Causes of Death and Poor Survival Prognostic Factors in Thai Patients with Systemic Sclerosis

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Abstract

Causes of death and poor prognostic factors for patients with systemic sclerosis (SSc) were studied in 222 cases. Their mean age at the onset and duration of disease was 48.9 ± 12.0 years and 23.3 ± 29.3 months, respectively. Fifty-three per cent were diffuse subtype. Patients with diffuse SSc had more digital pitting scars and more muscle, heart, lung, and esophageal involvement than those with limited subtypes ($p \leq 0.02$). One hundred and six patients were lost to follow-up. With a median follow-up duration of 25 months, 31 of the remaining 116 patients (26.7%) died. SSc related death occurred in 18 cases, in which the lung, heart and kidney (renal crisis) were the major causes. Infection contributed to the remaining 13 deaths. When compared with living patients, using a univariate analysis, factors associated with a reduced survival rate were age of > 45 years at the onset, diffuse skin thickness, and lung, gastrointestinal tract, heart, kidney and muscle involvement ($p \leq 0.001$). In the multivariate analysis, only age of > 45 years at onset and cardiac involvement remained poor prognostic factors ($p = 0.04$ and 0.001, respectively).

Key word : Scleroderma, Systemic Sclerosis, Causes of Death, Prognostic Factor, Survival Rate

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Systemic sclerosis (SSc) or scleroderma is a connective tissue disease characterized by diffuse infiltration of fibrous tissue in various organs, particularly the skin, lung, gastrointestinal tract, kidney and heart. The disease is usually accompanied by the destruction of small blood vessels throughout the

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body. The pathogenesis of this disease is not clearly understood, but there is evidence that immunologic mechanisms play important roles[1,2].

Studies have shown that patients with SSc have a mortality rate of approximately 5 folds greater than that of the general population[3,4]. Factors that have been associated with a poor survival rate in these patients have included older age at onset[5], male sex[6], diffuse skin thickening[5], and internal organ involvement[5-7]. Moreover, an increase in the incidence of malignancy and ischemic heart has also been found to cause death in these patients[7-10].

In Thailand, SSc is not an uncommon disease. However, the clinical features and cause of death in these patients have rarely been described. The authors, herein, report experience of the cause of death and prognostic factors of survival in patients with SSc, who were seen in a university hospital over a 14-year period.

PATIENTS AND METHOD

The medical records of patients diagnosed with SSc and seen at the Division of Rheumatology, Department of Medicine, Faculty of Medicine, Chiang Mai University, from 1987-2001 were reviewed. The diagnosis of SSc followed the preliminary criteria for the classification of systemic sclerosis of the American Rheumatism Association Subcommittee [11]. The following data were obtained from all patients at the time of presentation: sex, age at the time of diagnosis, clinical presentation, organ involvement, and laboratory investigations. Patients were usually followed-up at regular intervals of 6-8 weeks. In patients with severe disease or significant internal organ involvement, a more frequent follow-up was scheduled.

Patients were divided into 2 subtypes: 1) diffuse SSc subtype that referred to those with skin thickening proximal to the elbow and knee, and 2) limited SSc subtype, which referred to those with skin thickening distal to the elbow and the knee[2]. Causes of death were classified into 2 groups: 1) death related to SSc, which referred to death directly related to a disease, such as, pulmonary artery hypertension secondary to interstitial lung disease, cardiomyopathy, or acute scleroderma renal crisis; and 2) death unrelated to SSc, which referred to death that was not related to diseases, such as, infection, ischemic heart disease etc.

Statistical analysis

An SPSS version 10.0 microcomputer program (SPSS Inc., Chicago, Illinois. USA) was used for statistical analysis. Continuous data were described as mean and standard deviation (SD). Categorical variables were described as percentages. Comparisons were made using the Student's *t*-test for a continuous variable, and the Chi-square or Fisher exact test for ordinal and discrete variables. The cox proportional hazards model was used to determine potentially important factors that had an impact on mortality. Survival analysis was determined by the Kaplan-Miere method. A p-value of < 0.5 was considered clinically significant.

RESULTS

During the study period, there were a total of 222 patients with SSc. One hundred and twenty seven patients (57.2%) had diffuse SSc and 95 patients (42.8%) had a limited subtype. There were 169 females and 53 males, giving a female to male ratio of 3.2:1. The mean ± SD age at onset was 49.0 ± 21.2 years (range 32 - 58 years). One hundred and thirty-four patients had their disease onset after the age of 45.

Details of the demographic data and clinical features are shown in Table 1. Digital sclerosis was the most common presentation, and it was seen in all patients, followed by Raynaud's phenomenon (94.1%), digital pitting scar (53.6%), arthralgia or arthritis (52.3%), interstitial lung disease (44.6%), esophageal hypomotility or dysphagia (41.9%) and polymyositis (37.8%). Patients with diffuse SSc had significantly more digital pitting scar, polymyositis, esophageal hypomotility, interstitial lung disease and cardiomyopathy than those with limited SSc. In contrast, limited SSc patients had significantly more telangiectasia than those with diffuse SSc.

Antinuclear antibody tests were carried out in all patients and 190 cases were positive (85.6%). The speckled and speckled plus peripheral patterns were the 2 most common immunofluorescent patterns seen. The nucleolar pattern was seen in only 8 per cent of cases, and there was no difference between the diffuse and limited SSc (Table 2). The speckled pattern was the most common, especially in patients with diffuse SSc.

During the study period, 106 patients were lost to follow-up or being referred to a primary hos-

Table 1. Demographic data and clinical manifestation of patients with systemic sclerosis.

	Total (n = 222)	%	Limited SSc (n = 95)	%	Diffuse SSc (n = 127)	%	P-value
Female : male	169 : 53		88 : 7		81 : 46		< 0.01
Mean ± SD age at onset (years)	49.0 ± 21.2		42.4 ± 11.9		47.7 ± 12.8		< 0.01
Mean ± SD duration of disease (months)	43.6 ± 43.3		55.2 ± 48.8		35.0 ± 36.6		< 0.01
Sclerodactyly	222	100.0	95	100.0	127	100.0	1.00
Raynaud's phenomenon	209	94.1	90	94.7	119	93.7	0.75
Digital pitting scar	119	53.6	39	41.0	80	63.0	< 0.01
Telangiectasia	21	9.5	15	15.8	6	4.7	< 0.01
Arthralgia/arthritis	116	52.3	55	57.9	61	48.0	0.15
Polymyositis	84	37.8	25	26.3	59	46.5	< 0.01
Esophageal hypomotility	93	41.9	31	32.6	62	48.8	0.02
Interstitial lung disease	99	44.6	33	34.7	66	52.0	0.02
Pulmonary artery hypertension	43	19.4	16	16.8	27	21.3	0.41
Dilated cardiomyopathy	25	11.3	4	4.2	21	16.5	< 0.01
Cardiac arrhythmia	5	2.3	0		5	3.9	0.05
Acute renal crisis	13	5.8	2	2.1	11	8.7	0.07

Table 2. Antinuclear antibodies tests.

	Total (n = 222)	%	Limited SSc (n = 95)	%	Diffuse SSc (n = 127)	%	P-value
No. with positive test	190	85.6	74	77.9	116	91.3	0.01
Pattern							
Peripheral	9	4.70	3	4.1	6	5.2	0.78
Speckle	87	45.8	43	58.1	44	37.9	0.01
Peripheral + speckle	70	36.8	23	31.1	47	40.5	0.24
Nucleolar	15	7.9	3	4.1	12	10.3	0.20
Homogeneous	9	4.7	2	2.7	7	6.1	0.48

pital. Therefore, the causes of death and prognostic factors for survival were determined in the remaining 116 patients (diffuse SSc in 58 and limited SSc in 58) who had complete data for analysis. Their mean ± SD duration of follow-up was 34.7 ± 33.2 months (median 25.0 months). Thirty-one of these 116 patients (26.7%) died (diffuse SSc in 25 and limited SSc in 6). In 18 cases (58.1%) of diffuse SSc related disease, the lung, heart and kidney (renal crisis) were involved in 16 (88.9%), 16 (88.9%) and 8 (44.4%) cases, respectively. The remaining 13 deaths (diffuse SSc in 7 and limited SSc 6) were due to infection, which comprised pulmonary infection in 11 cases, and urinary tract infection in 2. The 5-year and 10-year survival rate of those with limited SSc were 92.4 per cent and 80.8 per cent respectively and of those with diffuse SSc 52.4 per cent and 6.9 per cent, respectively ($p < 0.001$). None of the presented patients with the diffuse subtype lived longer than 15 years after the onset of the disease.

In order to identify the prognostic factors for death, the authors analyzed the relationship between death and clinical manifestations. Patients who died had an age at onset higher than those still living at 53.2 ± 12.5 *vs* 41.6 ± 11.2 years, $p < 0.001$. Table 3 shows the results of a univariate analysis between clinical manifestations and all causes of death. In this model, age at onset, age > 45 years, diffuse SSc, dysphagia, polymyositis, interstitial lung disease, dilated cardiomyopathy and acute scleroderma renal crisis were all significantly associated with poor survival ($p < 0.001$). In the multivariate analysis, only age of > 45 years at onset and dilated cardiomyopathy remained poor prognostic factors ($p = 0.039$, odd ratio 2.65, 95% CI 1.05-6.69, and $p = 0.001$, odd ratio 5.46, 95% CI 1.94-15.35, respectively).

DISCUSSION

In this study, the authors found 222 SSc patients over a 15-year period, indicating that SSc

Table 3. Cox proportional hazard model of SSc related death and clinical manifestations. (Univariate analysis)

	Death (n = 31)	Alive (n = 85)	P-value	Odd ratio	95% CI
Age at onset ≥ 45	23	32	0.001	4.02	1.72-9.40
Male	10	12	0.010	2.90	0.99-8.50
Diffuse SSc	25	33	< 0.001	5.66	2.30-13.94
Dysphagia	25	32	< 0.001	6.90	2.35-21.20
Polymyositis	20	22	0.001	5.21	1.99-13.88
Arthralgia/Arthritis	14	45	0.459	0.77	0.38-1.56
Interstitial lung disease	24	27	< 0.001	7.37	2.60-21.63
Cardiomyopathy	21	0	< 0.001	9.50	5.29-17.07
Acute renal crisis	9	1	< 0.001	4.32	2.83-6.64

was not an uncommon disease. A female to male of incidence 3.2: 1 in this series was in line with previous reports of 2-8.8: 1[5-7,12,13]. The female preponderance raised the question that female hormones might play a role in the pathogenesis of the disease. The clinical features, such as, Raynaud's phenomenon, sclerodactyly, digital pitting scars, dysphagia, arthralgia/arthritis, interstitial lung disease and myositis were similar to those described.

With a median follow-up duration of 25 months, 31 of 116 patients (16.7%) died, giving a 5 and 10-year survival rate of 72.96 per cent and 67.35 per cent, respectively. The mortality rate showed a marked increase in diffuse SSc. This finding was similar to several others, which have shown that the extent of skin involvement influenced the survival rate[6,12,14-16]. There was a greater increase in mortality of 4-5 fold in patients with truncal sclerosis and of 2 fold in those with digital sclerosis, when compared with that of the general population, as previously described[7].

In addition to the extent of skin involvement, older age at onset, and heart, lung, renal and gastrointestinal involvement have been shown to be associated with a poor survival rate[3,5,7,13-15,17-21]. Pulmonary involvement, particularly pulmonary artery hypertension, was the major cause of death in Lee's, Simeon's and Bryan's series[14-15,19]. Severe restrictive lung disease, secondary to interstitial pneumonitis and interstitial fibrosis, was also a common pulmonary cause of death. Altman et al[17] found that acute scleroderma renal crisis was the major cause of death in their patients. Patients with renal involvement, especially those with scleroderma renal crisis, tended to have the lowest survival rate. The scleroderma renal crisis has been reported as common in those who presented with a rapid progression of skin thickening early in the course of their disease, anemia, pericardial effusion or congestive heart failure[22]. Other factors that have been associated with a poor survival rate have included black race[20], female sex[21], cardiac arrhythmia[23], anemia (17,21, elevated blood urea nitrogen)[17,24], proteinuria[21], reduced diffusing capacity and forced vital capacity of the lungs[17,25]. In the present study, all scleroderma related deaths occurred in those with heart, lung and renal involvement, and was more common in patients with diffuse rather than limited SSc.

A number of deaths not related to SSc have been described. Many of these deaths were related to ischemic cardiovascular events[19]. An association between macrovascular disease and SSc has been documented[26,27]. Previous studies also suggested an increased incidence of cancer (2.6-7.3%) in patients with SSc[8-10]. Rosenthal et al found a 2.4 fold increase in the incidence of lung cancer and 9.6 fold in lymphoma, when compared to the standard population[10]. Roumm et al found a 1.8 fold increase in the incidence of lung cancer[9]. Abu-Shaka et al found that lung and breast were the two most common cancers associated with SSc[8]. The authors did not find a case of cancer in this study. All of the non-SSc related deaths were due to infection.

Several studies have focused on the presence of specific autoantibodies and the prognosis of SSc. Steen et al[28] found that two-thirds of the patients who had anti-Scl70 had diffuse scleroderma, and anti-Scl70 was associated with peripheral vascular disease and interstitial pulmonary fibrosis. However, the presence of this antibody did not predict heart or renal involvement, or survival. A study

from Japan found that patients with positive anti-centromere antibody (ACA), which was related to limited SSc, had the best survival rate, while those with anti-RNA polymerase (anti-RNAP) were associated with heart and renal involvement, and they had the worst prognosis[29]. Unfortunately, these autoantibodies were not available at our institution.

One of the limitations in the present study was that almost half of the patients were lost to follow-up or being transferred to other hospitals. Therefore, the outcome in that group could not be evaluated. Whether there could be cases with malignancies, or deaths that were related to cardiovascular disease remains unknown.

In conclusion, the authors reviewed the clinical features and causes of death in Thai patients with SSc. The clinical features and organ involvement were similar to those reported from Western countries. Old age, male sex, diffuse SSc and visceral organ involvement signified a poor prognosis.

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สาเหตุการเสียชีวิตและปัจจัยที่มีผลต่อการอยู่รอดในผู้ป่วยโรคผิวหนังแข็งในคนไทย

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ได้ทำการศึกษาสาเหตุการเสียชีวิตและปัจจัยที่มีผลต่อการอยู่รอดในผู้ป่วยโรคผิวหนังแข็ง (systemic sclerosis) จำนวน 222 ราย พบอายุเฉลี่ยเมื่อเริ่มเป็นโรคและระยะเวลาของการเป็นโรคเท่ากับ 48.9 ± 12.0 ปี และ 23.3 ± 29.3 เดือนตามลำดับ พบผู้ป่วยเป็นโรคผิวหนังแข็งชนิดทั่วตัว (diffuse subtype) ร้อยละ 73 ตรวจพบรอยแผลที่ปลายนิ้ว (digital pitting scar) และความผิดปกติของกล้ามเนื้อหัวใจ ปอด และระบบทางเดินอาหารในผู้ป่วยโรคผิวหนังแข็งชนิดทั่วตัวมากกว่าชนิดเฉพาะที่ (limited subtype) อย่างมีนัยสำคัญทางสถิติ ($p \leq 0.02$) ผู้ป่วย 106 รายขาดการติดตามการรักษา ในจำนวนผู้ป่วยที่เหลืออยู่ 116 รายที่มีค่ามัทยฐานระยะเวลาการติดตามการรักษานาน 25 เดือน มีผู้ป่วยเสียชีวิต 31 ราย สาเหตุการเสียชีวิตเป็นจากตัวโรคผิวหนังแข็งเอง 18 ราย ซึ่งพบว่าความผิดปกติของปอด หัวใจ และไต เป็นสาเหตุการเสียชีวิตที่พบบ่อยที่สุด ผู้ป่วยอีก 13 รายเสียชีวิตจากการติดเชื้อ เมื่อศึกษาปัจจัยที่มีผลต่อการเสียชีวิตด้วยวิธี univariate analysis พบว่าอายุที่เริ่มเป็นโรคมากกว่า 45 ปี โรคผิวหนังแข็งชนิดทั่วตัว ความผิดปกติของปอด ระบบทางเดินอาหาร หัวใจ ไตและกล้ามเนื้อจะมีผลต่อการเสียชีวิตเพิ่มขึ้น ($p \leq 0.001$) เมื่อทำการศึกษาด้วยวิธี mulitvariate analysis พบว่าอายุที่เริ่มเป็นโรคมากกว่า 45 ปี และความผิดปกติของหัวใจเท่านั้นที่มีผลต่อการเสียชีวิตเพิ่มขึ้น ($p = 0.04$ และ 0.001 ตามลำดับ)

คำสำคัญ : โรคผิวหนังแข็ง, สาเหตุการเสียชีวิต, ปัจจัยการพยากรณ์โรค, อัตราการอยู่รอด

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