of primary PAH[44]. In addition, plexiform lesions in patients with primary PAH were associated with sudden death[45]. Several autopsy studies of patients with PAH who died suddenly found no evidence of myocardial infarction or pulmonary embolism[46,47]. Therefore, except for rare cases of fatal arrhythmias[48] or dissection of the pulmonary artery[49,50,51], the primary cause of death in patients with SSc who have PAH may be PAH itself, i.e., acute right ventricular failure leading to biventricular failure[52,53,54], but the detailed mechanism is still unclear.

We investigated risk factors affecting the prognosis for Japanese patients with SSc, and identified male sex, dcSSc, organ involvement (lungs, heart, kidneys, SRC, or PAH), and overlap with myositis. Patients with SSc had a significantly higher mortality than that of the general population, but those with ACA or overlapping SS did not. The major causes of death included malignancy, infection, and heart failure, while more than a quarter of patients with SSc died of unknown causes including sudden death. Patients with such risk factors should be followed carefully, and those with factors linked to a favorable prognosis do not require intensive treatment or followup. These findings can support clinical decisions and contribute to elucidating the pathogenesis of SSc.

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