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ORIGINAL ARTICLE

Survival rate, causes of death, and risk factors in systemic sclerosis: a large cohort study

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Abstract

To investigate the clinical pattern, survival rate, causes of death and risk factors in a large cohort of Chinese Han patients with systemic sclerosis (SSc). Inpatients treated from 2002 to 2014 were included in this study. Patients were classified into diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc), and SSc-overlap syndrome groups. Data were analyzed using Chi-squared tests, Kaplan–Meier curves, log-rank tests, and Cox proportional hazards modeling. Among a total of 201 patients, dcSSc (50.2%) was the major subtype, followed by lcSSc (30.3%) and SSc-overlap (19.4%). Interstitial lung disease (ILD, 148/201, 74%) was the most frequent organ involvement. The overall survival rates were 98% and 95% at 5 and 10 years, respectively. The overall standard mortality ratio (SMR) was 2.22. The most common cause of death was ILD combined with infection (8/16, 50%), followed by kidney failure (2/16, 12.5%). On crude analysis, pulmonary hypertension, ILD, cardiac involvements, renal involvements, and digital ischemia were associated with poor prognosis. On multivariate analysis, pericardial effusion ($p = 0.000$) and digital ischemia ($p = 0.016$) were independent prognostic factors of death. The mortality rate of patients with SSc is mildly increased in comparison with the general population. ILD is the most common systemic involvement and the principal cause of death in SSc. Pericardial effusion and digital ischemia are independent factors associated with death.

Keywords Clinical pattern · Death causes · Risk factor · Survival · Systemic sclerosis

Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by inflammation, vasculopathy, and fibrosis, resulting in skin and multi-organ involvement. In 1988, LeRoy et al. elaborated a descriptive clinical criteria allowing sub-classification of SSc into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) [1]. Furthermore, Moinzadeh et al. have newly suggested that SSc-overlap syndrome should be regarded as a distinct SSc subset because it exhibits a unique form of progression [2]. Until now, the proportion and prognosis of different SSc subsets in Chinese Han patients have rarely been studied.

Genetic studies performed so far reveal the genetics and epigenetics in the pathogenesis of systemic sclerosis in SSc [3], which add to clinical heterogeneity in different ethnical groups. Actually, epidemiology studies suggest such difference. For example, African Americans with systemic sclerosis have more severe disease complications than Caucasians [4]; SSc-related autoantibodies among SSc patients varied in different ethnicities like Caucasian Americans, African Americans, and Latin Americans [5]. To our knowledge, comparison of clinical patterns between Chinese Han population and other ethnics has not been reported.

A recent meta-analysis of 17 cohorts studied from 1964 to 2005 showed a higher risk of mortality in SSc patients than the general population (standard mortality ratio [SMR] = 2.72) [6]. Cumulative survival (from the time of diagnosis) has been estimated at 74.9% at 5 years and 62.5% at 10 years [6]. However, the mortality rates have varied over time and among different areas. A previous study showed that the 10-year survival rate improved steadily from 54 to 66% between 1972

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and 2002 [7], while limited studies have reported the long-term survival in Asian subjects during the latest years.

This study firstly report the clinical patterns, survival rate, causes of death, and risk factors of SSc in a large cohort of Chinese Han patients compared with other ethnic groups, and analyze the inner connections between clinical patterns and survival.

Patients and methods

Patients and data

Chinese Han inpatients diagnosed with SSc in Peking University People's Hospital (PKUPH) from September 2002 to September 2014 were analyzed in this study. Symptoms and organ involvements were obtained throughout the entire follow-up period. Body mass index (BMI) and serological data collected at the first visit were included in the database. The initial timepoint of the study is the onset of SSc-related symptoms, including Raynaud's phenomenon. In our institution, survival duration and causes of death were recorded from the medical record. If no follow-up was available in our center, we contacted the family members to acquire the survival duration, and the accurate cause of death was confirmed by medical certificate of death. This study was approved by the Ethics Committee of Peking University People's Hospital.

Classification criteria and disease subtypes

Each SSc patient was diagnosed by an experienced medical group. All of these patients met the 1980 American College of Rheumatology (ACR) criteria for systemic sclerosis [8]. Patients were categorized as dcSSc or lcSSc using LeRoy's criteria [1]. SSc-overlap syndrome was defined as SSc combined with other connective tissue diseases (CTDs).

Clinical features

Pulmonary manifestations included interstitial lung disease (ILD) and pulmonary hypertension (PH). ILD was defined by chest X-ray and/or computed tomography (CT), including ground glass changes and fibrotic features, and other possible causes were excluded. PH was considered present when the estimated right-side ventricular systolic pressure was >36 mmHg, as determined by echocardiography [9]. Heart manifestations included pericardial effusion evident on an echocardiogram or CT; conduction disturbance apparent on an electrocardiograph; and heart failure comprehensively diagnosed on the basis of clinical manifestations, laboratory tests, and echocardiogram (excluding other heart diseases). Renal involvements were considered present when (1) proteinuria ≥ 300 mg/24 h was evident; (2) renal hypertension (excepting other forms of hypertension); (3) chronic kidney disease (CKD) was present (the estimated glomerular filtration rate (GFR) ≤ 60 mL/min $\times$ 1.73 m^2 for more than 3 months; (4) renal crisis was defined as new-onset hypertension accompanied by a progressive elevation in creatinine level. Reflux esophagitis was defined subjectively when patients complained of symptoms such as heartburn, retrosternal pain, and difficulty swallowing, with or without esophageal manometric examination and gastroscopy.

Laboratory parameters

Laboratory data included the levels of serum globin, C-reactive protein (CRP), immunoglobulin G (IgG), complement, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rheumatoid factor (RF), anti-u1RNP antibody, anti Scl-70 antibody, and anti-centromere antibody (ACA). All tests were performed by our laboratory.

Statistical analyses

The SMR was calculated by comparing the observed and expected number of deaths, adjusted for age and gender. Mortality data from national sampling surveys performed from 2000 to 2009 and 2010 national census were acquired from China Population and Employment Statistics Yearbook (2002–2010) and used to calculate the SMR.

All statistical analyses were performed using SPSS for Windows software (ver. 20.0; IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous variables are expressed as means ± SD, and categorical variables as numbers with percentages. The significance of differences among SSc subtypes was evaluated using the Chi-squared test. The univariate effects of covariates on mortality were assessed by constructing Kaplan–Meier curves; the log-rank test was used to assess differences in survival. A multivariate Cox's proportional hazards model (forward selection) was employed to identify independent predictors of survival, and the possible risk factors, including PH, ILD, pericardial effusion, CKD, renal hypertension, proteinuria, renal crisis, and digital ischemia, were used for multivariate analysis.

Results

Demographic variables

Two hundred and one Chinese Han inpatients with SSc were included in this retrospective study, who came from all over China. The female-to-male ratio is 9.6:1.

The average observation time (time from disease onset to end of observation) was 11.2 ± 8.6 years. The detailed demographic variables were listed in Table 1. The family histories of rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), were reported by 3.5% (7/201) of the patients. The proportion of smokers was 6.0% (12/201), with a female-to-male ratio of 1:1.

Clinical patterns

DcSSc (50.2%, 101/201) was the major subtype in this cohort, followed by lcSSc (30.3%, 61/201) and SSc-overlap (19.4%, 39/201). The clinical features of lcSSc group were compared with dcSSc group, showing that dcSSc group had a larger proportion of ILD ($p = 0.000$), pericardial effusion ($p = 0.004$), and a smaller proportion

Table 1 Demographic and clinical characteristics of 201 systemic sclerosis patients

	Total ($n = 201$)	lcSSc ($n = 61$)	dcSSc ($n = 101$)	SSc-overlap ($n = 39$)
Demographic characteristics				
Female, *n* (%)	182 (91)	57(93)	86 (85)	39 (100)
Male, *n* (%)	19 (9)	4 (7)	15 (15)	0 (0)
Age at onset, mean (SD) years	41.6 (13.5)	41.4 (13.2)	42.8 (13.9)	38.8 (13.0)
Time between onset and diagnosis, mean (SD) years	7.9(8.1)	9.3 (8.1)	6.9 (8.4)	8.4 (7.0)
Time from onset to end of observation, mean (SD) years	11.2(8.6)	12.6 (8.8)	10.0 (8.9)	12.1 (6.9)
Clinical characteristics, *n* (%)				
RP	173/201 (86)	52/61 (85)	86/101 (85)	35/39 (90)
Finger/toe ischemia	54/201 (27)	15/61 (30)	29/101 (29)	10/39 (19)
Joint involvement	61/201 (30)	18/61 (30)	23/101 (23)	21/39 (54)
PH	35/184 (19)	8/55 (15)	15/94 (16)	12/35 (34)
ILD	148/201 (74)	35/61 (57)	84/101 (83) **	29/39 (74)
Cardiac disease	57/201(28)	7/61(12)	28/101(28) *	22/39(56)
Pericardial effusion	37/182 (20)	1/53 (2)	17/94 (18) **	19/35 (54)
Arrhythmia	25/201 (12)	6/61 (10)	12/101 (12)	7/39 (18)
Chronic heart failure	6/201 (3)	0/46 (0)	5/101 (5)	1/39 (3)
Renal disease	23/201 (11)	2/61 (3)	7/101 (7)	14/39 (36)
Renal hypertension	8/201 (4)	1/61 (2)	2/101 (1)	5/39 (13)
Proteinuria	18/201 (9)	3/61 (5)	4/101 (4)	11/39 (3)
CKD	13/201 (7)	2/61 (3)	5/101 (5)	6/39 (15)
Renal crisis	3/201 (2)	0/61 (0)	1/101 (1)	2/39 (5)
Reflux esophagitis	51/201 (25)	14/61 (23)	29/101 (29)	8/39 (21)
Hypothyroidism	21/201 (10)	8/61 (13)	12/101 (12)	1/39 (3)
BMI < 18 kg/m^2	19/91 (21)	5/31 (16)	10/43 (23)	4/17 (24)
Elevated IgG	82/180 (46)	25/52 (48)	36/91 (40)	21/37 (57)
Elevated ESR	96/185 (52)	25/58 (43)	46/92 (50)	25/35 (71)
Elevated CRP	59/174 (34)	9/51 (18)	24/84 (29)	26/39 (67)
RF +	67/186 (36)	18/55 (33)	29/93 (31)	20/38 (53)
Reduced C3	68/185 (37)	17/54 (32)	33/92 (36)	18/39 (46)
Reduced C4	73/184 (40)	20/53 (38)	32/92 (35)	21/39 (54)
ANA +	162/172 (94)	50/53 (94)	80/85 (94)	32/34 (94)
Anti-Scl70 +	43/148 (29)	10/40 (25)	27/81 (33)	6/27 (22)
ACA +	26/201 (13)	16/61 (26)	9/101 (9)*	1/39 (3)
Anti-u1RNP +	48/189 (25)	15/58 (26)	20/93 (22)	13/38 (34)

ACA anti-centromere antibody, *ANA* antinuclear antibody, *BMI* body mass index, *C3* complement 3, *C4* complement 4, *CKD* chronic kidney disease, *CRP* C-reactive protein, *dcSSc* diffuse cutaneous systemic sclerosis, *ESR* sedimentation rate, *lcSSc* limited cutaneous systemic sclerosis, *IgG* immunoglobulin G, *ILD* interstitial lung disease, *PH* pulmonary hypertension, *RF* rheumatoid factor, *RNP* ribonucleoprotein, *RP* Raynaud's phenomenon; + positive

dcSSc versus lcSSc: * $p < 0.05$;** $p < 0.005$

of ACA positivity ($p = 0.003$). Patients with SSc-overlap syndrome included 18 with RA, 15 with SLE, and 6 with dermatomyositis.

ILD was the most frequent organ involvement in this cohort (74%, 148/201), and developed in 52% of patients within 5 years after the onset of SSc. Renal involvements (11%, 23/201), including renal hypertension, proteinuria, CKD, and renal crisis, were the least common in the cohort, especially in the lcSSc group (3%, 2/61) and dcSSc group (7%, 7/101).

Assessment of SMR and survival rates

In this research, there were 656 person-years of follow-up, and the mortality rate was 0.024 deaths per person-year. The calculation of SMR showed that SSc patients were at a 2.22-fold greater risk of death than the general population. The overall survival rates in our cohort were 98% and 95% at 5 and 10 years respectively. Figure 1 shows the cumulative survival of patients with different SSc subtypes. Apparently, lcSSc was associated with a better prognosis than dcSSc ($p = 0.012$) and SSc-overlap ($p = 0.013$), while the prognoses of patients with dcSSc and SSc-overlap did not differ.

Causes of death

Of the 201 patients, 16 died during the period of study, and were consisted of 10 patients with dcSSc, 1 patient with lcSSc, and 5 patients with SSc-overlap. The detailed causes of death are listed in Table 2. All deceased patients had ILD, half of which died from ILD and combined with infection. The only lcSSc patient died after a sudden chest pain, without a history of cardiovascular disease. Among the 5 patients with SSc-overlap, 2 died of ILD and combined with SLE or RA, 2 died of kidney failure and combined with SLE, and the patient who died of PBC overlapped with RA and SS.

Table 2 The causes of death of 16 patients with systemic sclerosis

Item	Definite	Probable
ILD combined with infection	3	5
Kidney failure	1	1
Severe AIHA (incompatible cross matching)	1	
Chronic heart failure		1
Cardiovascular events		1
PBC and gastric esophagus varicosity burst	1	
Drug allergy	1	
Lung cancer	1	

AIHA autoimmune hemolytic anemia. *DIC* disseminated intravascular coagulation, *ILD* interstitial lung disease, *PBC* primary biliary cirrhosis

Risk factors

Crude analysis showed that the following variables were associated with a shorter survival period: PH ($p = 0.016$), ILD ($p = 0.048$), cardiac involvement (including pericardial effusion [$p = 0.000$] and chronic heart failure [$p = 0.001$]), renal involvement (including renal hypertension [$p = 0.000$], proteinuria [$p = 0.002$], and renal crisis [$p = 0.004$]), and digital ischemia ($p = 0.044$) (Table 3). On multivariate analysis, pericardial effusion ($p = 0.000$) and digital ischemia ($p = 0.016$) were independent predictors for mortality (Table 4).

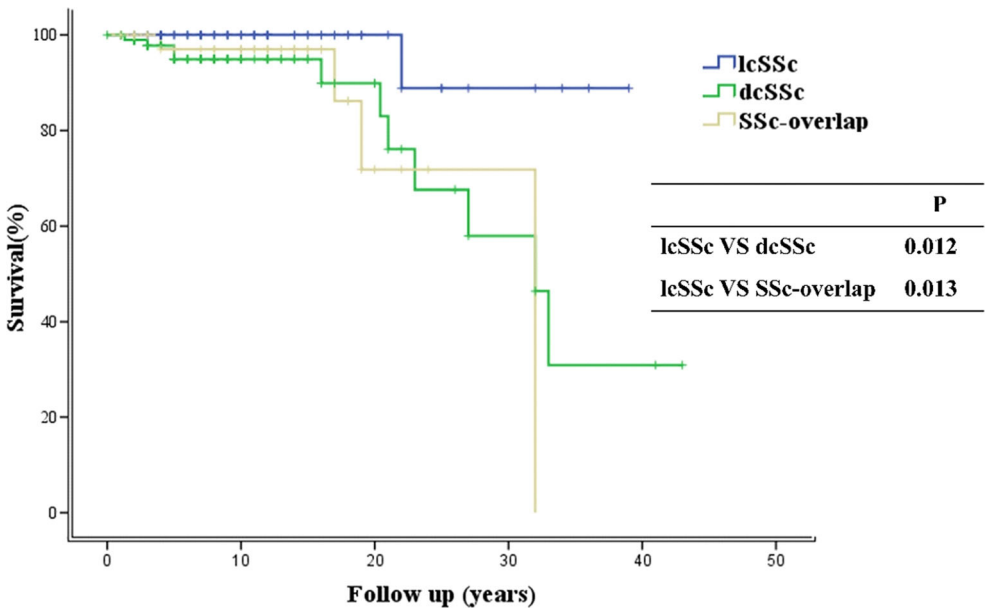

Fig. 1 Cumulative survival of systemic sclerosis patients as determined by the Kaplan–Meier method. dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis

Table 3 Univariate analyses of the effects of covariates on mortality

Risk factor	*P* value	Risk factor	*p* value
PH	0.016	Renal hypertension	0.000
ILD	0.048 0.048	Proteinuria	0.002
Pericardial effusion	0.000	Renal crisis	0.004
Arrhythmia	0.084	Digital ischemia	0.044
Chronic heart failure	0.001	Positive for anti-Scl70	0.164
CKD	0.002	Positive for ACA	0.078

ACA anti-centromere antibody, *CKD* chronic kidney disease, *ILD* interstitial lung disease, *PH* pulmonary hypertension

Discussion

This research firstly reported the clinical pattern and survival analysis of Chinese Han patients with SSc from 2002 to 2014. The survival rate of our cohort was higher than the latest published large cohort studies (initiated after 1990s) mainly consisted of Caucasian patients (5-year survival 84.2–95.6%, 10-year survival 82–91.3%), and the SMR is lower than most of the previous studies [6, 10]. Researches have shown that the gene polymorphisms with susceptibility to systemic sclerosis in Chinese Han population were distinct from those in Caucasian populations [11–13]. Compared with the clinical patterns of Chinese Han population and Caucasian populations, our research reported a lower proportion of renal involvement, especially renal crisis in Chinese population (1% dcSSc, 0% lcSSc; versus 4.2% Caucasian dcSSc, 1.1% Caucasian lcSSc) [14], which could partly explained the better survival of our cohort.

The proportions of patients with different SSc subtypes varied in previous studies (dcSSc, 3–71.3% [6] overlap syndrome, 10–38% [2]), and the proportions in our cohort were within the ranges. Our study demonstrated a significant difference in the clinical pattern and prognosis between dcSSc and lcSSc patients, proving the significance of LeRoy's criterion in evaluating the prognosis of SSc. The prognosis of patients with overlap syndrome was approximately the same as that of patients with dcSSc alone, showing that overlap syndrome did not own distinct characteristics of survival.

ILD is reported to be the most common organ involvement in Chinese patients, and the proportion in our cohort (83% in dcSSc, 57% in lcSSc) is larger than that in Caucasian population (53.4% in dcSSc, 34.7% in lcSSc) [14]. Futhermore, ILD combined with infection is also the primary cause of death, in agreement with a meta-analysis for the death causes of SSc [15]. PH is also proved to be a significant prognostic factor for mortality in our cohort, and patients with PH are reported more likely to have diffuse disease, worse pulmonary function, and right cardiac function [16]. Nevertheless, the prognostic factor analysis showed that ILD and PH were weaker factors of prognosis than cardiac and renal involvement. The meta-analysis of Rubio-Rivas et al. came to a similar conclusion [6], and pericardial effusion is also reported to be a significant prognostic factor of early SSc [17]. These results support that ILD is the most common cause of death due to its high incidence, while cardiac and renal involvements are more significant factors related to death.

Apart from organ involvement, digital ischemia was also associated with a poor prognosis. Previous work also found that ischemia was associated with PH, cardiovascular events, and a poor prognosis [18], which may be regarded as a reflection of severe visceral vasculitis.

Our work had certain limitations. Firstly, the retrospective cohort design meant that the onset time of most clinical characteristics could hardly be evaluated, adding to deviation of the prognostic factors. Secondly, ultrasonic cardiogram examination was used for estimating the pulmonary pressure instead of right heart catheterization, leading to possible deviations; however, it is believable with a sensitivity of 87% and specificity of 79% in a large cohort [19] and widely used in previous studies [14, 20, 21]. Thirdly, some SSc-related autoantibodies (e.g., anti-RNAp III) were not able to be reported.

In summary, this is the first study to investigate the survival of SSc in Chinese Han patients, reporting an overall survival of 98% and 95% at 5 and 10 years respectively, supporting a better prognosis compared with researches in Caucasian population, which may be explained by gene polymorphisms and a less proportion of renal involvement. ILD represents the most common organ involvement and the leading cause of death. PH, ILD, cardiac involvement, renal involvement, and digital ischemia were risk factors related with poor outcome. These findings prompt us to carry out more researches on SSc-ILD in Chinese populations, and provide warning signs for strengthening the therapy of patients with poor prognosis.

Table 4 Summary of the results of Cox's regression modeling of predictors of survival

Risk factor	Hazard ratio (95% CI)	*p* value
Pericardial effusion	15.802 (4.290–58.208)	0.000
Digital ischemia	4.343 (1.315–14.342)	0.016

CI confidence interval

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Compliance with ethical standards

Disclosures None.

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