Prevalence, risk factors, and outcomes of systemic sclerosis–associated interstitial lung disease in a Chinese population

Dennis TH Chan *, Lydia HP Tam, Tommy TO Lam, Jacqueline So, LY Ho, LS Tam, Ho So

ABSTRACT

Introduction: Systemic sclerosis–associated interstitial lung disease (SSc-ILD) is a leading cause of mortality among systemic sclerosis (SSc) patients. This multicentre cohort study sought to determine the prevalence of SSc-ILD, identify risk factors for ILD development in SSc patients, and explore poor prognostic factors in SSc-ILD patients.

Methods: Medical records were retrospectively reviewed for Chinese patients who met the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc. Univariable and multivariable analyses were performed to compare SSc patients with and without ILD, as well as SSc-ILD patients with and without disease progression. Survival analysis was also conducted.

Results: The study cohort comprised 223 SSc patients with a median follow-up duration of 8.1 years. The prevalence of ILD was 49.8%. A history of bibasal crackles (hazard ratio [HR]=2.813; P=0.001) was independently associated with ILD development. Among ILD patients, 64.1% exhibited progressive disease. An elevated C-reactive protein (CRP) level at ILD diagnosis (HR=1.064; P=0.002) constituted an independent predictor of ILD progression. The overall mortality rate was 24.2% and pneumonia was the most common cause of death. Predictors of mortality included age at SSc diagnosis (HR=1.101; P=0.002), history of smoking (HR=5.173; P=0.028), and CRP level at SSc diagnosis (HR=1.103; P=0.009).

Conclusion: Interstitial lung disease was prevalent among SSc patients in this cohort and the majority exhibited disease progression. Comprehensive clinical assessment, supported by investigations such as CRP level measurement, is essential to identify predictors of poor prognosis.

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New knowledge added by this study

- Interstitial lung disease (ILD) is common and often progressive among systemic sclerosis (SSc) patients in the Hong Kong Chinese population.
- Baseline C-reactive protein level is independently associated with ILD progression and mortality in SSc patients.

Implications for clinical practice or policy

- Interstitial lung disease screening is recommended for all SSc patients.
- C-reactive protein level may serve as a predictor of ILD progression and mortality in SSc patients.
- Prospective studies are necessary to develop personalised monitoring and treatment strategies.

Introduction

Systemic sclerosis (SSc) is a heterogeneous connective tissue disorder involving multiple organ systems. Its subtypes comprise limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc).[1] Common features include Raynaud's phenomenon, skin sclerosis, and musculoskeletal inflammation. Organ-based manifestations, such as interstitial lung disease (ILD), pulmonary hypertension (PH), and scleroderma renal crisis, are particularly important because they substantially affect patient quality of life and survival. Systemic sclerosis–associated interstitial lung disease (SSc-ILD) is the leading cause of mortality in SSc, contributing to 35% of disease-related deaths.[2] In Hong Kong, SSc has one of the highest standardised mortality ratios among rheumatic diseases.[3]

Systemic sclerosis–associated interstitial lung

華人群體中硬皮症併發間質性肺病的患病率、風險因素及結果

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引言：找硬皮症併發間質性肺病是硬皮症患者的主要死亡原因之一。本多中心隊列研究旨在確定硬皮症併發間質性肺病的患病率，辨識硬皮症患者發展間質性肺病的風險因素，並探討硬皮症併發間質性肺病患者的不良預後因素。

方法：我們對符合2013年美國風濕病學會與歐洲抗風濕病聯盟分類標準的華人硬皮症患者的醫療紀錄進行回顧性分析。研究採用單變量及多變量分析比較有與無間質性肺病的硬皮症患者，以及有與無疾病進展的硬皮症併發間質性肺病患者，並進行生存分析。

結果：研究隊列包括223名硬皮症患者，中位隨訪時間為8.1年。間質性肺病的患病率為49.8%。具有肺部濕囉音病史（風險比=2.813；P=0.001）與間質性肺病發展呈獨立相關。在間質性肺病患者中，64.1%表現出疾病進展。間質性肺病診斷時C反應蛋白水平升高（風險比=1.064；P=0.002）為疾病進展的獨立預測因素。總死亡率為24.2%，而肺炎是最常見的死亡原因。死亡的預測因素包括硬皮症診斷年齡（風險比=1.101；P=0.002）、吸煙史（風險比=5.173；P=0.028）及硬皮症診斷時的C反應蛋白水平（風險比=1.103；P=0.009）。

結論：在本研究隊列中，間質性肺病在硬皮症患者中相當普遍，且多數患者表現出疾病進展。透過全面的臨床評估（例如C反應蛋白水平測量等檢查）可有效識別影響預後的不良因素。

disease arises from chronic microinjuries to lung endothelial and epithelial cells, which activate the immune system and lead to the recruitment and transformation of fibroblasts into myofibroblasts that secrete excessive collagen-rich extracellular matrix.[4,5] This pathological process causes pathological lung stiffness and architectural disruption, producing restrictive lung disease through reductions of lung compliance and volume.[6]

It is well established that there is an ethnic disparity in SSc-ILD; prevalence rates considerably vary among ethnic groups, ranging from 25% to 90%.[7] The prevalence of SSc-ILD is reportedly higher in Asian populations than in Western populations.[8] However, data concerning the prevalence and predictive factors of SSc-ILD in Southern Chinese individuals remain limited. A prospective case-control study investigating functioning and health-related quality of life in Hong Kong showed that among 78 SSc patients recruited, 24 (30.8%) had ILD.[9]

The clinical course of SSc-ILD ranges from asymptomatic presentation to rapidly progressive disease, which can lead to mortality. Severe disease develops in approximately 25% to 33% of SSc-ILD patients.[4] Thus, it is essential to identify patients with early-stage SSc who are asymptomatic but exhibit a risk of ILD development and progression. This approach enables closer monitoring and facilitates timely treatment. Numerous risk factors for ILD development and progression in SSc patients have been reported.[8,10,11] According to the 2020 European consensus statements on the identification and management of ILD in SSc,[10] predictive factors include respiratory symptoms, smoking history, ethnicity (eg, native American or African heritage), dcSSc, presence of anti-topoisomerase antibody (ATA), and male sex. However, most of these findings were based on studies conducted in Western populations.[10]

To improve the identification and management of SSc patients at risk of ILD development or progression, we conducted a multicentre study that aimed to assess the prevalence of SSc-ILD in the Hong Kong Chinese population, investigate associated risk factors, and identify potential indicators of poor prognosis. The findings of this study are expected to enhance early detection and monitoring of ILD in SSc patients, enabling timely and effective interventions.

Methods

Study design and patients

This retrospective longitudinal study included SSc patients who attended Alice Ho Miu Ling Nethersole Hospital, Prince of Wales Hospital, and North District Hospital. These patients were identified via the Clinical Data Analysis and Reporting System, a database established for record keeping and research purposes in Hong Kong, which has been utilised in epidemiological studies.[12] The International Classification of Diseases, Ninth Revision, Clinical Modification code 710.1 (Systemic sclerosis) was used to identify SSc patients within the Clinical Data Analysis and Reporting System. The search period spanned from January 2008 to December 2022. Clinical information for each patient was reviewed in the electronic health record. Patients were included if they had attended more than one follow-up appointment and met the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc.[13] Exclusion criteria were age at onset <18 years, overlap syndrome, and non-Chinese ethnicity. Patients with ILD were identified based on radiologists' reports of high-resolution computed tomography (HRCT) of the thorax. For patients without HRCT records, chest radiographs were reviewed to identify evidence of ILD. Investigations, treatments, and the frequency of follow-ups were determined by the treating physicians.

Clinical variable collection

Demographic variables, including sex, smoking history, age at symptom onset, age at SSc diagnosis,

and age at ILD diagnosis, were recorded. The first clinical symptoms attributed to SSc, as judged by the treating physicians, and symptoms observed during the follow-up period were documented. These symptoms included Raynaud's phenomenon, puffy fingers, sclerodactyly, digital ulcers, oesophageal dysmotility, arthralgia, dyspnoea, and cough.[14] The presence of bibasal crackles on physical examination by the treating physicians was also documented. The status of PH was recorded based on findings from echocardiography or right heart catheterisation. Disease duration was defined as the time from onset of the first symptom to the last visit. The SSc subtype was categorised as dcSSc or lcSSc based on the extent of skin involvement, using criteria established by LeRoy and Medsger.[1]

Laboratory data, including autoantibodies, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) levels, were recorded. C-reactive protein and ESR levels at baseline and at ILD diagnosis were documented. Pulmonary function test (PFT) results at baseline and at the latest available assessment were retrieved. Forced expiratory volume in 1 second, forced vital capacity (FVC), and diffusing capacity of the lungs for carbon monoxide (DL_{CO}) were recorded. In ILD cases, the radiological pattern on HRCT, including non-specific interstitial pneumonitis, usual interstitial pneumonia, or other patterns, was noted.

Systemic sclerosis–associated interstitial lung disease outcomes were assessed based on ILD progression and mortality. Disease progression was defined as an increase in ILD extent on serial HRCT, as reported by radiologists, or a decline in FVC of ≥10% from baseline. Alternatively, progression was defined as an FVC decline of 5% to 9% accompanied by a DL_{CO} decline of ≥15%.[15] Causes of death were categorised as SSc-related or SSc-unrelated, based on assessment by the treating physicians (when available) or the authors. Clinical variables with >20% missing data were excluded from statistical analyses.

Statistical analyses

Descriptive data for continuous variables were presented as mean±standard deviation or median (interquartile range [IQR]), as appropriate. Categorical variables were presented as numbers with percentages. Student's *t* test or the Mann-Whitney *U* test was used for comparisons of continuous variables, depending on the data distribution. Categorical variables were compared using Fisher's exact test or the Chi squared test. Patients with and without ILD were compared using univariable and multivariable Cox regression analyses to identify risk factors associated with the development of SSc-ILD. Among SSc-ILD patients, those displaying progressive ILD were compared with those lacking progression via univariable and multivariable analyses to identify risk factors for disease progression. The univariate effects of covariates on survival were evaluated using Kaplan–Meier curves; the log-rank test was utilised to assess differences in survival. Multivariable Cox regression analyses were conducted to identify independent predictors of adverse outcomes. Variables with P value <0.2 in univariable analyses were included in the multivariable Cox regression analysis. All statistical analyses were performed using SPSS (Windows version 27.0; IBM Corp, Armonk [NY], United States). P values <0.05 were considered statistically significant.

Results

Demographics and clinical characteristics

In total, 223 SSc patients were included in this study (Fig). Table 1 summarises the patients' baseline characteristics. The median follow-up duration was 8.1 years (IQR=4.0-10.2) and the total cumulative follow-up period was 1951 person-years. The majority of patients were female (86.1%). The median age at SSc diagnosis was 55 years (IQR=48-64). A majority of patients (86.5%) underwent HRCT scans during the follow-up period. Among those without HRCT, none had chest radiographs suggestive of ILD. Limited cutaneous SSc was the most common subtype, displayed by 71.3% of the cohort. Anti-topoisomerase antibody was the most frequently detected autoantibody, present in 39.0% of patients.

The overall prevalence of ILD among SSc patients was 49.8%. The age at ILD diagnosis ranged

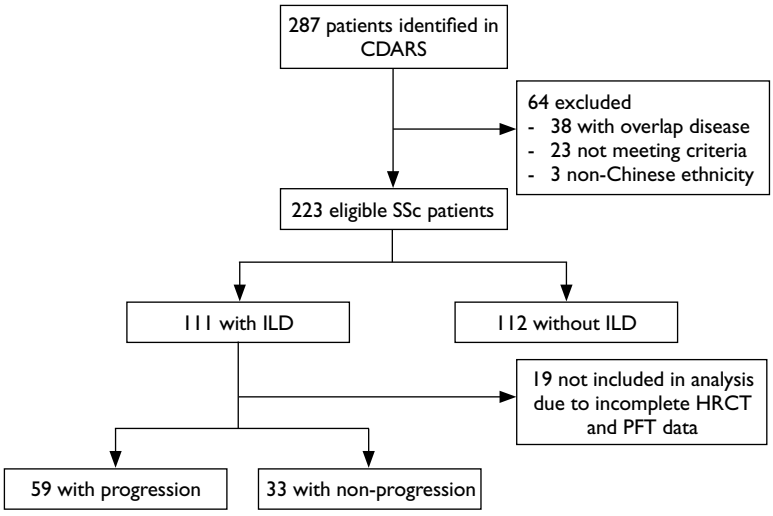

FIG. Patient recruitment

Abbreviations: CDARS = Clinical Data Analysis and Reporting System; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; PFT = pulmonary function test; SSc = systemic sclerosis

TABLE 1. Baseline characteristics of systemic sclerosis patients in this study*

	With ILD (n=111)	Without ILD (n=112)	Total (n=223)	P value
Female sex	96 (86.5%)	96 (85.7%)	192 (86.1%)	0.868
Age, y [mean (range)]	65 (26-97)	64 (21-93)	64 (21-97)	0.699
Smoking history				
Never	96 (86.5%)	91 (81.3%)	187 (83.9%)	0.288
Ex-smoker	9 (8.1%)	6 (5.4%)	15 (6.7%)	0.412
Current smoker	2 (1.8%)	7 (6.3%)	9 (4.0%)	0.171
Ever smoker	11 (9.9%)	13 (11.6%)	24 (10.8%)	0.683
Age at SSc diagnosis, y	55 (47-64)	55 (48-63)	55 (48-64)	0.649
Duration of disease, y	10.7 (6.2-16.3)	11.6 (5.3-17.3)	10.6 (6.1-16.5)	0.667
dcSSc	44 (39.6%)	18 (16.1%)	62 (27.8%)	<0.001
lcSSc	66 (59.5%)	93 (83.0%)	159 (71.3%)	<0.001
Autoantibodies				
ATA	64 (57.7%)	23 (20.5%)	87 (39.0%)	<0.001
ACA	6 (5.4%)	55 (49.1%)	61 (27.4%)	<0.001
RNP	15 (13.5%)	14 (12.5%)	29 (13.0%)	0.822
Others	20 (18.0%)	18 (16.1%)	38 (17.0%)	0.699

Abbreviations: ACA = anti-centromere antibody; ATA = anti-topoisomerase antibody; dcSSc = diffuse cutaneous systemic sclerosis; ILD = interstitial lung disease; lcSSc = limited cutaneous systemic sclerosis; RNP = ribonucleoprotein antibody; SSc = systemic sclerosis

* Data are shown as No. (%) or median (interquartile range), unless otherwise specified

from 20 to 85 years, with a median of 57 years. Most patients in the SSc-ILD subgroup were female (86.5%) and non-smokers (86.5%); these characteristics did not significantly differ relative to patients without ILD (Table 1). The median interval from onset of the first SSc symptom to ILD diagnosis was 2.4 years (IQR=1.3-5.4). Among ILD cases, 51.3% were diagnosed within the first 3 years after SSc symptom onset, and 64.0% were diagnosed within 5 years. Of the ILD patients, 18.9% were asymptomatic, whereas symptomatic patients experienced a median interval of 2.4 years (IQR=1.2-6.3) from respiratory symptom onset to ILD diagnosis.

The frequency of dcSSc was significantly greater in patients with ILD than in patients without ILD (39.6% vs 16.1%; P<0.001). Conversely, lcSSc was more common in patients without ILD than in patients with ILD (83.0% vs 59.5%; P<0.001). In the ILD group, ATA was the most frequently detected autoantibody (57.7%), whereas anti-centromere antibody (ACA) was more common in the non-ILD group (49.1%) [Table 1].

The frequencies of non-respiratory clinical features were comparable between the ILD and non-ILD groups. However, respiratory features, including dyspnoea, cough and bibasal crackles significantly differed between the two groups, both at presentation and during follow-up (P<0.001 for all comparisons). Pulmonary hypertension was significantly more frequent in the ILD group throughout the follow-up period (19.8% vs 2.7%; P<0.001). The ILD group also exhibited a numerically higher baseline ESR, with a median of 21.5 mm/hr (IQR=14-40.5), whereas the non-ILD group displayed a median of 18 mm/hr (IQR=11-30; P=0.074) [online supplementary Table 1].

Associative factors of interstitial lung disease development

Univariable analysis showed that several factors were associated with the presence of ILD (online supplementary Table 2). These included dcSSc, ATA, history of dyspnoea, history of cough, history of bibasal crackles, history of PH, and baseline ESR level. Conversely, ACA and lcSSc were negatively associated with ILD development. According to multivariable Cox regression analysis, a history of bibasal crackles was independently associated with the presence of ILD, and a history of dyspnoea showed a trend towards significance.

Predictors of interstitial lung disease progression

Among patients with ILD, 64.1% exhibited progression during follow-up. Patients with progressive ILD were younger at ILD diagnosis, displaying a mean age of 54 years (range, 20-85) compared with 60 years (range, 31-81; P=0.051) in patients with non-progressive ILD. The proportions of dcSSc and lcSSc were similar between the progressive and non-progressive ILD groups. Anti-topoisomerase antibody was the predominant autoantibody in both groups, with proportions of 62.7% and 54.5%, respectively (P=0.444) [online supplementary Table 3]. Regarding clinical characteristics, only a history of digital ulcers showed a significant difference; its prevalence was higher in the progressive ILD group (42.4% vs 15.2%; P=0.008) [online supplementary Table 4].

Table 2 compares the results of laboratory and PFT between the progressive and non-progressive ILD groups. C-reactive protein levels at both SSc diagnosis and ILD diagnosis were higher in the progressive ILD group; however, only CRP level at ILD diagnosis showed a trend towards significance (P=0.130). The latest values for the predicted percentages of forced expiratory volume in 1 second, FVC and DL_{CO} were significantly lower in the progressive ILD group (all P≤0.001), but baseline values did not differ between the groups. Regarding HRCT patterns, no significant differences were observed between the two groups.

The results of the Cox regression analysis for ILD progression are presented in Table 3. In the univariable analysis, factors associated with ILD progression included CRP level at ILD diagnosis

(hazard ratio [HR]=1.504; P=0.005) and the latest predicted percentage of DL_{CO} (HR=0.962; P<0.001). Multivariable analysis identified CRP level at ILD diagnosis (HR=1.064; P=0.002) as an independent factor associated with ILD progression, whereas a history of digital ulcers (HR=1.874; P=0.076) showed a trend towards significance.

Mortality

The overall mortality rate in the cohort during the follow-up period was 24.2%; a higher rate was observed in the SSc-ILD group relative to the non-ILD group (29.7% vs 18.8%, P=0.056) [online supplementary Fig]. Among the causes of death, infections were most common, followed by malignancy (online supplementary Table 5). In patients with ILD, 63.6% of deaths resulted from pneumonia; this proportion was 42.9% among patients without ILD. The univariable analysis indicated that factors associated with mortality were older age at SSc diagnosis, male sex, history of smoking, presence of PH, baseline CRP level, and baseline ESR level. Multivariable analysis revealed the following independent predictors of mortality: older age at SSc diagnosis (HR=1.101; P=0.002), history of smoking (HR=5.173; P=0.028), and higher baseline CRP level (HR=1.103; P=0.009) [Table 4].

TABLE 2. Laboratory and pulmonary function test results of systemic sclerosis patients with progressive and non-progressive interstitial lung disease*

	Progressive ILD (n=59)	Non-progressive ILD (n=33)	Total (n=92)	P value
Laboratory results				
CRP, mg/L				
At baseline	1.2 (1-5.6)	1.1 (0.8-2.2)	1.1 (1-3.2)	0.248
At ILD diagnosis	2.3 (1-5)	1.4 (0.9-3.4)	2.2 (1-4.8)	0.130
ESR, mm/hr				
At baseline	22 (12-49.5)	19 (14-30)	21 (13-42)	0.218
At ILD diagnosis	38 (16-72.3)	46 (24-65)	43 (18-68)	0.422
PFT results				
FEV_1 % predicted				
At baseline	86.4±15.6	82.6±18.8	84.8±17.0	0.328
Latest	73.1±19.2	87.8±18.9	78.9±20.3	0.001
FVC % predicted				
At baseline	83.8±16.4	80.5±18.5	82.5±17.3	0.387
Latest	70.0±18.7	85.2±19.6	76.1±20.3	0.001
FVC % predicted <70				
At baseline	8 (13.6%)	11 (33.3%)	19 (20.7%)	0.073
Latest	24 (40.7%)	7 (21.2%)	31 (33.7%)	0.017
DL_{CO} % predicted				
At baseline	61.2±17.7	58.6±17.3	60.3±17.5	0.546
Latest	43.3±15.5	62.3±19.3	51.2±19.5	<0.001
DL_{CO} % predicted <70				
At baseline	31 (52.5%)	20 (60.6%)	51 (55.4%)	0.285
Latest	40 (67.8%)	19 (57.6%)	59 (64.1%)	0.003
HRCT patterns				
NSIP	24 (40.7%)	10 (30.3%)	34 (37.0%)	0.323
UIP	24 (40.7%)	17 (51.5%)	41 (44.6%)	0.316
Others	11 (18.6%)	6 (18.2%)	17 (18.5%)	0.956

Abbreviations: CRP = C-reactive protein; DL_{CO} = diffusing capacity of the lung for carbon monoxide; ESR = erythrocyte sedimentation rate; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; NSIP = non-specific interstitial pneumonia; PFT = pulmonary function test; UIP = usual interstitial pneumonia

* Data are shown as No. (%), median (interquartile range) or mean±standard deviation, unless otherwise specified

Discussion

We observed an SSc-ILD prevalence of 49.8% in a multicentre cohort of Southern Chinese SSc patients. Among Asian countries, the reported prevalence of SSc-ILD varies. In Korea, prevalence rates range from 40% to 58%,[16,17] whereas in Japan, they range from 42% to 51%.[18,19] However, considerably higher prevalence estimates of 63% to 85% have been reported in centres from Northern China.[20,21] These findings suggest ethnic or geographic variations in the prevalence of SSc-ILD within the Asian population. Given the high prevalence in our cohort and the observed delay between respiratory symptom onset and ILD diagnosis (median=2.4 years), early universal screening for ILD is necessary among SSc patients. This is particularly important because a substantial proportion of patients (18.9%) were asymptomatic.

Consistent with previous studies, our findings confirmed that in Chinese SSc patients, the dcSSc subtype and presence of ATA were associated with a higher likelihood of ILD development, whereas the lcSSc subtype and presence of ACA were inversely related to ILD risk.[11,22,23] Also, our study showed that a history of bibasal crackles was independently associated with ILD development, similar to the findings of a retrospective cohort study in South Africa.[24] However, it is important to recognise that the presence of crackles often reflects established disease, and the new onset of respiratory symptoms may indicate ILD development. Irrespective of the presence of respiratory symptoms, all SSc patients are recommended to undergo screening for ILD via HRCT and PFTs, as specified by expert consensuses.[10,25] Regular auscultation for bibasal crackles during follow-up is equally important because it facilitates the identification of individuals who may require repeat investigations.

C-reactive protein has been proposed as a biomarker for predicting SSc-ILD progression.[26] Similar to our findings, a retrospective cohort study in France[27] revealed a significant difference in

TABLE 3. Univariable and multivariable Cox regression for predictors of interstitial lung disease progression

	Univariable analysis		Multivariable analysis*	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Ex-smoker	1.759 (1.111-7.462)	0.243		
Age at SSc diagnosis	1.015 (0.978-1.027)	0.150		
Ever had digital ulcers	1.592 (0.913-1.639)	0.122		
Dyspnoea during follow-up	1.145 (1.040-2.013)	0.640		
CRP at ILD diagnosis	1.504 (1.223-1.624)	0.005	1.064 (1.034-1.117)	0.002
Latest FVC % predicted	1.191 (0.646-2.004)	0.678		
Latest DL_{CO} % predicted†	0.962 (0.940-0.982)	<0.001		

Abbreviations: 95% CI = 95% confidence interval; CRP = C-reactive protein; DL_{CO} = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; ILD = interstitial lung disease; SSc = systemic sclerosis

* Included variables with P<0.2 in univariable analyses

† Excluded from multivariable analysis as it represents the expected outcome in progressive ILD

TABLE 4. Univariable and multivariable Cox regression for predictors of mortality

	Univariable analysis		Multivariable analysis*	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age	1.012 (0.987-1.038)	0.322		
Age at SSc diagnosis	1.057 (1.035-1.088)	<0.001	1.101 (1.034-1.172)	0.002
Male sex	2.624 (1.314-4.968)	0.005		
Ever-smoker	2.393 (1.194-4.785)	0.017	5.173 (1.712-16.28)	0.028
Presence of ILD	1.664 (0.946-3.074)	0.092		
Presence of ACA	0.552 (0.241-1.210)	0.149		
Progressive ILD	2.823 (0.829-9.609)	0.097		
Presence of PH	4.913 (2.584-8.696)	<0.001		
Baseline CRP	1.080 (1.045-1.115)	<0.001	1.103 (1.040-1.199)	0.009
Baseline ESR	1.016 (1.003-1.030)	0.024		

Abbreviations: 95% CI = 95% confidence interval; ACA = anti-centromere antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ILD = interstitial lung disease; PH = pulmonary hypertension; SSc = systemic sclerosis

* Included variables with P<0.2 in univariable analyses

CRP levels between SSc patients with and without ILD (P=0.003). The multivariate analysis in that study also demonstrated a negative correlation between CRP levels and FVC.[27] C-reactive protein production is driven by interleukin 6, and interleukin 6 inhibitors have shown efficacy in preserving lung function among SSc-ILD patients during a phase three randomised controlled trial.[28] These findings provide a mechanistic rationale for using CRP levels to identify SSc-ILD patients who may benefit from early investigation and treatment.

The cumulative survival rates reported in our study align with those observed in Western populations.[11,29] However, a European Scleroderma Trials and Research Group cohort study conducted in China[20] demonstrated a higher cumulative survival rate of 87.8% at 10 years, a lower overall mortality rate of 8.9%, and fewer SSc-ILD–related deaths (2.5%). This disparity may be attributed to the higher frequency of infection-related deaths and the greater proportion of patients with progressive disease in our cohort. Although assessments of treatment regimen and response were beyond the scope of our study, due to the confounding by indication involved in its retrospective design, immunosuppressive agents commonly used in the past may have predisposed patients to infections. Indeed, infection has previously been identified as the leading cause of death in local SSc patients.[3] Considering the high rate of infection-related mortality, recently available antifibrotic treatments may be preferable to immunosuppressive therapy

in selected patients who exhibit increased infection risk. Furthermore, consistent with well-established evidence, we identified increased age[15,30-32] and elevated CRP levels at SSc diagnosis[33,34] as predictors of mortality. It remains unclear whether more aggressive early treatment in patients with elevated baseline CRP levels would improve survival; further investigation is warranted.

Limitations

Some limitations should be acknowledged in our study. The data were extracted from the electronic health record, making undercoding of diagnoses unavoidable. Due to the retrospective study design, some clinical data essential to this study might not have been fully documented, and disease progression monitoring was not systematic, which could introduce bias. The presence of symptoms and ILD was assessed by the treating physicians and radiologists, respectively; these assessments potentially lacked specificity or sensitivity. Follow-up investigations were primarily ordered based on clinical judgement, leading to potential selection bias. Our analyses did not adjust for patients with progressive disease who may have received treatment leading to ILD stabilisation, which could have resulted in classification of their ILD as non-progressive. Furthermore, no standardised criteria currently exist for defining SSc-ILD progression. Quantitative assessments of ILD involvement on HRCT, such as percentage involvement or the Warrick score,[35] and the extensiveness of skin disease using the modified Rodnan skin score,[36] were also unavailable.

Conclusion

This is the first multicentre cohort study to investigate SSc-ILD in Hong Kong. Our findings demonstrated a high prevalence of ILD among Chinese SSc patients, with a significant proportion of these patients exhibiting disease progression. Universal ILD screening is recommended for SSc patients, with particular attention to those who develop respiratory symptoms and signs. In addition to imaging and PFTs, CRP levels could serve as a biomarker for ILD progression and poor prognosis.

Author contributions

Concept or design: DTH Chan, H So.
Acquisition of data: DTH Chan, LHP Tam.
Analysis or interpretation of data: DTH Chan, H So.
Drafting of the manuscript: DTH Chan, H So.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Declaration

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Ethics approval

This research was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, Hong Kong (Ref No.: CREC-2023-393). The requirement for informed patient consent was waived by the Committee due to the retrospective nature of the research.

Supplementary material

The supplementary material was provided by the authors, and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2411807).

References

1. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573-6.
2. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809-15.
3. Mok CC, Kwok CL, Ho LY, Chan PT, Yip SF. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. Arthritis Rheum 2011;63:1182-9.
4. Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. Am J Respir Crit Care Med 2020;201:650-60.
5. Mostmans Y, Cutolo M, Giddelo C, et al. The role of endothelial cells in the vasculopathy of systemic sclerosis: a systematic review. Autoimmun Rev 2017;16:774-86.
6. Khanna D, Lescoat A, Roofeh D, et al. Systemic sclerosis–associated interstitial lung disease: how to incorporate two Food and Drug Administration–approved therapies in clinical practice. Arthritis Rheumatol 2022;74:13-27.
7. Qiu M, Nian X, Pang L, Yu P, Zou S. Prevalence and risk factors of systemic sclerosis–associated interstitial lung disease in East Asia: a systematic review and meta-analysis. Int J Rheum Dis 2021;24:1449-59.
8. Chan DT, So H. Systemic sclerosis–associated interstitial lung disease: prevalence and risk factors. J Clin Rheumatol

Immunol 2023;23:15-24.
9. Chan PT, Mok CC, Chan KL, Ho LY. Functioning and health-related quality of life in Chinese patients with systemic sclerosis: a case-control study. Clin Rheumatol 2014;33:659-66.
10. Hoffmann-Vold AM, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatol 2020;2:e71-83.
11. Nihtyanova SI, Schreiber BE, Ong VH, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66:1625-35.
12. So H, So J, Lam TT, et al. Performance of the 2017 European Alliance of Associations for Rheumatology/American College of Rheumatology classification criteria in patients with idiopathic inflammatory myopathy and anti–melanoma differentiation–associated protein 5 positivity. Arthritis Rheumatol 2022;74:1588-92.
13. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism Collaborative Initiative. Arthritis Rheum 2013;65:2737-47.
14. van den Hombergh WM, Carreira PE, Knaapen-Hans HK, van den Hoogen FH, Fransen J, Vonk MC. An easy prediction rule for diffuse cutaneous systemic sclerosis using only the timing and type of first symptoms and auto-antibodies: derivation and validation. Rheumatology (Oxford) 2016;55:2023-32.
15. Goh NS, Hoyles RK, Denton CP, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol 2017;69:1670-8.
16. Jung E, Suh CH, Kim HA, Jung JY. Clinical characteristics of systemic sclerosis with interstitial lung disease. Arch Rheumatol 2018;33:322-7.
17. Kim J, Park SK, Moon KW, et al. The prognostic factors of systemic sclerosis for survival among Koreans. Clin Rheumatol 2010;29:297-302.
18. Sekiguchi A, Inoue Y, Yamazaki S, et al. Prevalence and clinical characteristics of earlobe crease in systemic sclerosis: possible association with vascular dysfunction. J Dermatol 2020;47:870-5.
19. Aozasa N, Hatano M, Saigusa R, et al. Clinical significance of endothelial vasodilatory function evaluated by EndoPAT in patients with systemic sclerosis. J Dermatol 2020;47:609-14.
20. Hu S, Hou Y, Wang Q, Li M, Xu D, Zeng X. Prognostic profile of systemic sclerosis: analysis of the clinical EUSTAR cohort in China. Arthritis Res Ther 2018;20:235.
21. Wang J, Assassi S, Guo G, et al. Clinical and serological features of systemic sclerosis in a Chinese cohort. Clin Rheumatol 2013;32:617-21.
22. Sánchez-Cano D, Ortego-Centeno N, Callejas JL, et al. Interstitial lung disease in systemic sclerosis: data from the Spanish scleroderma study group. Rheumatol Int 2018;38:363-74.
23. Gelber AC, Manno RL, Shah AA, et al. Race and association with disease manifestations and mortality in scleroderma: a 20-year experience at the Johns Hopkins Scleroderma Center and review of the literature. Medicine (Baltimore) 2013;92:191-205.
24. Ashmore P, Tikly M, Wong M, Ickinger C. Interstitial lung disease in South Africans with systemic sclerosis. Rheumatol Int 2018;38:657-62.
25. Rahaghi FF, Hsu VM, Kaner RJ, et al. Expert consensus on the management of systemic sclerosis–associated interstitial lung disease. Respir Res 2023;24:6.
26. Distler O, Assassi S, Cottin V, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. Eur Respir J 2020;55:1902026.
27. Chikhoune L, Brousseau T, Morell-Dubois S, et al. Association between routine laboratory parameters and the severity and progression of systemic sclerosis. J Clin Med 2022;11:5087.
28. Khanna D, Lin CJ, Furst DE, et al. Long-term safety and efficacy of tocilizumab in early systemic sclerosis–interstitial lung disease: open-label extension of a phase 3 randomized controlled trial. Am J Respir Crit Care Med 2022;205:674-84.
29. Pokeerbux MR, Giovannelli J, Dauchet L, et al. Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. Arthritis Res Ther 2019;21:86.
30. Volkmann ER, Tashkin DP, Sim M, et al. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. Ann Rheum Dis 2019;78:122-30.
31. Volkmann ER, Saggar R, Khanna D, et al. Improved transplant-free survival in patients with systemic sclerosis–associated pulmonary hypertension and interstitial lung disease. Arthritis Rheumatol 2014;66:1900-8.
32. Takei R, Arita M, Kumagai S, et al. Radiographic fibrosis score predicts survival in systemic sclerosis–associated interstitial lung disease. Respirology 2018;23:385-91.
33. Liu X, Mayes MD, Pedroza C, et al. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res (Hoboken) 2013;65:1375-80.
34. Le Gouellec N, Duhamel A, Perez T, et al. Predictors of lung function test severity and outcome in systemic sclerosis–associated interstitial lung disease. PLoS One 2017;12:e0181692.
35. Warrick JH, Bhalla M, Schabel SI, Silver RM. High resolution computed tomography in early scleroderma lung disease. J Rheumatol 1991;18:1520-8.
36. Khanna D, Furst DE, Clements PJ, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord 2017;2:11-8.

