An Analysis of Connective Tissue Disease-associated Interstitial Lung Disease at a US Tertiary Care Center: Better Survival in Patients with Systemic Sclerosis

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ABSTRACT. ***Objective.*** To compare survival of patients with connective tissue disease-associated interstitial lung disease (CTD-ILD) versus idiopathic pulmonary fibrosis (IPF) and patients with systemic sclerosis-associated ILD (SSc-ILD) versus other CTD-ILD followed at our center.

Methods. We used the Stanford ILD database, which contains prospectively collected information on patients with ILD evaluated at our tertiary care center from 2002 to 2009. Survival at last followup from time of ILD diagnosis was calculated using the Kaplan-Meier estimator. Prognostic factors for survival in the overall cohort (IPF and CTD-ILD) and in the CTD-ILD group were identified with univariate and multivariate Cox regression models.

Results. Of 427 patients with ILD, 148 (35%) had IPF and 76 (18%) had CTD-ILD at the baseline visit. The cumulative incidence of CTD was 4%. After a median followup of 4 years, 67 patients (36.4%) had died and 4 (2.2%) were lost to followup. Patients with IPF (n = 122) and CTD-ILD (n = 62) experienced similar survival rates (5-year survival about 50%). Patients with SSc-ILD (n = 24) experienced better survival than those with other CTD-ILD (n = 38), with 1-year, 3-year, and 5-year survival rates of 100%, 90%, and 77%, respectively, versus 78%, 42%, and 38% (p = 0.01). The presence of SSc in patients with CTD-ILD decreased the risk of death by > 80% even after correcting for age at ILD diagnosis, sex, and ethnicity (HR = 0.17, 95% CI 0.04–0.83).

Conclusion. Survival in patients with SSc-ILD was better than in patients with other CTD-ILD, potentially related to routine screening for and early detection of ILD in patients with SSc at our center. (J Rheumatol First Release Feb 1 2011; doi:10.3899/jrheum.100675)

Key Indexing Terms:
SYSTEMIC SCLEROSIS | IDIOPATHIC PULMONARY FIBROSIS
CONNECTIVE TISSUE DISEASE | INTERSTITIAL LUNG DISEASE | SURVIVAL

Interstitial lung disease (ILD) represents a heterogeneous group of diseases that involves inflammation and interstitial fibrosis of the lung parenchyma. The most common types of ILD include idiopathic pulmonary fibrosis (IPF) and connective tissue disease (CTD)-associated ILD (CTD-ILD). Prevalence estimates of CTD at the time of ILD diagnosis have ranged between 8.8% and 33%[1,2], while incidence rates for a new diagnosis of CTD have been estimated at 6%–15%[1,2,3]. CTD associated with ILD include systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis and dermatomyositis (PM/DM), Sjögren's syndrome, and mixed connective tissue disease (MCTD)[4].

IPF carries a poor prognosis, with a 5-year survival of nearly 50% and mean survival time estimated at 3.2 to 5 years after diagnosis[5]. Several studies comparing IPF with CTD-ILD indicate that patients with IPF experience poorer outcomes and survival[6,7,8]. However, other studies showed that CTD-ILD was associated with a worse prognosis than IPF when adjusted for age[9,10]. The contradictory results in these studies may be related to differences in the patient populations with respect to CTD diagnosis.

ILD affects up to 70% of patients with SSc[4], and is the most common cause of hospitalizations and death in patients with SSc[11,12]. Therefore, guidelines have been published recommending that all patients with SSc undergo baseline and annual screening for ILD with pulmonary function test-

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ing and chest imaging[13,14]. A recent double-blind placebo-controlled study showed that patients with SSc-ILD treated with 1 year of oral cyclophosphamide experienced a statistically significant improvement in lung function, dyspnea, and health-related quality of life compared with those treated with placebo[15,16]. The effect of cyclophosphamide therapy on longterm survival in patients with SSc-ILD is still unclear.

We hypothesized that patients with SSc-ILD may experience better outcomes than patients with other CTD-ILD because these patients undergo routine screening for ILD at our center. We compared the clinical features and survival of patients with SSc-ILD to those with ILD associated with other CTD (non-SSc CTD-ILD), including RA, SLE, PM/DM, Sjögren's syndrome, and MCTD. We also identified factors predictive of mortality in patients with CTD-ILD.

MATERIALS AND METHODS

All patients included in our analyses were enrolled in the Stanford ILD Database (n = 427), a prospective collection of information on patients with ILD evaluated at Stanford Hospital and Clinics between January 1, 2002, and January 1, 2009. Institutional Review Board approval was obtained prior to the initiation of the ILD database and prior to data collection for our study. All patients provided informed consent prior to enrollment in the database.

All patients carrying a diagnosis of ILD were included in the determination of incident CTD cases. Diagnosis of ILD was determined by a panel of ILD expert clinicians and chest radiologists based on serology, clinical signs, and high-resolution chest computerized tomography (HRCT) analysis. A nonspecific interstitial pneumonia (NSIP) pattern, with features of reticulation, ground-glass opacities, and traction bronchiectasis, was most frequently observed on HRCT. Patients with both subclinical (changes on HRCT alone) and clinical (changes on HRCT *and* restrictive pattern on pulmonary function tests *or* symptoms) diagnoses of ILD were included in our cohort. Subsequent analyses included only patients with IPF and CTD-associated ILD. Patients were classified as having IPF using American Thoracic Society/European Respiratory Society criteria for the diagnosis of IPF[17], and the diagnosis was confirmed by a pulmonologist at the Stanford ILD Clinic prior to entry into the database. The diagnosis of various CTD was determined by the treating rheumatologist as confirmed by medical record review. Patients were classified as having SSc, RA, SLE, or Sjögren's syndrome based on American College of Rheumatology criteria[18,19,20,21]. Bohan and Peter criteria were applied for the diagnosis of inflammatory myopathies, including PM and DM[22]. The diagnosis of MCTD was based on clinical features described by Sharp, *et al*[23]. Patients with > 1 CTD diagnosis were excluded from our study.

Clinical data. Demographic information was uniformly recorded in the ILD database upon enrollment. Data collected were age at ILD diagnosis, sex, ethnicity, smoking history, family history of lung disease, baseline body mass index (BMI), New York Heart Association (NYHA) functional class, Borg dyspnea score[24], and date of first Stanford ILD clinic visit. Results of the following serologic tests, if performed at any time during the patient's evaluation at Stanford, were recorded and confirmed by medical record review: rheumatoid factor (RF), antinuclear antibody (ANA) titer and pattern, antineutrophil cytoplasmic antibody titer, dsDNA, anti-Scl-70, anticentromere, anti-Ro, anti-La, anti-Smith, anti-Jo-1, anticyclic citrullinated peptide antibody, antiphospholipid, and anti-U1-ribonucleoprotein (RNP) antibodies. Laboratory data also included baseline hematocrit, hemoglobin, thyroid function tests, blood urea nitrogen, creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and muscle enzymes, which included creatine phosphokinase, aldolase, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase. Clinical signs of CTD were collected by medical record review. The signs included cutaneous subtype of scleroderma, Raynaud's phenomenon, digital ulcers, telangiectasias, calcinosis, renal disease, gastroesophageal reflux disease (GERD), dysphagia, myositis, arthritis, and sicca symptoms.

If diagnostic procedures were done at an outside institution, the results were reviewed by a Stanford pulmonologist and entered into the database. Pulmonary function tests included forced vital capacity (FVC), forced expiratory volume (FEV1), total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLCO). Oxygen saturation with exercise and desaturation to < 90% was collected. The majority of patients underwent HRCT to evaluate radiographic evidence of ILD. Transthoracic echocardiography assessed right ventricular systolic pressure (RVSP) to determine whether pulmonary hypertension, defined as an RVSP > 40 mm Hg, was present. Confirmatory right-heart catheterization was performed in a minority of patients. A limited number of patients underwent bronchoscopy or surgical biopsy.

Included in the database were antiinflammatory/immunosuppressive medications, disease-modifying antirheumatic drugs, antireflux medications, aspirin, warfarin, home oxygen, antidepressants, statins, diuretics, ß-blockers, digoxin, calcium channel blockers, and other medications for pulmonary hypertension (prostacyclins, endothelin receptor antagonists, and phosphodiesterase inhibitors). For analytic purposes, medications were classified as ever versus never used. Deaths and dates of death were confirmed with the Social Security Death Index (SSDI; http://ssdi.rootsweb.ancestry.com/).

Statistical analysis. The cumulative incidence of CTD was calculated as the number of patients who received a new diagnosis of CTD over the study period divided by the number of total patients with ILD, excluding those patients with a CTD at baseline. We compared the baseline clinical features of patients with CTD-ILD to those with IPF, and patients with SSc-ILD to non-SSc CTD-ILD, using Student's t test, Wilcoxon signed-rank test, or Mann-Whitney U test for continuous variables, and chi-squared or Fisher's exact test for categorical variables. P values < 0.05 were considered statistically significant. Followup times were calculated from the date of ILD diagnosis, and patients who were alive at last followup or lost to followup were censored. Survival curves were compared using the left-truncated Kaplan-Meier estimates. Prognostic factors for survival in the overall cohort (IPF and CTD-ILD) and in the CTD-ILD group were evaluated with left-truncated univariate and multivariate Cox regression analyses. We calculated univariate estimated hazard ratios (HR) with 95% CI for the ILD subgroup (IPF vs CTD in the overall cohort, and SSc vs non-SSc in the CTD subgroup), which was the variable of interest, as well as other clinically relevant predictors to identify significant variables predicting survival status. We then used backward stepwise elimination to determine the final regression model, excluding variables that were highly correlated with the variable of interest, and retaining those nondemographic factors with a p value < 0.05. All statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Incidence of CTD in patients with ILD. The Stanford ILD Database enrolled 427 patients with ILD from 2002 through 2009. Of these, 148 subjects (35%) had IPF and 76 (18%) had a confirmed diagnosis of a CTD at their baseline visit. Among subjects with CTD-ILD, the frequencies of specific CTD subtypes were RA (n = 27), SSc (n = 26), MCTD (n = 12), PM/DM (n = 4), SLE (n = 4), and Sjögren's syndrome (n = 3). Of patients with SSc-ILD, 54% had limited cutaneous SSc (lcSSc), 31% had diffuse cutaneous SSc (dcSSc), 4% had sine scleroderma, and 11% were unclassified.

Autoantibody results were not available for all patients. Of the SSc group, 21 of 22 patients (95%) had a positive ANA; 8 of 17 (47%) had a positive anti-SCL-70 antibody; 0 of 12 (0%) had a positive anticentromere antibody; 8 of 15 (53%) had a nucleolar pattern on ANA; and 3 of 12 (25%) had a positive anti-U1-RNP antibody. Of the 351 patients without evidence of CTD at the initial time of enrollment into the database, 14 were subsequently diagnosed with an underlying CTD. This corresponds to a cumulative incidence of CTD in patients with ILD of 3.99% (14/351), or 14 per 978 person-years.

Clinical features of patients with IPF and CTD-ILD. Comparison of baseline clinical features revealed that patients with CTD-ILD (n = 76) were younger, more often female, and had a longer duration of ILD at enrollment than patients with IPF (n = 148; Table 1). The CTD-ILD group was less likely to have ever smoked, but more likely to experience Raynaud's phenomenon and to have a positive ANA (titer ≥ 1:80). The CTD-ILD group had better NYHA functional status at baseline, and their unadjusted DLCO and exercise oxygen saturation were slightly higher than those in patients with IPF. A lower proportion of the CTD-ILD group had ever desaturated < 90% compared with the IPF group. The groups did not differ with regard to FVC and FEV1 results. Radiographic evidence of usual interstitial pneumonia (UIP) was more prevalent in patients with IPF than in patients with CTD-ILD (68% vs 37%; p < 0.0001).

Although treatment with methotrexate, hydroxychloroquine, and tumor necrosis factor (TNF) inhibitors was higher in patients with CTD-ILD, there were no significant differences in cyclophosphamide, azathioprine, mycophenolate mofetil, and prednisone use between the CTD-ILD and IPF groups (Table 2).

We compared the baseline clinical features of patients with SSc-ILD (n = 26) to those with ILD associated with all other CTD (non-SSc CTD-ILD group, n = 50; Table 1). We found that patients with SSc-ILD were younger and had a lower BMI. The groups did not differ in ILD duration at the time of enrollment. All patients with SSc-ILD who were tested had a positive ANA, compared with 67% of the non-SSc patients with CTD-ILD (p = 0.003). As expected, a higher proportion of patients with SSc suffered from Raynaud's phenomenon, compared with the non-SSc group. Patients with SSc-ILD had significantly higher FVC, FEV1, TLC, DLCO, and exercise oxygen saturation than patients with non-SSc CTD-ILD at baseline. Patients with SSc also

Table 1. Baseline clinical characteristics of the connective tissue disease-associated interstitial lung disease (CTD-ILD) group are compared to those of the idiopathic pulmonary fibrosis (IPF) group, and baseline characteristics of the systemic sclerosis-associated ILD (SSc-ILD) group are compared to those of the non-SSc_ILD group. If a baseline value was unavailable for a subject, the first available observation for the variable was used. P values are derived from t-tests, Wilcoxon signed-rank tests, Mann-Whitney U test, or exact tests where appropriate. Data are mean (SD) unless otherwise specified. Values represented as percentages indicate the proportion of subjects who are positive for the variable.

Variable	N	CTD, n = 76	N	IPF n = 148	p, CTD vs IPF	N	SSc n = 26	N	Non-SSc n = 50	p, SSc vs Non-SSc
Baseline age, yrs	75	56.1 (13.7)	147	68.6 (12.1)	< 0.0001	25	49.8 (14.2)	50	59.2 (12.5)	0.004
BMI, kg/m^2	61	29.1 (6.6)	117	29.4 (6.4)	0.758	19	26.2 (4.8)	42	30.5 (7)	0.017
ILD disease duration, yrs	63	6.2 (7.2)	123	1.7 (4)	< 0.0001	24	4.7 (5.6)	39	6.8 (7.7)	0.273
White, %	72	58	130	69	0.119	26	50	46	63	0.281
Sex, % women	76	80	148	42	< 0.0001	26	85	50	78	0.492
Ever smoker, %	65	52	126	68	0.041	25	56	40	50	0.638
GERD, %	76	32	131	34	0.767	26	39	50	28	0.352
Raynaud's, %	76	40	125	2	< 0.0001	26	73	50	22	< 0.0001
Anemia, %	54	22	80	18	0.498	22	23	32	22	0.941
ANA-positive, %	48	81	40	25	< 0.0001	21	100	27	67	0.003
High muscle enzymes, %	51	18	72	14	0.570	18	17	33	18	0.892
Thyroid disease, %	76	15	148	11	0.425	26	12	50	16	0.600
UIP on HRCT, %	76	37	148	68	< 0.0001	26	27	50	42	0.265
FVC, % predicted	72	67.4 (21.9)	143	67.3 (20.2)	0.956	24	77.6 (20.2)	48	62.3 (21.1)	0.005
FEV1, % predicted	71	72 (22.2)	135	75.9 (23.3)	0.247	24	79.4 (19.5)	47	68.3 (22.7)	0.045
TLC, % predicted	45	71.8 (19.6)	118	66.9 (18.1)	0.133	15	80.9 (19.6)	30	67.3 (18.2)	0.026
DLCO, unadjusted % predicted	68	52 (18.4)	139	44.9 (18.7)	0.015	24	58.4 (19)	44	48.6 (17.3)	0.029
NYHA class	47	2 (0.8)	116	2.4 (0.8)	0.007	16	1.5 (0.7)	31	2.2 (0.7)	0.003
Exercise O_2 sat, %	36	93.3 (6)	55	89.7 (6.2)	0.002	11	96.3 (3.6)	25	91.9 (6.4)	0.016
O_2 sat ever < 90%, %	71	13	140	26	0.029	23	4	48	17	0.144

BMI: body mass index; GERD: gastroesophageal reflux disease; ANA-positive: antinuclear antibody ≥ 1:80; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; TLC: total lung capacity; DLCO: diffusion capacity for carbon monoxide; NYHA: New York Heart Association; O_2 sat: oxygen saturation.

Table 2. Comparisons of immunosuppressive therapies. Treatment is defined as ever vs never exposure to the medications. Data are percentages of subjects taking each medication.

Medication	CTD-ILD n = 76	IPF, n = 148	p	SSc-ILD, n = 26	Non-SSC CTD-ILD, n = 50	p
Cyclophosphamide	10.5	8.1	0.5479	7.7	12.0	0.7078
Azathioprine	30.3	37.8	0.2613	11.5	40.0	0.0104
Methotrexate	18.4	1.4	< 0.0001	7.7	24.0	0.1200
Mycophenolate mofetil	23.7	14.9	0.1027	11.5	30.0	0.0725
Hydroxychloroquine	22.4	6.1	0.0003	15.4	26.0	0.2921
Prednisone	57.9	48.7	0.1898	23.1	76.0	< 0.0001
TNF inhibitor	21.1	0	< 0.0001	0	32.0	0.0012

CTD-ILD: connective tissue disease-associated interstitial lung disease; IPF: idiopathic pulmonary fibrosis; SSc-ILD: systemic sclerosis-associated ILD; non-SSc CTD-ILD: nonsystemic sclerosis CTD-ILD; TNF: tumor necrosis factor.

had a better NYHA functional class at baseline. The prevalence of UIP on HRCT in the SSc-ILD and non-SSc ILD groups was not significantly different (27% and 42%, respectively; p = 0.27). Treatment with cyclophosphamide, methotrexate, mycophenolate mofetil, and hydroxychloroquine was similar between the groups, but patients with non-SSc CTD-ILD were much more likely to have been treated with azathioprine and prednisone. No patients with SSc-ILD were treated with TNF inhibitors, while 32% of the non-SSc patients with CTD-ILD (RA, n = 14; PM/DM, n = 1; SLE, n = 1) had received treatment with these biologic agents (Table 2).

Survival in patients with IPF and CTD-ILD. Of the 224 total patients with IPF and CTD-ILD, the date of ILD diagnosis was unknown in 40 patients, who were therefore excluded from the survival analyses. Of the remaining 184 patients (122 IPF, 62 CTD-ILD), 67 patients (36.4%) died and 4 (2.2%) were lost to followup during the study period. The total followup time from the initial ILD diagnosis was 1145 person-years, with a median followup time of 4.5 years. Survival of patients with IPF was similar to that of patients with CTD-ILD, with 1-year, 3-year, and 5-year survival estimates of 84%, 67%, and 52%, respectively, in patients with IPF compared with 88%, 61%, and 53% in patients with CTD-ILD (Figure 1; p = 0.08). Among patients with CTD-ILD, the median time of followup from initial diagnosis to the last followup was 7.2 years for patients with SSc and 6.8 years for non-SSc patients (p = 0.62). The SSc-ILD group (n = 24) had significantly better survival rates than the non-SSc CTD-ILD group (n = 38; Figure 2; p = 0.01). The 1-year, 3-year, and 5-year survival estimates were 100%, 90%, and 77%, respectively, for the SSc-ILD group, versus 78%, 42%, and 38% for the non-SSc CTD-ILD group.

Prognostic factors for survival in patients with IPF and CTD-ILD. Univariate Cox regression analysis in the overall cohort (IPF and CTD-ILD) identified age at ILD diagnosis,

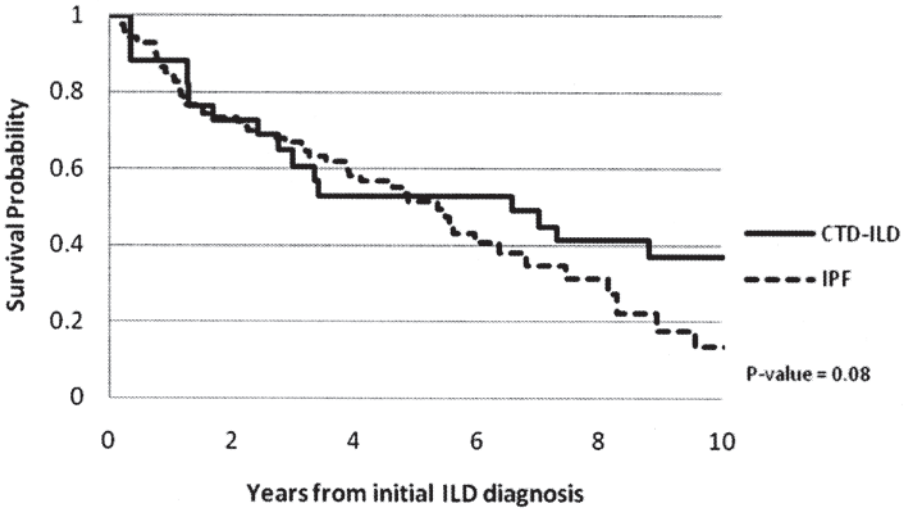

Figure 1. Kaplan-Meier survival curves of patients with idiopathic pulmonary fibrosis (IPF) compared to patients with connective tissue disease-associated interstitial lung disease (CTD-ILD). Patients with IPF and CTD-ILD had similar survival rates, with 1-year, 3-year, and 5-year estimates of 84%, 67%, and 52%, respectively, in patients with IPF compared with 88%, 61%, and 53% in patients with CTD-ILD (p = 0.08).

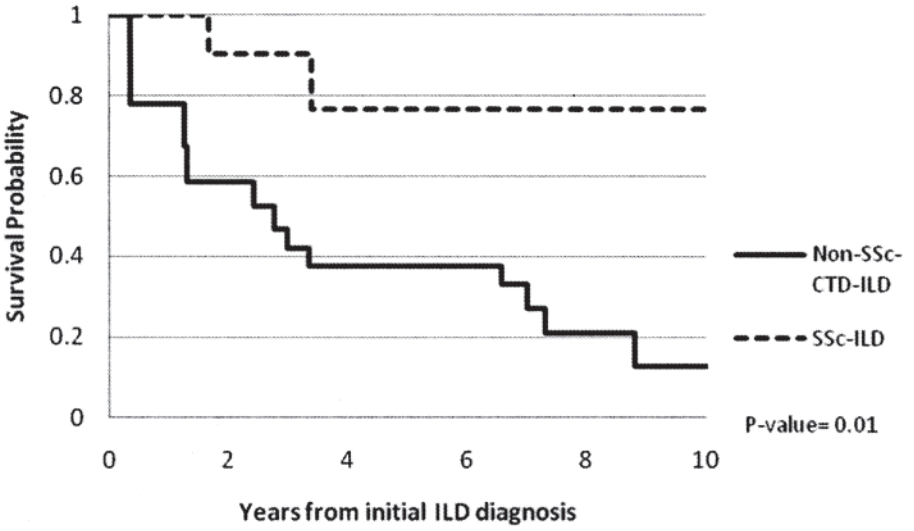

Figure 2. Kaplan-Meier survival curves of patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) compared to other connective tissue disease-associated ILD (CTD-ILD). The SSc-ILD group had significantly better survival rates than the non-SSc CTD-ILD group (p = 0.01). The 1-year, 3-year, and 5-year survival estimates were 100%, 90%, and 77%, respectively, for the SSc-ILD group, compared to 78%, 42%, and 38% for the non-SSc CTD-ILD group.

anemia, RF positivity, and poorer NYHA functional status as predictive of mortality (Table 3A). The presence of GERD or Raynaud's phenomenon conferred a survival benefit. In addition, higher DLCO, FVC, FEV1, and exercise oxygen saturation were all associated with better survival. Longer ILD duration at the time of enrollment showed a trend toward poorer survival (HR 1.20, 95% CI 0.98–1.48, p = 0.08). Use of immunosuppressants intended to treat ILD (including prednisone, azathioprine, mycophenolate mofetil, and cyclophosphamide) were associated with a higher risk of death (HR 2.45, 95% CI 1.35–4.44).

Univariate Cox regression analysis within the CTD-ILD group identified SSc, ANA positivity, and Raynaud's as protective factors, with HR of 0.15 (95% CI 0.03–0.67), 0.05 (95% CI 0.005–0.49), and 0.10 (95% CI 0.02–0.49), respectively (Table 3B). Higher DLCO and FVC were also protective, but the latter was not statistically significant. Use of immunosuppressants for treatment of ILD was associated with worse survival (HR 4.79, 95% CI 1.05–21.80).

Multivariate Cox regression modeling was performed to evaluate for significant predictors of mortality, adjusting for confounding variables. In the overall cohort, older age at ILD diagnosis was associated with a higher risk of death (HR 1.05, 95% CI 1.02–1.07), while higher baseline FVC (HR 0.98, 95% CI 0.96–0.99) was protective (Table 4A).

Among the patients with CTD-ILD, a diagnosis of SSc decreased the risk of death by 83% (HR 0.17, 95% CI 0.04–0.83) when adjusted for age at ILD diagnosis, sex, and ethnicity (Table 4B). Because FVC was not significantly associated with death in the univariate Cox regression model for the CTD-ILD group (Table 3B), we did not include this variable in the multivariate analysis.

DISCUSSION

Our study represents a comprehensive analysis of patients with CTD-ILD evaluated at our tertiary care center from 2002 through 2009. Similar to other studies[1,3], we found that the incidence of CTD in our ILD cohort was about 4%. In contrast to previous studies, we demonstrated that all-cause mortality of patients with IPF is similar to that of patients with CTD-ILD. We found that survival in patients with SSc-ILD is superior to that of patients with non-SSc CTD-ILD. In fact, the presence of SSc in patients with CTD-ILD decreased the risk of death by > 80% even after correction for age at ILD diagnosis, sex, and ethnicity.

Our finding of similar survival between IPF and CTD-ILD differs from previously published studies. Park, *et al*[7] found that patients with IPF had poorer survival rates than patients with CTD-ILD, particularly those with idiopathic UIP. In contrast, Kocheril, *et al* demonstrated higher mortality rates in the CTD-ILD group compared with IPF[9]. Indeed, the patient populations in these 2 studies differed: the largest group of patients in the Park, *et al* study had SSc-ILD (38%)[7], while the largest subgroup in the Kocheril, *et al* study had RA-ILD (30%). In our CTD-ILD cohort, we had equal numbers of patients with SSc-ILD (34%) and RA-ILD (35%), potentially explaining the similar outcomes we observed between the IPF and CTD-ILD groups.

ILD affects about 70% of patients with SSc[4], and has been identified as the leading cause of death[11]. Our estimat-

Table 3. Prognostic factors for patients with idiopathic pulmonary fibrosis (IPF) and connective tissue disease-associated interstitial lung disease (CTD-ILD) using univariate Cox regression analysis. Immunosuppressants include prednisone, azathioprine, cyclophosphamide, and mycophenolate mofetil.

A. IPF and CTD-ILD population

Variable	N Used	p	Hazard Ratio	LCL	UCL
CTD vs IPF	184	0.083	0.571	0.304	1.075
Age at diagnosis	182	0.0001	1.042	1.021	1.064
ILD disease duration	184	0.075	1.204	0.981	1.479
Sex (women)	184	0.062	0.631	0.389	1.023
Ethnicity (white)	173	0.067	1.725	0.962	3.093
Anemia	120	0.003	3.003	1.471	6.131
GERD	180	0.021	0.517	0.296	0.904
Raynaud's	176	0.003	0.159	0.048	0.525
RF-positive	53	0.041	2.925	1.047	8.171
DLCO	174	< 0.0001	0.965	0.939	0.974
FVC	178	0.001	0.977	0.965	0.990
FEV1	173	0.002	0.982	0.971	0.994
NYHA class	143	< 0.0001	2.497	1.750	3.563
O_2 exercise	83	0.006	0.911	0.852	0.974
O_2 sat ever < 90%	176	0.232	1.405	0.804	2.455
Immunosuppressants	184	0.003	2.448	1.351	4.436

GERD: gastroesophageal reflux disease; RF: rheumatoid factor; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; NYHA: New York Heart Association; O_2 exercise: oxygen saturation with exercise; LCL: lower confidence limit; UCL: upper confidence limit.

B. CTD-ILD population only

Variable	N Used	p	Hazard Ratio	LCL	UCL
SSc vs non-SSc	62	0.014	0.147	0.032	0.673
Age at diagnosis	61	0.069	1.047	0.996	1.100
ILD disease duration	62	0.963	0.992	0.694	1.416
Sex (women)	62	0.640	1.431	0.319	6.429
Ethnicity (white)	60	0.788	1.177	0.358	3.867
ANA-positive	42	0.010	0.051	0.005	0.486
Raynaud's	62	0.004	0.104	0.022	0.492
DLCO	57	0.019	0.953	0.916	0.992
FVC	59	0.077	0.977	0.953	1.002
O_2 sat ever < 90%	58	0.694	0.658	0.082	5.269
Immunosuppressants	62	0.043	4.788	1.052	21.799

SSc: systemic sclerosis-associated ILD; non-SSc: nonsystemic sclerosis CTD-associated ILD; ANA-positive: antinuclear antibody ≥ 1:80; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; LCL: lower confidence limit; UCL: upper confidence limit; O_2 sat: oxygen saturation.

ed 5-year survival rate of 77% in the SSc-ILD group is consistent with a study published by Bouros, *et al*[25]. Steen and Medsger[26] found a much lower 5-year survival rate of about 50% in subjects with dcSSc and severe ILD, defined by an FVC < 55% predicted. It is not surprising that survival rates were worse in Steen and Medsger, since survival was calculated from the onset of severe ILD rather than from the time of initial ILD diagnosis (including subclinical disease), as in our study[26].

The prevalence of clinical and subclinical ILD on HRCT in patients with RA has been estimated as 19%–56%[27,28,29,30]. A previous study found a 5-year survival rate of 39% in patients hospitalized for ILD associated with RA[31]. A more recent study found that patients with RA who had a definite UIP pattern on HRCT had significantly poorer survival (25% at 5 years) compared with patients with RA who had non-UIP patterns on HRCT (60% at 5 years; p = 0.04)[32].

Our analysis is the first to demonstrate that the diagnosis of SSc had a protective effect on mortality in patients with CTD-ILD after adjustment for age, sex, and ethnicity. In contrast, Park, *et al*[7] found that survival of patients with SSc-interstitial pneumonia (IP) and non-SSc CTD-IP were similar after adjustment for age, sex, and FVC. At the time of this study by Park, *et al*[7], guidelines for routine screening for ILD in SSc were not yet implemented. We hypothesize that routine screening for and early detection of ILD in patients with SSc at our center may be in part responsible for

Table 4. Prognostic factors for patients with IPF and CTD associated ILD (CTD-ILD) using multivariate Cox regression analysis. Immunosuppressants include prednisone, azathioprine, cyclophosphamide, and mycophenolate mofetil.

A. Idiopathic pulmonary fibrosis and CTD-ILD population.

Variable	p	Hazard Ratio	LCL	UCL
Age at diagnosis of ILD	0.0002	1.047	1.02	1.07
Ethnicity (white)	0.4099	1.311	0.69	2.50
Sex (women)	0.3357	0.760	0.43	1.33
CTD	0.9843	1.007	0.48	2.10
Immunosuppressants	0.0818	1.803	0.93	3.50
FVC	0.0004	0.975	0.96	0.99

B. CTD-ILD population only.

Variable	p	Hazard Ratio	LCL	UCL
Age at diagnosis of ILD	0.2027	1.030	0.98	1.08
Sex (women)	0.7332	1.316	0.27	6.39
Ethnicity (white)	0.8347	1.133	0.35	3.67
SSc	0.0280	0.172	0.04	0.83

the better outcomes observed in this subgroup in our study. At our institution, patients with other CTD do not undergo routine screening for ILD, and therefore are likely to have more severe disease at the time of ILD diagnosis. The significantly poorer FVC, TLC, and exercise oxygen saturation levels in the patients with non-SSc CTD-ILD support this hypothesis. Patients with SSc-ILD were less likely than non-SSc patients to receive immunosuppressive therapies, and given the modest improvements in pulmonary function tests (PFT) with immunosuppression in SSc-ILD[15], early and aggressive therapy cannot explain the better outcomes observed in this subgroup.

Alternatively, the non-SSc CTD-ILD subgroup had a higher prevalence of the UIP pattern on HRCT than the SSc group, although this did not reach statistical significance. The presence of UIP is frequently associated with RA-ILD[33,34], while NSIP historically is more common in SSc-ILD[25,35]. In IPF, histological UIP and radiographic findings consistent with probable and definite UIP on HRCT are associated with a poorer prognosis[7,36,37]. Similarly, radiographic evidence of definite UIP in patients with RA-ILD is also associated with poorer outcomes, as described[32]. In contrast, UIP had no effect on survival in patients with SSc-ILD in Bouros, *et al*[25]. Also, Park, *et al* found no differences in survival between patients with collagen vascular disease-UIP and collagen vascular disease-NSIP[7]. In our study, UIP was not a significant predictor of mortality in either the overall cohort (IPF and CTD-ILD) or the CTD-ILD subgroup (data not shown), therefore additional factors must contribute to the better survival we observed in the SSc-ILD group.

The disparity between SSc-ILD versus non-SSc CTD-ILD survival may also be in part attributable to differences in treatments. In univariate analysis, treatment of ILD with immunosuppression was associated with a higher risk of death. This may be confounded by the association with the non-SSc CTD subgroup, and an increased risk of death due to infection or other immunosuppressant-induced complications. Patients treated with immunosuppression may also have had higher ILD severity. Regarding other medications commonly used to treat ILD, we were unable to demonstrate any survival benefit to cyclophosphamide, mycophenolate mofetil, or azathioprine treatment in our CTD-ILD cohort (data not shown).

Steen and Medsger demonstrated that patients with dcSSc who develop severe end-organ damage typically show the most rapid decline in organ function within the first 5 years of SSc onset[26]. Although the mean SSc disease duration at the first visit to the Stanford ILD clinic was 4.7 years (data not shown), perhaps indicating that our patients had already survived the high-risk period, the majority of our cohort had limited cutaneous disease or sine sclerosis. These patients tend to develop internal organ damage later in their disease course than patients with diffuse cutaneous disease[38].

Our study does have some limitations. Our results reflect the practices of a single tertiary care center, and are not generalizable to community practices or other academic institutions. The referral patterns to our center during the time of this study likely affected the composition of our CTD-ILD cohort, resulting in a high proportion of patients with RA-ILD. The primary outcome assessed in this analysis was all-cause mortality, therefore some patients, particularly in the CTD-ILD subgroup, may have died of causes other than endstage ILD, including nonpulmonary complications of their underlying rheumatologic disease, infections, coronary artery disease, cancer, or other complications related to immunosuppression. Although the study was prospective in design, missing data were unavoidable. In particular, the diagnosis of ILD was determined by radiographic imaging without lung biopsies to confirm the diagnosis in the majority of our patients. Identification of UIP and NSIP was based on radiographic patterns observed on HRCT, which does not always reliably correlate with histologic diagnoses[39,40], and we did not determine fibrosis severity scores. In addition, autoantibody data were incomplete and therefore we were unable to assess the prognostic effects on the survival of patients with CTD-ILD of autoantibodies, such as anti-Scl-70, RF, or anticyclic citrullinated peptide. Lastly, we were not able to compare patients with SSc-ILD to those with other specific CTD-ILD diagnoses, given the small numbers of patients with SLE, MCTD, Sjögren's syndrome, and the inflammatory myopathies. We did, however, observe a trend toward poorer survival in RA-ILD compared with SSc-ILD (5-year survival 51% vs 77%; p = 0.08).

Our study demonstrates the importance of diagnosing and differentiating CTD subtypes in patients with ILD.

While the incidence of CTD among patients with ILD is relatively low, the identification of a specific CTD subtype may significantly affect prognosis. Routine screening for ILD in patients with SSc may in part be responsible for the better survival we observed in this subgroup compared with other patients with CTD-ILD. Our study supports the American College of Chest Physicians' recommendation that all patients with SSc undergo annual PFT to screen for ILD. Larger, multicenter studies are necessary to confirm our findings.

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