excluded from further evaluation. The data of 74 RA patients who did not develop PCP within 12 months after the beginning of etanercept treatment were collected and these patients were termed the 'non-PCP' group. These patients' were randomly extracted from consecutive RA patients receiving etanercept at hospitals that participated in this study. All patients in this study fulfilled the 1987 American College of Rheumatology (formerly the American Rheumatism Association) diagnostic criteria for RA [23].

Diagnostic criteria for PCP

For this study, we used previously established diagnostic criteria for PCP [22, 24]. A diagnosis of PCP was considered definitive if: (1) *P. jirovecii* was found on microscopic analysis of respiratory samples from patients with concurrent clinical manifestations (fever, dry cough, or dyspnea), (2) the patients presented with hypoxemia, and (3) radiographic findings were indicative of PCP. The diagnosis of PCP was considered presumptive if a patient fulfilled the clinical and radiographic conditions [i.e., criteria (2) and (3)] in the absence of evidence of other infectious diseases and in the presence of either a positive PCR test for *P. jirovecii* DNA (qualitative PCR analysis by SRL, Tokyo, Japan, or Mitsubishi Chemical Medicine Corporation, Tokyo, Japan) or increased serum BDG levels above the upper limit of normal (ULN) (Fungitec *G* test MK; Seikagaku, Tokyo, Japan, or Wako β-D-glucan test; Wako Pure Chemical Industries, Tokyo, Japan) and responded to standard treatments for PCP with trimethoprim/sulfamethoxazole (TMP/SMX) or pentamidine isethionate. Both the PCR test for *P. jirovecii* DNA and the serum BDG test are commercially available, validated, and officially approved as clinical laboratory tests by the Ministry of Health, Labour, and Welfare in Japan.

Collection and analysis of clinical data

Data were collected from medical records using a standardized format including demographic information, comorbidities, concomitant drugs, laboratory data, radiographic data, treatments, and outcomes. Chest radiographs and computed tomography (CT) scans of the thorax were evaluated by a radiologist (F.S.) and a pulmonologist (H.S.).

Ethics

The guidelines of the Helsinki Declaration and the ethical guidelines for epidemiological research in Japan were followed. The study protocol was approved by the Institutional Ethics Committee of the Tokyo Medical and Dental University Hospital (#545 in 2008). The ethical guidelines for epidemiological studies in Japan required notifying eligible RA patients of this study and allowed us to implement this study without obtaining individual written informed consent. Patients were notified of this study by leaflets or posters at the outpatients clinics of each participating institution and on the website of the Department of Pharmacovigilance of the Tokyo Medical and Dental University. Patients were excluded from the study when they expressed their unwillingness to participate in this study.

Statistical analyses

Fisher's exact test was used for categorical variables and the Mann–Whitney *U*-test was used for continuous variables, with the Bonferroni correction for multiple pair comparisons. To identify risk factors for PCP, the Cox proportional-hazards regression model was used. The cumulative probability of PCP was calculated using the Kaplan–Meier method and the comparison among groups was performed using the log-rank test. All analyses were performed using SPSS software, version 17.0 (SPSS Japan, Tokyo, Japan).

Results

Demographics and treatment of RA patients who developed PCP

The demographics and treatment of RA patients at the onset of PCP are summarized in Table 1. The mean age of the PCP group was 66 years. The median interval between the first injection of etanercept and the onset of PCP was 14 weeks. Thirteen patients (86.7%) developed PCP within 26 weeks after the first injection of etanercept. All patients were treated with 50 mg/week of etanercept, except for patient 14, who was given 25 mg/week. At the onset of PCP, ten patients (66.7%) were receiving concomitant methotrexate (MTX) and 12 patients (80%) were receiving concomitant corticosteroids with etanercept. The median dosage of MTX was 8 mg/week and the median dosage of prednisolone (PSL) was 5 mg/day. Patient 8 received concomitant cyclophosphamide. None of the patients received chemoprophylaxis for PCP. Seven patients had pulmonary comorbidities, including interstitial pneumonia (IP) ($n = 4$), prior pleuritis ($n = 1$), pneumoconiosis ($n = 1$), and prior pulmonary tuberculosis ($n = 1$). Three patients had diabetes mellitus.

Table 1 Demographics and treatment of rheumatoid arthritis patients at the onset of *Pneumocystis jirovecii* pneumonia (PCP)

Pt	Age (years)	Number of injections[a]	Duration of ETN (weeks)[b]	MTX (mg/week)	PSL (mg/day)	Lung disease	Diabetes mellitus
1	66	38	21	8	3	–	–
2	32	8	7	12	0	–	+
3	74	55	27	8	0	–	–
4	61	35	19	6	8	–	–
5	79	51	27	0	2.5	IP	–
6	74	80	43	10	1	IP	+
7	72	28	13	0	10	Old pleuritis	–
8	73	25	14	0	30	Pneumoconiosis	–
9	72	29	13	8	5	IP	–
10	61	13	10	10	5	–	–
11	63	7	3	0	25	IP	–
12	72	12	11	0	4	Prior tbc	–
13	61	33	9	10.5	7.5	–	–
14	79	17	17	4	17.5	–	+
15	58	6	3	10	0	–	–
Median (IQR)	72 (61–73)	28 (12.5–36.5)	14 (9.5–20)	8 (0–10)	5 (1.75–9)		

Pt patient, *M* male, *F* female, *ETN* etanercept, *MTX* methotrexate, *PSL* prednisolone, *IP* interstitial pneumonia, *tbc* tuberculosis, *IQR* interquartile range

[a] Number of etanercept injections prior to the diagnosis of PCP

[b] Duration of treatment with etanercept before the onset of PCP

Clinical characteristics of RA patients who developed PCP

The clinical characteristics of each patient at the onset of PCP are summarized in Table 2. All had fever, 14 patients (93%) showed dyspnea on effort, and seven patients (46.7%) had a dry cough. Hypoxemia was observed in all patients at the onset of PCP; most had either severe hypoxemia with oxygen partial pressure in arterial blood (PaO_2) <60 mmHg on room air or required immediate oxygen therapy. Chest radiographs and CT scans were performed for all patients. On CT scans, ground-glass opacity (GGO) was observed in all patients. Six patients had GGO with sharp demarcation by interlobular septa (type A), while eight patients had GGO without interlobular septal boundaries (type B) (Fig. 1). One patient showed a combination of consolidation and GGO without interlobular septal boundaries. These thoracic CT findings in RA patients receiving etanercept who developed PCP were essentially the same as those in RA patients receiving infliximab who developed PCP [22, 24].

Serum levels of BDG, a reliable serum marker for PCP [18], were elevated above the ULN in 10 patients, with marked elevation (BDG >100 pg/ml) observed in 3 patients (Table 2). The PCR test for detection of *P. jirovecii* was utilized for 11 patients, using either induced sputum (nine patients) or bronchoalveolar lavage (BAL) fluid (two patients). All test results were positive. *P. jirovecii* was microscopically identified in BAL samples from patient 14 (Table 2).

Laboratory test results for PCP patients

Laboratory data from each patient at the onset of PCP are summarized in Table 3. Severe lymphopenia (<500 cells/μl) was observed in only 3 patients, while 4 patients had 500–1,000 cells/μl, and 8 patients had >1,000 cells/μl. The median serum level of C-reactive protein (CRP) was 9.5 mg/dl ($n = 15$); that of IgG was 1,341 mg/dl ($n = 9$); that of albumin (Alb) was 3.1 g/dl ($n = 15$); and that of the KL-6 antigen was 666 U/ml ($n = 13$). The KL-6 antigen is produced by type II alveolar epithelial cells and is reported to be elevated in patients with active IP [25], as well as in those with PCP [26].

Clinical course of PCP in RA patients treated with etanercept

All patients developed PCP rapidly and were hospitalized 3 or 4 days after the appearance of the clinical manifestations. Three patients required mechanical ventilation immediately upon admission because of progressive respiratory failure. Disease- modifying anti-rheumatic drugs (DMARDs), immunosuppressive drugs, and etanercept were discontinued in all patients. All patients received therapeutic doses of TMP/SMX immediately after the laboratory and radiographic examinations. Treatment with TMP/SMX was changed to pentamidine isethionate in three patients who had adverse drug reactions. Eight patients were treated with methylprednisolone (mPSL) pulse therapy, three with high-dose PSL, and five with increasing dosages of PSL within a few days after admission.

Table 2 Clinical characteristics and diagnostic indicators in rheumatoid arthritis patients at the onset of *Pneumocystis jirovecii* pneumonia (PCP)

Pt	Clinical manifestations	PaO_2 (Torr) [O_2 (l/min)][a]	CT findings	Response to treatments	PCR test	Serum β-D-glucan (pg/ml)
1	Fever/DOE	56 [3]	A	+	+	134[b]
2	Fever/cough/DOE	60.6 [0]	B	+	+	13.5[c]
3	Fever	SpO_2 86% [0]	B	+	+	14.6[c]
4	Fever/cough/DOE	SpO_2 86% [0]	B	+	+	21[c]
5	Fever/cough/DOE	57.6 [0]	A	+	+	<3.6[c]
6	Fever/cough/DOE	67.4 [0]	A	+	NA	14.2[c]
7	Fever/DOE	83.1 [0]	B	+	+	49.2[c]
8	Fever/DOE	68.5 [1]	C	+	+	20.2[c]
9	Fever/cough/DOE	66.3 [0]	A	+	+	27.4[c]
10	Fever/DOE	50 [0]	A	+	+	14.8[c]
11	Fever/DOE	64.8 [4]	B	+	NA	181[b]
12	Fever/DOE	49.4[10]	B	+	+	7.5[b]
13	Fever/DOE	SpO_2 90% [0]	A	+	+	43.3[c]
14	Fever/cough/DOE	55.6 [0]	B	+	NA[d]	187[c]
15	Fever/cough/DOE	61.7 [3]	B	+	NA	18.6[c]

Pt patient, *PaO_2* oxygen partial pressure in arterial blood, *cough* dry cough, *DOE* dyspnea on effort, *CT* thoracic computed tomography, *PCR test* polymerase chain reaction test for *P. jirovecii*, *NA* not assessed

[a] Oxygen therapy during the measurement of PaO_2 or oxygen saturation (SpO_2). SpO_2 was measured with a pulse oximeter

[b] Upper limit of normal (ULN) <20 pg/ml

[c] ULN <11 pg/ml

[d] *P. jirovecii* was detected microscopically as the cystic form in the bronchoalveolar lavage fluid

Although 14 patients responded well to these treatments and survived, one patient (patient 8) died. Patient 8 initially showed clinical and radiographic improvement arising from treatment for PCP with TMP/SMX and mPSL pulse therapy, but he later developed bacterial and fungal infections and finally died due to pulmonary hemorrhage 8 weeks after his admission.

While 13 patients were empirically treated with antibiotics and 4 patients were empirically treated with antifungal agents, cultures of respiratory samples from these patients before the commencement of these therapies revealed no causative bacteria, mycobacterium, or fungi. Anti-*Mycoplasma pneumoniae* antibody was positive in one of the five patients tested. Testing for urinary *Legionella* antigen was conducted in five patients and testing for serum *Aspergillus* antigen was conducted in eight patients; all results were negative. Detection of *Candida* antigen in the serum was positive at a low titer in two of the seven patients who were examined, but *Candida* species were not detected in sputum cultures from these two patients. Five patients were empirically treated with ganciclovir, but the *Cytomegalovirus* antigenemia assay was negative for all of them. These data, combined with other clinical and laboratory data and the GGO on the thoracic CT, suggested a low possibility of other infectious diseases in the PCP group patients.

Case–control study

To more precisely characterize the PCP group, we compared demographics, comorbidities, concomitant drugs, and laboratory data between the PCP and the non-PCP groups at the time of initiation of treatment with etanercept (Table 4). On univariate analysis, the PCP group was significantly older ($p < 0.001$), and had a significantly lower percentage of females ($p = 0.049$) and a significantly higher percentage of patients with lung diseases ($p = 0.002$) than the non-PCP group. Also, the PCP group was treated with significantly higher dosages of concomitant PSL ($p = 0.045$) and MTX ($p = 0.007$) than the non-PCP group.

Based on the results of the univariate analysis, we identified independent risk factors for PCP in RA patients treated with etanercept using Cox proportional hazard models. The results showed that the development of PCP was significantly associated with age (≥65 vs. <65 years) [hazard ratio (HR) 3.35, 95% confidence interval (CI) 1.01–10.42, $p = 0.037$], the coexistence of lung disease

(yes vs. no) (HR 4.48, 95% CI 1.46–13.72, $p = 0.009$), and the concomitant use of MTX (yes vs. no) (HR 4.68, 95% CI 1.59–13.81, $p = 0.005$).

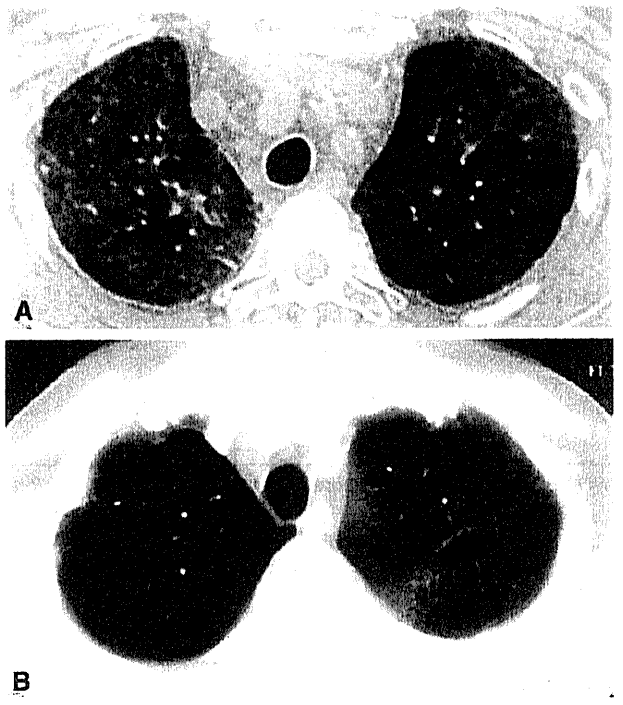

Fig. 1 Thoracic computed tomography findings of rheumatoid arthritis patients who developed *Pneumocystis jirovecii* pneumonia while receiving etanercept. **a** Ground-glass opacity (GGO) with sharp demarcation by interlobular septa and geographic pattern. **b** GGO without interlobular septal boundaries

Accumulation of risk factors and development of PCP

We calculated the cumulative probability for developing PCP in patient groups stratified by the number of coexisting risk factors. When all patients ($n = 89$) were stratified by the number of risk factors, including age (≥65 years, yes/no), coexistence of lung disease, and use of MTX, the cumulative probability for the occurrence of PCP was significantly higher in patients with one risk factor compared to patients with no risk factor ($p = 0.015$); as well, the cumulative probability for the occurrence of PCP was significantly higher in patients with two or three risk factors compared to patients with no risk factor ($p < 0.001$) or compared to patients with one risk factor ($p = 0.001$) (Fig. 2).

Discussion

The highest available number of patients with RA who developed PCP during treatment with etanercept was located and the clinical, laboratory, and radiographic characteristics of these 15 patients were described. Independent risk factors for the development of PCP in these patients were also identified.

This study clarified important characteristics of PCP in RA patients receiving etanercept: (1) rapid development with a severe clinical course; (2) relatively low levels of plasma BDG and a low microscopic detection rate for *P. jirovecii*; and (3) infection occurring even in patients with normal peripheral lymphocyte counts and normal serum IgG levels. Of note, PCP in non-AIDS patients develops

Table 3 Laboratory findings in rheumatoid arthritis patients at the onset of *Pneumocystis jirovecii* pneumonia (PCP)

Pt	WBC (/μl)	Lymphocytes (/μl)	CRP (mg/dl)	Serum Alb (g/dl)	Serum IgG (mg/dl)	KL-6 (U/ml)
1	2,900	397	22.8	2.2	NA	821
2	7,200	1,900	7.92	4.1	NA	385
3	8,540	1,836	2.59	3.8	NA	NA
4	14,300	686	3.2	3.65	NA	487
5	7,000	1,260	4.81	3.4	2,230	1,516
6	5,000	860	9.49	3.4	1,645	687
7	8,700	1,305	23.7	3.5	1,405	162
8	10,300	309	19.1	2.2	707	820
9	5,700	627	6.0	3.1	1,120	864
10	7,600	1,547	21	4.2	1,090	485
11	6,340	628	9.86	2.44	1,341	666
12	20,730	2,094	22.41	2.57	NA	779
13	9,200	1,435	9.53	2.6	1,714	197
14	8,900	462	5.0	2.4	NA	420
15	13,260	2,386	18.05	2.3	665	NA
Median (IQR)	8,540 (6,670–9,750)	1,260 (628–1,692)	9.5 (5.5–20.1)	3.1 (2.4–3.6)	1,341 (1,090–1,645)	666 (420–820)

Pt patient, *WBC* white blood cells, *CRP* C-reactive protein, *Alb* albumin, *NA* not assessed, *KL-6* a serum marker for interstitial pneumonia and PCP, *IQR* interquartile range

Table 4 Clinical characteristics of rheumatoid arthritis patients treated with etanercept at initiation of therapy

Characteristics	PCP group (n = 15)	Non-PCP group (n = 74)	p value
Age (years)[a]	66.4 ± 11.7	54.7 ± 13.5	<0.001†
Age (≥65 years, %)	60	17.6	0.001‡
Female (%)	53.3	78.4	0.049‡
Disease duration (months)[a]	120.2 ± 102.5	114.4 ± 88.1	0.908†
Coexistence of lung disease (%)[b]	46.7	9.5	0.002‡
Coexistence of diabetes mellitus (%)	20.0	4.1	0.057‡
Concomitant use of MTX (%)	66.7	31.1	0.009‡
Dosage of MTX (mg/week)[a]	5.5 ± 4.6	2.5 ± 4.1	0.007†
Concomitant use of PSL (%)	80.0	64.9	0.204‡
Dosage of PSL (mg/day)[a]	11.4 ± 16.3	3.7 ± 3.4	0.045†
Dosage of PSL (≥5 mg/day, %)	53.3	28.4	0.06‡
Concomitant use of immunosuppressants, except for MTX (%)	6.7	20.3	0.193‡
White blood cells (/μl)[a]	8,279 ± 3,352	8,603 ± 3,021	0.587†
Lymphocytes(/μl)[a]	1,591 ± 810	1,379 ± 591	0.254†
Serum albumin (g/dl)[a]	3.4 ± 0.7	3.8 ± 0.4	0.06†
Serum IgG (mg/dl)[a]	1,447 ± 430	1,568 ± 570	0.557†

After the Bonferroni's correction, only the differences in age and pulmonary diseases retained statistical significance

p Values were calculated using the Mann–Whitney U-test test (†) or the χ^2 test (‡)

PCP Pneumocystis jirovecii pneumonia, *MTX* methotrexate, *PSL* prednisolone

[a] Mean ± SD

[b] Four interstitial pneumonia cases, one old pleuritis, one pneumoconiosis, and one prior tuberculosis

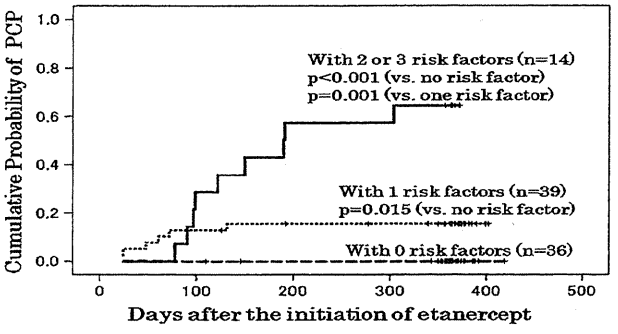

Fig. 2 Cumulative probability of developing *Pneumocystis jirovecii* pneumonia (*PCP*) in rheumatoid arthritis patients with associated risk factors when treated with etanercept. The patients were stratified by the number of risk factors, including age ≥65 years, coexistence of lung disease, and concomitant use of methotrexate (MTX). The cumulative probability for developing PCP according to the number of risk factors was calculated using the Kaplan–Meier method and comparison between the groups was performed using the log rank test

more rapidly and is more severe with a poorer prognosis than PCP in AIDS patients [13, 26–31]. We also have reported that in RA patients treated with infliximab [22] PCP developed rapidly and progressed to severe respiratory failure. In agreement with these previous reports, we found that all 15 patients who received etanercept in the present study showed acute-onset PCP and severe hypoxemia or requirement for oxygen therapy. While some studies suggest that low peripheral blood lymphocyte counts are associated with the development and severity of PCP in patients with rheumatic diseases [32–34], the immunological status of the patients with PCP in the present study, as judged from conventional laboratory tests, was not seriously impaired; peripheral blood lymphocyte counts at the onset of PCP were more than 500 cells/μl in 12 patients (80%) and serum IgG levels were normal in 7 of 9 patients (77.8%).

Fourteen of the 15 patients had presumptive diagnoses of PCP without microscopic detection of *P. jirovecii*. Because it has been reported that PCP in patients without AIDS presented with fewer numbers of the pathogen in the lung [13], we, and other investigators who have studied PCP in RA patients, included patients who did not have microscopic detection of the organism but who were positive for the PCR test or had an elevated serum BDG level. Recently, Kameda et al. [20] conducted a retrospective, multicenter study of acute-onset diffuse interstitial lung disease in patients with RA receiving biological agents. They defined 'definite PCP' as microscopically positive, or double-positive for the PCR test and serum BDG level, and 'probable PCP' as positive for either the PCR test or serum BDG level. They found that the two groups (i.e., definitive and probable PCP) were clinically

and radiologically indistinguishable. Because our criteria for presumptive PCP were not stringent by definition, it was mandatory to exclude other infectious diseases, as far as possible, by means of bacteriological examinations, laboratory tests, and radiological characteristics. As mentioned in the "Results" section, in our PCP patients there were no definitive data for other infectious lung diseases. Based on these data and discussion, we included presumptive PCP patients in the present study for analysis, in addition to the microscopically diagnosed PCP patients.

The efficacy of the use of corticosteroids for the treatment of PCP that develops in patients with rheumatic diseases is controversial [33, 35]. Pareja et al. [33] and Tokuda et al. [21] reported good clinical outcomes in PCP patients without HIV infection who received concomitant high-dose corticosteroids with TMP/SMX. In our study, 9 of the 15 patients received high-dose corticosteroids concomitant with TMP/SMX. In our previous study of PCP in RA patients during infliximab therapy, 19 of 21 patients received high-dose corticosteroids concomitantly with TMP/SMX [22, 24]. The mortality of the patients with PCP receiving infliximab (0%) or etanercept (6.7%) is considerably lower than the mortality found in previous studies of PCP in patients without HIV infection (32–45.7%) [34, 36]. Our diagnostic criteria included good response to standard treatment for PCP with TMP/SMX or pentamidine isethionate; concomitant corticosteroid therapy with TMP/SMX might also have contributed to the lower mortality seen in our study.

The risk factors for the development of PCP were similar for both RA patients receiving infliximab and for those given etanercept, the risk factors in common being age of $\geq$65 years and the coexistence of lung disease [24]. The concomitant use of MTX was another risk factor for PCP in RA patients receiving etanercept. An association between MTX therapy and increased risk of infection or serious infection in RA patients remains controversial [7, 37, 38]. It seems possible that the association between MTX and PCP is specific to the ethnic group studied or the concomitant drug used (i.e., etanercept). Because the number of patients in our study was small, further investigations of more patients are needed to answer these questions.

In our study, no patients received chemoprophylaxis for PCP. In HIV-infected patients, primary prophylaxis for PCP is recommended when the CD4+ lymphocyte count is <200 cells/μl or when a patient has a history of oropharyngeal candidiasis [39]. However, the peripheral blood lymphocyte counts of most patients with PCP in the present study were higher than 500 cells/μl. Based on the results of our Kaplan–Meier analysis (Fig. 2), chemoprophylaxis for PCP might be considered when a patient has all of the risk factors at the initiation of etanercept therapy.

There are definite limitations to our study. First is the inclusion of presumptive cases. The traditional diagnosis of PCP, the microscopic detection of *P. jirovecii*, was made in only one of the 15 patients. The other 14 patients, however, had clinical, laboratory, and radiological characteristics compatible with PCP, but did not have evidence for other pulmonary infectious diseases. The interpretation of the results of our study should take our diagnostic criteria into account. Second, because our criteria included the presenting characteristics of the patients, we cannot exclude the possibility that milder PCP cases were missed; however, such cases are less clinically relevant than those of the patients included in this study. Third, the p value for age from the Cox proportional hazard analysis for risk factors for PCP was 0.037 and the lower limit of the 95% CI of the risk factors was about 1.0. Although this value has limited statistical significance, older age has been recognized as an important risk factor for infections in RA patients [40] and it is safest to assume this risk factor for PCP is real for RA patients receiving etanercept.

In conclusion, physicians must be alert to the possibility of PCP developing during etanercept therapy in RA patients, particularly if one or more risk factors are present, and physicians must also be vigilant for clinical manifestations, indicative laboratory tests, and radiological findings.

Acknowledgments We would like to thank Drs. Saburo Matsubara (Center for Arthritis and Clinical Rheumatology Matsubara Clinic), Kenichi Miyagi (Miyagi Clinic), Masao Sato (Nishimino Welfare Hospital), Kazuaki Katsumata (Nissei Hospital), Tetsu Oyama (Oyama Clinic), Tsuyoshi Kasama (Showa University Hospital), Masahito Koiwa (Shuwa General Hospital), Kazuhide Tanimura (Hokkaido Medical Center for Rheumatic Diseases), Yoshiko Sato (Yokkaichi Social Insurance Hospital), and Hideaki Oka (Yokohama City University Hospital), for their critical discussions during our study group meetings concerning all patients who had or were suspected to have PCP. We also thank Drs. Koichi Amano (Saitama Medical Center, Saitama Medical University), Masahiro Iwamoto (Jichi Medical University), and Noriyoshi Ogawa (Hamamatsu University School of Medicine), who were the members of the Japan College of Rheumatology (JCR) subcommittee for interstitial pneumonia and PCP during the post-marketing surveillance program of etanercept in Japan, for their discussion about some cases in the present study during the meeting of the subcommittee.

Conflict of interest Masayoshi Harigai and Nobuyuki Miyasaka have received research grants from Abbott Japan, Astellas, Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Mitsubishi-Tanabe Pharma Corp., Novartis Pharma K.K., Takeda Pharmaceutical Co. Ltd., and Wyeth K.K. (now Pfizer). Tsutomu Takeuchi has received grants and consultant fees from Abbott Japan, Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd., Janssen Pharmaceutical Co. Ltd., Mitsubishi-Tanabe Pharma Corp., Novartis Pharma K.K., Takeda Pharmaceutical Co. Ltd., and Wyeth K.K. (now Pfizer). Yoshiya Tanaka has received consultant fees from Abbott Japan, Astellas, Banyu Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Mitsubishi-Tanabe Pharma Corp., and Takeda Pharmaceutical Co. Ltd. There is no other competing

interest for the other authors regarding this article. This work was supported by Grants-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Science to R.K. (#19590530), M.H. (#20390158) and M.T. (#23590171), and by Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan (H19-meneki-ippan-009 to M.N. and M.H. and H22-meneki-ippann-001 to T.T. and M.H.). This work was also supported by the Global Center of Excellence (GCOE) program, 'International Research Center for Molecular Science in Tooth and Bone Diseases'.

References

1. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol. 1996;14:397–440.
2. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354(9194): 1932–9.
3. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005;52(11):3381–90.
4. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet. 2007; 370(9602):1861–74.
5. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum. 2007;56(9):2896–904.
6. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006;54(8):2368–76.
7. Komano Y, Tanaka M, Nanki T, Koike R, Sakai R, Kameda H, et al. Incidence and risk factors for serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. J Rheumatol. 2011; 38(7):1258–64.
8. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275–85.
9. Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, et al. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. J Rheumatol. 2009;36(5):898–906.
10. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008;67(2):189–94.
11. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients. Mod Rheumatol. 2011 (Epub ahead of print).
12. Furrer H, Egger M, Opravil M, Bernasconi E, Hirschel B, Battegay M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. N Engl J Med. 1999;340(17):1301–6.
13. Limper AH, Offord KP, Smith TF, Martin WJ 2nd. *Pneumocystis carinii* pneumonia. Differences in lung parasite number and inflammation in patients with and without AIDS. Am Rev Respir Dis. 1989;140(5):1204–9.
14. Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. Drug Saf. 2004;27(5):307–24.
15. Takeuchi T, Kameda H. The Japanese experience with biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol. 2010; 6(11):644–52.
16. Krajicek BJ, Thomas CF Jr, Limper AH. Pneumocystis pneumonia: current concepts in pathogenesis, diagnosis, and treatment. Clin Chest Med. 2009;30(2):265–78, vi.
17. Khot PD, Fredricks DN. PCR-based diagnosis of human fungal infections. Expert Rev Anti Infect Ther. 2009;7(10):1201–21.
18. Marty FM, Koo S, Bryar J, Baden LR. (1 → 3)Beta-D-glucan assay positivity in patients with *Pneumocystis (carinii) jirovecii* pneumonia. Ann Intern Med. 2007;147(1):70–2.
19. Tasaka S, Hasegawa N, Kobayashi S, Yamada W, Nishimura T, Takeuchi T, et al. Serum indicators for the diagnosis of pneumocystis pneumonia. Chest. 2007;131(4):1173–80.
20. Kameda H, Tokuda H, Sakai F, Johkoh T, Mori S, Yoshida Y, et al. Clinical and radiological features of acute-onset diffuse interstitial lung diseases in patients with rheumatoid arthritis receiving treatment with biological agents: importance of pneumocystis pneumonia in Japan revealed by a multicenter study. Intern Med. 2011;50(4):305–13.
21. Tokuda H, Sakai F, Yamada H, Johkoh T, Imamura A, Dohi M, et al. Clinical and radiological features of Pneumocystis pneumonia in patients with rheumatoid arthritis, in comparison with methotrexate pneumonitis and Pneumocystis pneumonia in acquired immunodeficiency syndrome: a multicenter study. Intern Med. 2008;47(10):915–23.
22. Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, et al. *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case–control study of 21 patients. Arthritis Rheum. 2009; 61(3):305–12.
23. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315–24.
24. Harigai M, Koike R, Miyasaka N. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med. 2007;357(18): 1874–6.
25. Nakajima H, Harigai M, Hara M, Hakoda M, Tokuda H, Sakai F, et al. KL-6 as a novel serum marker for interstitial pneumonia associated with collagen diseases. J Rheumatol. 2000;27(5):1164–70.
26. Nakamura H, Tateyama M, Tasato D, Haranaga S, Yara S, Higa F, et al. Clinical utility of serum beta-D-glucan and KL-6 levels in *Pneumocystis jirovecii* pneumonia. Intern Med. 2009;48(4): 195–202.
27. Thomas CF Jr, Limper AH. Pneumocystis pneumonia. N Engl J Med. 2004;350(24):2487–98.
28. Monnet X, Vidal-Petiot E, Osman D, Hamzaoui O, Durrbach A, Goujard C, et al. Critical care management and outcome of severe Pneumocystis pneumonia in patients with and without HIV infection. Crit Care. 2008;12(1):R28.
29. Ewig S, Bauer T, Schneider C, Pickenhain A, Pizzulli L, Loos U, et al. Clinical characteristics and outcome of *Pneumocystis carinii* pneumonia in HIV-infected and otherwise immunosuppressed patients. Eur Respir J. 1995;8(9):1548–53.
30. Thomas CF Jr, Limper AH. Pneumocystis pneumonia: clinical presentation and diagnosis in patients with and without acquired

immune deficiency syndrome. Semin Respir Infect. 1998;13(4): 289–95.
31. Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. Clin Infect Dis. 2002;34(8):1098–107.
32. Iikuni N, Kitahama M, Ohta S, Okamoto H, Kamatani N, Nishinarita M. Evaluation of Pneumocystis pneumonia infection risk factors in patients with connective tissue disease. Mod Rheumatol. 2006;16(5):282–8.
33. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV *Pneumocystis carinii* pneumonia. Chest. 1998;113(5):1215–24.
34. Godeau B, Coutant-Perronne V, Le Thi Huong D, Guillevin L, Magadur G, De Bandt M, et al. *Pneumocystis carinii* pneumonia in the course of connective tissue disease: report of 34 cases. J Rheumatol. 1994;21(2):246–51.
35. Delclaux C, Zahar JR, Amraoui G, Leleu G, Lebargy F, Brochard L, et al. Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in non-human immunodeficiency virus-infected patients: retrospective study of 31 patients. Clin Infect Dis. 1999;29(3):670–2.
36. Ward MM, Donald F. *Pneumocystis carinii* pneumonia in patients with connective tissue diseases: the role of hospital experience in diagnosis and mortality. Arthritis Rheum. 1999;42(4):780–9.
37. Greenberg JD, Reed G, Kremer JM, Tindall E, Kavanaugh A, Zheng C, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2009;69(2):380–6.
38. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006: 54(2):628–34.
39. Masur H, Kaplan JE, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. Ann Intern Med. 2002;137(5 Pt 2):435–78.
40. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum. 2002;46(9):2294–300.

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

ATSUSHI HASHIMOTO, SATOKO TEJIMA, TOSHIHIRO TONO, MAIKO SUZUKI, SUMIAKI TANAKA, TOSHIHIRO MATSUI, SHIGETO TOHMA, HIRAHITO ENDO, and SHUNSEI HIROHATA

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

From the Department of Rheumatology and the Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization; Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa; and Division of Rheumatology, Department of Internal Medicine, Toho University, Tokyo, Japan.

A. Hashimoto, MD, Department of Rheumatology, Sagamihara National Hospital, and Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine; S. Tejima, MD, Research Associate; T. Tono, MD, Research Associate; M. Suzuki, MD, Research Associate, Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine; S. Tanaka, MD, Lecturer; T. Matsui, MD, Department of Rheumatology, Sagamihara National Hospital; S. Tohma, MD, Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital; H. Endo, MD, Associate Professor, Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine; S. Hirohata, MD, Professor, Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine.

Address correspondence to Dr. A. Hashimoto, Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization, 18-1 Sakuardai, Minami-ku, Sagamihara, Kanagawa, 252-0392, Japan. E-mail: hashi@med.kitasato-u.ac.jp

Accepted for publication April 27, 2011.

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).

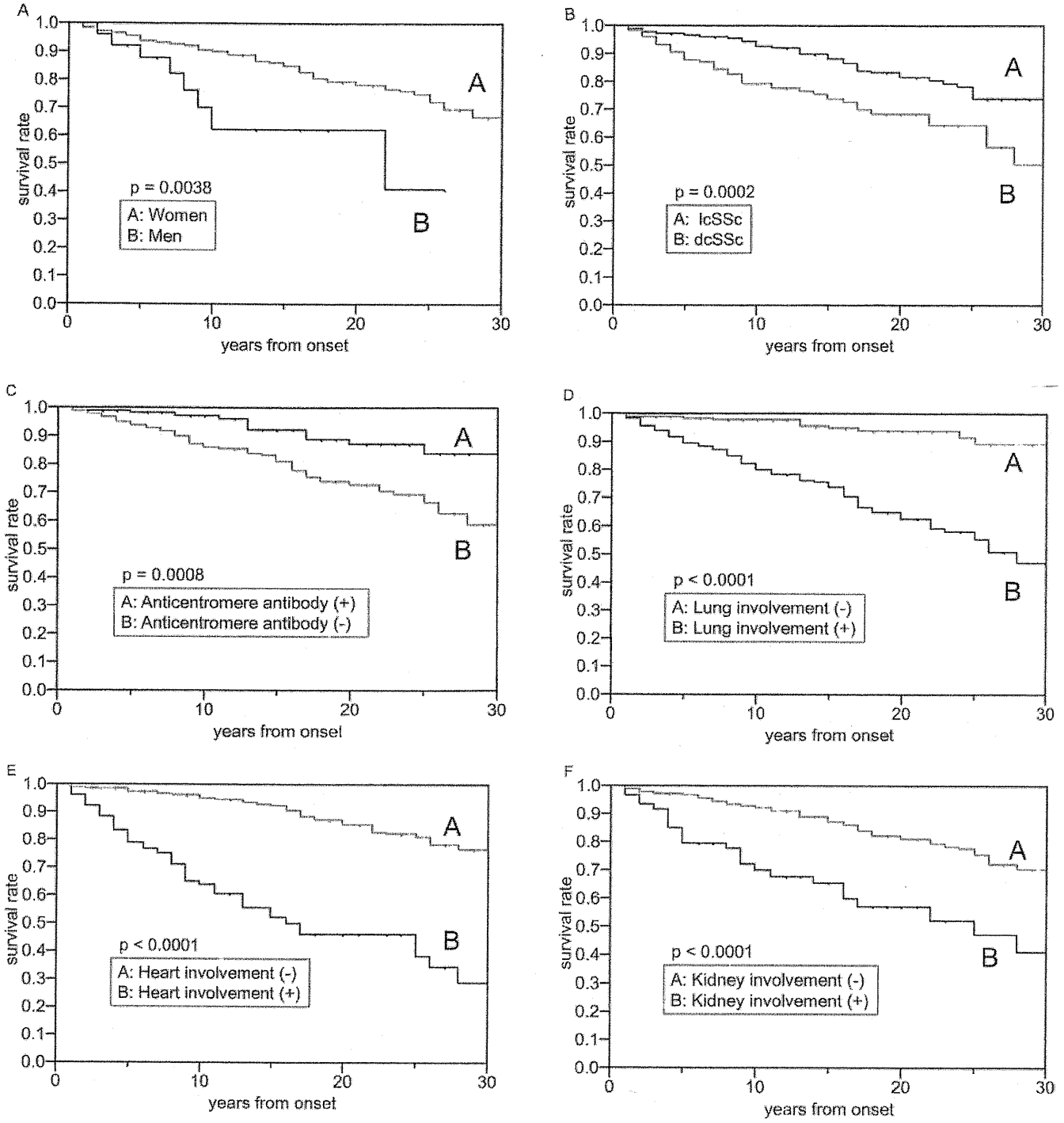

Figure 1. Kaplan-Meier survival curves of patients with systemic sclerosis (SSc) and results of the log-rank test. Horizontal axis represents the duration from the onset of SSc. A. Females showed significantly better survival than males ($p = 0.0038$). The longest disease duration in male patients was 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 ($p = 0.0240$).

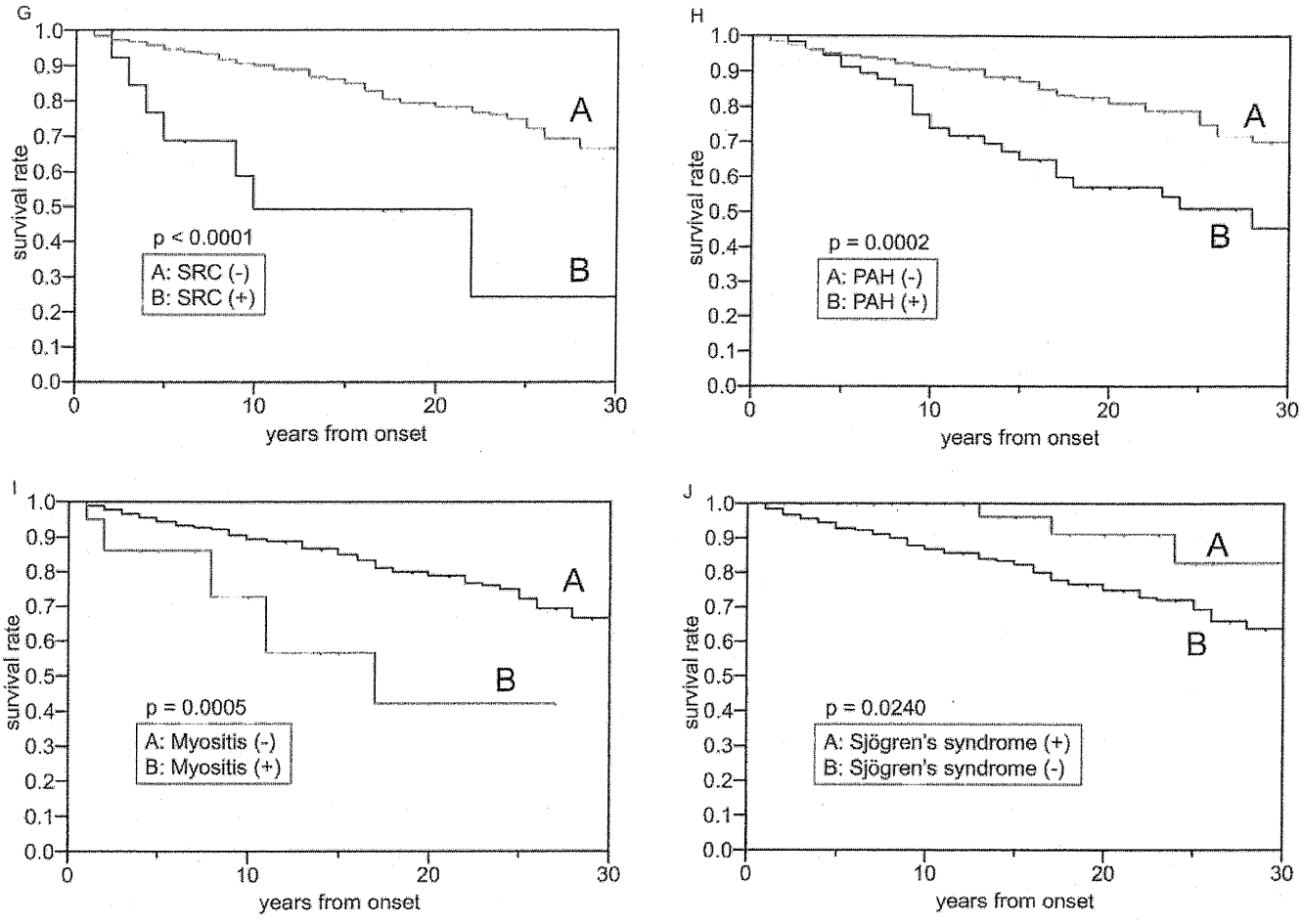

Figure 1. Continued

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.

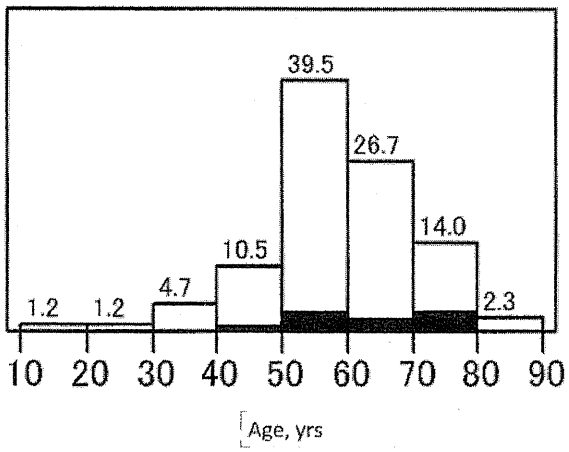

Figure 2. Age of death for 86 patients with systemic sclerosis. The horizontal axis denotes age and each division on the scale represents 1 decade. Numbers on the bars indicate the percentage of the population in that decade. Shaded areas represent male patients.

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 over-

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)

lapping 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

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.

REFERENCES

1. Hashimoto A, Endo H, Tanaka S, Matsui T, Tohma S, Hirohata S. Clinical features and autoantibodies in Japanese patients with systemic sclerosis [abstract]. Ann Rheum Dis 2010;69 Suppl 3:691.
2. 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.
3. Barnett AJ, Coventry DA. Scleroderma. 1. Clinical features, course of illness and response to treatment in 61 cases. Med J Aust 1969;1:992-1001.
4. Doria A, Ghirardello A, de Zambiasi P, Ruffatti A, Gambari PF. Japanese diagnostic criteria for mixed connective tissue disease in Caucasian patients. J Rheumatol 1992;19:259-64.
5. Poormoghim H, Lucas M, Fertig N, Medsger TA Jr. Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. Arthritis Rheum 2000;43:444-51.
6. 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.
7. Rose S, Young MA, Reynolds JC. Gastrointestinal manifestations

of scleroderma. Gastroenterol Clin North Am 1998;27:563-94.
8. Steen VD, Medsger TA Jr, Osial TA Jr, Ziegler GL, Shapiro AP, Rodnan GP. Factors predicting development of renal involvement in progressive systemic sclerosis. Am J Med 1984;76:779-86.
9. Steen VD, Syzd A, Johnson JP, Greenberg A, Medsger TA Jr. Kidney disease other than renal crisis in patients with diffuse scleroderma. J Rheumatol 2005;32:649-55.
10. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089-100.
11. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol 2007;11:41-50.
12. Denolin H. Diagnosis of pulmonary hypertension by direct measurement. In: Report on a WHO meeting: primary pulmonary hypertension. Hatano S, Strasser T, editors. Geneva: World Health Organization; 1975:40-5.
13. Schachna L, Wigley FM, Chang B, White B, Wise RA, Gelber AC. Age and risk of pulmonary arterial hypertension in scleroderma. Chest 2003;124:2098-104.
14. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
16. Fujibayashi T, Sugai S, Miyasaka N, Hayashi Y, Tsubota K. Revised Japanese criteria for Sjögren syndrome (1999): availability and validity. Mod Rheumatol 2004;14:425-34.
17. Barnett AJ, Miller MH, Littlejohn GO. A survival study of patients with scleroderma diagnosed over 30 years (1953-1983): the value of a simple cutaneous classification in the early stages of the disease. J Rheumatol 1988;15:276-83.
18. Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. J Am Coll Cardiol 1985;5:141B-9B.
19. Baba S, Ozawa H, Sakai Y, Terao A, Konishi M, Tatara K. Heart disease deaths in a Japanese urban area evaluated by clinical and police records. Circulation 1994;89:109-15.
20. Tan EM, Kunkel HG. Characteristics of a soluble nuclear antigen precipitating with sera of patients with systemic lupus erythematosus. J Immunol 1966;96:464-71.
21. Genth E, Mierau R, Genetzky P, von Mühlen CA, Kaufmann S, von Wilmowsky H, et al. Immunogenetic associations of scleroderma-related antinuclear antibodies. Arthritis Rheum 1990;33:657-65.
22. Moroi Y, Peebles C, Fritzler MJ, Steigerwald J, Tan EM. Autoantibody to centromere (kinetochore) in scleroderma sera. Proc Natl Acad Sci USA 1980;77:1627-31.
23. Bryan C, Howard Y, Brennan P, Black C, Silman A. Survival following the onset of scleroderma: results from a retrospective inception cohort study of the UK patient population. Br J Rheumatol 1996;35:1122-6.
24. Walsh SJ, Fenster JR. Geographical clustering of mortality from systemic sclerosis in the Southeastern United States, 1981-90. J Rheumatol 1997;24:2348-52.
25. Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). Br J Rheumatol 1998;37:750-5.
26. 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.
27. Simeón 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.
28. 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.
29. 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.
30. 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.
31. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine 2002;81:139-53.
32. 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.
33. Czirják L, Kumánovics G, Varjú C, Nagy Z, Pákozdi A, Szekanecz Z, et al. Survival and causes of death in 366 Hungarian patients with systemic sclerosis. Ann Rheum Dis 2008;67:59-63.
34. Altman RD, Medsger TA Jr, Bloch DA, Michel BA. Predictors of survival in systemic sclerosis (scleroderma). Arthritis Rheum 1991;34:403-13.
35. Czirják L, Nagy Z, Szegedi G. Survival analysis of 118 patients with systemic sclerosis. J Intern Med 1993;234:335-7.
36. Kuwana M, Kaburaki J, Okano Y, Tojo T, Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. Arthritis Rheum 1994;37:75-83.
37. Nagy Z, Czirják L. Predictors of survival in 171 patients with systemic sclerosis (scleroderma). Clin Rheumatol 1997;16:454-60.
38. Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of morbidity and mortality of systemic sclerosis in Canada. Semin Arthritis Rheum 2010;39:269-77.
39. Kim J, Park SK, Moon KW, Lee EY, Lee YJ, Song YW, et al. The prognostic factors of systemic sclerosis for survival among Koreans. Clin Rheumatol 2010;29:297-302.
40. Artinian V, Kvale PA. Cancer and interstitial lung disease. Curr Opin Pulm Med 2004;10:425-34.
41. Youssef P, Brama T, Englert H, Bertouch J. Limited scleroderma is associated with increased prevalence of macrovascular disease. J Rheumatol 1995;22:469-72.
42. 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.
43. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66:940-4.
44. Denton CP, Black CM. Pulmonary hypertension in systemic sclerosis. Rheum Dis Clin North Am 2003;29:335-49.
45. Bjornsson J, Edwards WD. Primary pulmonary hypertension: a histopathologic study of 80 cases. Mayo Clin Proc 1985;60:16-25.
46. Brown DL, Wetli CV, Davis JH. Sudden unexpected death from primary pulmonary hypertension. J Forensic Sci 1981;26:381-6.
47. Ackermann DM, Edwards WD. Sudden death as the initial manifestation of primary pulmonary hypertension. Report of four cases. Am J Forensic Med Pathol 1987;8:97-102.
48. Kanemoto N, Sasamoto H. Arrhythmias in primary pulmonary hypertension. Jpn Heart J 1979;20:765-75.
49. Yamamoto ME, Jones JW, McManus BM. Fatal dissection of the

pulmonary trunk. An obscure consequence of chronic pulmonary hypertension. Am J Cardiovasc Pathol 1988;1:353-9.
50. Walley VM, Virmani R, Silver MD. Pulmonary arterial dissections and ruptures: to be considered in patients with pulmonary arterial hypertension presenting with cardiogenic shock or sudden death. Pathology 1990;22:1-4.
51. Arena V, De Giorgio F, Abbate A, Capelli A, De Mercurio D, Carbone A. Fatal pulmonary arterial dissection and sudden death as initial manifestation of primary pulmonary hypertension: a case report. Cardiovasc Pathol 2004;13:230-2.
52. Kawato H, Hitosugi M, Kido M, Yufu T, Nagai T, Tokudome S. An autopsy case of sudden death in a boy with primary pulmonary hypertension: a case report. Med Sci Law 2005;45:361-3.
53. Brun H, Holmström H, Thaulow E. Sudden death during a change in treatment for pulmonary hypertension. Cardiol Young 2005;15:223-5.
54. Kanemoto N. Natural history of pulmonary hemodynamics in primary pulmonary hypertension. Am Heart J 1987;114:407-13.

Mod Rheumatol
DOI 10.1007/s10165-011-0515-7

ORIGINAL ARTICLE

Clinical features of 405 Japanese patients with systemic sclerosis

Atsushi Hashimoto · Hirahito Endo · Hirobumi Kondo · Shunsei Hirohata

Received: 10 June 2011 / Accepted: 11 August 2011

Abstract We aimed to clarify the clinical features of Japanese patients with systemic sclerosis (SSc), especially with reference to organ involvement and autoantibodies. A cohort of 405 patients with SSc who attended our institution from 1973 to 2008 was identified retrospectively. Data on clinical features, including autoantibodies, organ involvement, and overlap of other connective tissue diseases, were obtained by following the medical records until 2009. The percentage of male patients during or after 1990 was greater than that before 1990 (3.9 vs. 10.6%, respectively). Limited cutaneous SSc (lSSc) was twice as frequent as diffuse cutaneous SSc (dSSc). About half of the patients had lung involvement (50.4%), while only 3.2% had scleroderma renal crisis. Male gender was associated with lung involvement, and dSSc was associated with most organ involvements except for pulmonary arterial hypertension (PAH). Anti-Scl-70 antibody was associated with lung or heart involvement, while anti-U1-RNP antibody was only associated with PAH. Conversely, patients with anti-centromere antibody had less organ involvement. SSc–Sjögren overlap syndrome was related to lSSc, further overlapping systemic lupus erythematosus (SLE), and less lung or heart involvement. In conclusion, these results not only confirmed previous reports but revealed several other findings, such as the increased proportion of male patients in recent years and the relationships between clinical features.

Keywords Antibody · Scleroderma · Scleroderma renal crisis · Sjögren's syndrome · Systemic sclerosis

A. Hashimoto (✉) · S. Hirohata
Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan
e-mail: hashi@med.kitasato-u.ac.jp

H. Endo
Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan

H. Kondo
Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan

Introduction

Systemic sclerosis (SSc) is a connective tissue disease (CTD) of uncertain etiology, characterized by thickening of the skin that results from fibrotic and degenerative changes, with a wide spectrum of clinical and laboratory manifestations [1]. SSc patients are classified into two groups according to the extent of skin involvement: (1) patients with diffuse cutaneous SSc (dSSc) have skin thickening proximal to the elbows and knees, and (2) patients with limited cutaneous SSc (lSSc) only have involvement of the distal extremities. Antinuclear antibody (ANA) is detected in sera from patients with several CTDs and also from most SSc patients. ANA can be classified into various subtypes by its specific anti-extractable nuclear antigens (ENAs), among which anti-Scl-70 antibody (anti-topoisomerase-I) and anti-centromere antibody are specific for SSc, whereas anti-U1-RNP antibody is found in SSc patients but is mainly associated with mixed connective tissue disease (MCTD). Although it is not established that these antibodies have any pathological effects, various associations between antibodies and clinical features have been reported. In general, anti-centromere antibody is found in patients who have lSSc without severe organ involvement except for pulmonary hypertension [2, 3]. On the other

Published online: 28 August 2011

hand, anti-Scl-70 antibody is associated with dSSc and pulmonary fibrosis [4]. The association between the involvement of organs and each antibody varies among reports, and this variation is at least partially attributable to differences of ethnic background [5]. In this study, we attempted to comprehensively assess the clinical features of Japanese patients with SSc presenting to a single institution, with reference to organ involvement and antibodies, in order to improve our understanding of SSc.

Patients, materials, and methods

Patients who visited Kitasato University Hospital from 1973 to 2008 with bilateral symmetrical skin thickening, including those with only sclerodactyly [6], were enrolled in this study, as reported previously [7]. Patients who met the Japanese diagnostic criteria for MCTD were excluded [7]. Overall, 376 female patients and 29 male patients (total: $n = 405$) were enrolled. Their antibody profiles and clinical features, including age, sex, disease duration, organ involvements, and overlap with other CTDs, were obtained by following their medical records until 2009. When examined retrospectively, at least 60.0% of the patients met the criteria for SSc of the American Rheumatism Association (now the American College of Rheumatology) [8] and 87.9% met the criteria for SSc of the Japanese Ministry of Health and Welfare [9]. The study was approved by the ethics committee of the Kitasato University Hospital. The onset of SSc was judged to correspond to that of Raynaud's phenomenon and/or joint symptoms occurring before skin sclerosis, as well as the characteristic symptoms caused by organ involvement [10].

Measurements of autoantibodies, including ANA and anti-ENA antibodies such as anti-Scl-70, anti-U1-RNP, and anti-centromere antibodies, as well as definitions of organ involvements and the diagnosis of overlapping CTDs were described previously [7]. In brief, the evaluation of skin thickening was based on a modified Rodnan total skin thickness score (mTSS) [11]. Gastrointestinal tract (GI) involvement was defined as gastroesophageal reflux disease (GERD), dysphagia, bacterial overgrowth requiring antibiotics, and/or paralytic ileus [12]. 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 of less than 40% measured by echocardiography, conduction disturbance or arrhythmia requiring therapy, or congestive heart failure. Scleroderma renal crisis (SRC) was defined by the occurrence of malignant arterial hypertension or rapidly progressive oliguric renal failure without other discernible causes during the course of SSc [13]. Renal involvement was defined as present or past SRC, as well as continuous proteinuria or a glomerular filtration rate of less than 60 ml/min per 1.73 m^2. Pulmonary arterial hypertension (PAH) was diagnosed from a mean pulmonary arterial pressure of more than 25 mmHg measured directly by right heart catheterization [14], or an estimated pulmonary arterial pressure of more than 35 mmHg calculated from the tricuspid flow velocity by Doppler echocardiography [15]. PAH secondary to left heart failure was excluded. Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) were diagnosed according to the 1982 and 1987 criteria of the American Rheumatism Association (now American College of Rheumatology), respectively [16, 17]. Sjögren's syndrome was diagnosed according to the 1999 Japanese Ministry of Health and Welfare's diagnostic criteria for Sjögren's syndrome [18]. Myositis was defined as inflammation of skeletal muscle associated with a serum creatine kinase level above the normal institutional range. Myositis not only included muscle involvement due to SSc, but also polymyositis or dermatomyositis complicated by SSc. It should be noted that the occurrence of such conditions could have been underestimated because not all patients were examined for every organ involvement or overlapping CTD.

Statistics

The between-groups comparisons for univariate analysis were conducted with the Wilcoxon rank sum test for numerical values or Fisher's exact test (χ^2 test only for correlation between anti-ENA antibodies and each organ involvement; see Table 4) for proportions, including calculation of the relative risk (RR) and 95% confidence interval (CI), done with Jmp 5.1 software (SAS Institute Japan, Tokyo, Japan). Results were expressed as the median ± standard error of the mean (SEM). P values of less than 0.05 were regarded as significant.

Results

Clinical background

A total of 405 patients with SSc–376 females (92.8%) and 29 males (7.2%)–were enrolled in the analysis. When patients were divided into two groups according to the onset of SSc, of up to 1989 and from 1990 onward, the latter group ($n = 199$) had a significantly higher percentage of males (21 males, 10.6%) than the former group ($n = 206$, 8 males, 3.9%) (RR 2.9; 95% CI 1.3–6.8; $P = 0.0115$).

Basic demographic data are shown in Table 1. Of the 405 patients, 135 (33.3%) had dSSc and the others ($n = 270$, 66.7%) had lSSc. Of the 29 male patients with

Table 1 Demographic and clinical features of all 405 SSc patients

$n = 405$	Sex			Skin involvement		
	Female	Male	*P* value	lSSc	dSSc	*P* value
No. of patients (% of entire SSc cohort)	376 (92.8)	29 (7.2)	–	270 (66.6)	135 (33.3)	–
dSSc (% of each sex)	121 (32.2)	14 (48.3)	0.1006	–	–	–
Age at onset (years)	46 ± 0.8	51 ± 2.2	0.0251	47.5 ± 0.8	45 ± 1.4	0.0362
Onset to diagnosis (years)	2 ± 0.4	1 ± 1.0	0.1877	3 ± 0.5	2 ± 0.6	0.1216
Age at diagnosis (years)	51 ± 0.7	52 ± 2.4	0.1668	52 ± 0.7	48 ± 1.3	0.0036
Disease duration (years)	15 ± 0.6	7 ± 1.2	<0.0001	15 ± 0.7	13 ± 1.0	0.1492

Values are presented as medians ± SEM

SSc systemic sclerosis, *dSSc* diffuse cutaneous sclerosis, *lSSc* limited cutaneous sclerosis

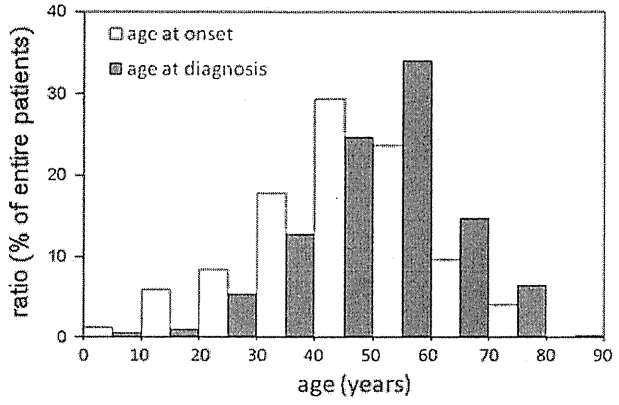

Fig. 1 Age at the onset or diagnosis of systemic sclerosis (SSc). *Horizontal axis* indicates age and each division on the scale is one decade. *Vertical axis* indicates percentages. *Open bars* represent the percentages of patients with onset in each decade and *gray bars* show the percentages of those diagnosed in each decade

SSc, about half ($n = 14$) had dSSc and the others ($n = 15$) had lSSc.

Figure 1 displays the age at onset and age at diagnosis for the 405 SSc patients. The range of age at onset was 5–78 years, with 40–49 years being the most frequent (29.4% of all patients), followed by 50–59 years (23.7%) and then 30–39 years (17.8%). The overall median age at onset was 47 ± 0.7 years (median ± SEM). The age at onset was significantly higher for males than females (51 ± 2.2 vs. 46 ± 0.8 years, respectively, $P = 0.0251$). The age at onset was also significantly higher for patients with lSSc than for those with dSSc (47.5 ± 0.8 vs. 45 ± 1.4 years, respectively, $P = 0.0362$). On the other hand, the range of age at diagnosis was 6–80 years for all patients, with the fifties being the most common (34.1%), followed by the forties (24.7%) and then the sixties (14.8%). The overall median age at diagnosis was 51 ± 0.6 years, and it was also significantly higher for patients with lSSc than for those with dSSc (52 ± 11.5 vs. 48 ± 14.9 years, respectively, $P = 0.0036$). In contrast to the age at onset, sex did not influence the age at diagnosis.

The overall median period from onset to diagnosis was 2 ± 0.4 years, with a range of 0–44 years. No significant correlation was found between the period from onset to diagnosis and sex or the type of skin involvement. The median disease duration was 14 ± 0.6 years, with a range of 1 to 59 years; it was significantly longer for females than for males (15 ± 0.6 vs. 7 ± 1.2 years, respectively, $P < 0.0001$). No significant correlation was found between the type of skin involvement and disease duration. Moreover, no organ involvement was significantly associated with disease duration.

Sex and organ involvement

About half of all SSc patients had GI or lung involvement; the rates are shown in Table 2. Among patients with GI involvement, six (3.2% of patients with GI involvement) were treated with hyperalimentation; all six were female and five had dSSc. SRC was rare (3.2%). Investigation of the relation between sex and organ involvement showed a significant excess of lung involvement in males (RR 3.4; 95% CI 1.5–8.6; $P = 0.0061$). dSSc was significantly associated with most types of organ involvement, except for PAH. However, in 48 (35.6%) of the 135 dSSc patients who had an mTSS score of more than 20, a significant correlation was shown only with PAH (RR 3.1; 95% CI 1.3–7.7; $P = 0.0120$). Correlations between organ involvements are shown in Table 3.

Overlap with CTD

Of the 405 SSc patients, 97 (24.0%) showed overlap with one or more CTD (SLE, RA, Sjögren's syndrome, or myositis). There were 51 SSc patients with Sjögren's syndrome (12.6%; 44 had lSSc and 7 had dSSc), 22 patients with myositis (5.4%; 14 and 8), 21 patients with SLE (5.2%; 17 and 4), and 19 patients with RA (4.7%; 15 and 4). Among the 51 patients with SSc–Sjögren overlap syndrome, 7 also had SLE. The SSc–Sjögren overlap syndrome was significantly associated with lSSc (RR 3.6; 95% CI 1.7–8.9; $P = 0.0013$), and also with overlap of SLE (RR 3.9; 95% CI 1.4–9.8;