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ORIGINAL ARTICLE

Comparison of Disease Progression and Mortality of Connective Tissue Disease-Related Interstitial Lung Disease and Idiopathic Interstitial Pneumonia

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Objective. **To compare disease progression and mortality between idiopathic interstitial pneumonia (IIP) and interstitial lung disease (ILD) due to connective tissue diseases (CTD) including scleroderma, rheumatoid arthritis, systemic lupus, polymyositis, dermatomyositis, Sjögren's syndrome, and mixed CTD.**

Methods. **A case-control study of patients with CTD-ILD (n = 46) and IIP controls (n = 51), seen at the University of Michigan between July 1,1998 and June 30,1999 and followed until March 30, 2002, was conducted. Survival analysis and Cox regression were performed to estimate survival, accounting for demographic and clinical parameters, including pulmonary function tests and high resolution computed tomography (HRCT) diagnosis and scoring.**

Results. **Median followup time was 4.4 person-years. Five-year survival in the IIP group was 51.9% (95% confidence interval [95% CI] 30.8–69.4) versus 43.4% (95% CI 21.1–63.9) in the CTD-ILD group. There were no significant differences among HRCT diagnostic categories between IIP and CTD-ILD. A fibrotic score ≥2 was associated with decreased survival among the entire group. Age at diagnosis and most recent forced vital capacity were significant predictors of mortality when adjusted for IIP versus CTD-ILD diagnosis, sex, and interstitial score.**

Conclusion. **Contrary to expectation, CTD-ILD compared with IIP appears to be associated with a worse prognosis when adjusted for age. A higher fibrotic score is suggestive of decreased survival.**

KEY WORDS. Interstitial lung disease; Connective tissue disease; Idiopathic interstitial pneumonia.

INTRODUCTION

Interstitial lung disease (ILD) represents a heterogeneous group of noninfectious acute and chronic diseases that involve the lung parenchyma. ILDs are associated with significant morbidity and mortality, particularly when fibrosis occurs. They may either occur as an idiopathic condition termed idiopathic interstitial pneumonia (IIP), or in association with many systemic connective tissue diseases (CTD). The clinical presentations of IIP and CTD-ILD are similar, with the typical patient presenting with insidious onset of dyspnea, sometimes associated with a nonproductive cough, and having bibasilar end-inspiratory dry rales on auscultatory examination. Although the clinical course is variable, there may be a progression to "end-stage lung" in which there is almost complete loss of alveolar-capillary units. Patients may eventually develop cor pulmonale; death usually results from respiratory insufficiency and anoxia (1).

The most common pathologically distinct categories of ILD are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). Histopathologically, UIP is characterized by fibrosis, fibroblastic foci, inflammation, and architectural destruction. NSIP is characterized by a patchy pattern of inflammation and fibrosis (2). An international consensus statement in 2001 determined that the term idiopathic pulmonary fibrosis (IPF) should be assigned only to those patients with UIP (3,4). However, older studies do not make this distinction, and IPF in most cases represents heterogeneous histopathologic categories. This may cause difficulty in interpreting survival in previous studies because the presence of histologic UIP is the

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most important determinant of survival (5). Overall, CTD-ILDs are more often associated with NSIP than UIP in comparison with patients with IIP, and NSIP is seen more frequently in systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), and mixed connective tissue diseases (MCTD), though rheumatoid arthritis (RA) is more frequently associated with UIP (2).

In the absence of pathologic material, high resolution computed tomography (HRCT) has assumed a greater role in the diagnosis and management of IIP and CTD-ILD. The diagnostic accuracy of HRCT in conjunction with clinical evaluation by experienced physicians has been shown to diagnose IPF with a positive predictive value of 80% (6). The patterns of ILD on HRCT are described as either ground glass or honeycombing for alveolar and interstitial findings, respectively. Honeycombing is defined as cystic spaces, usually peripheral in location and with the presence of clearly definable walls. A diffuse or focal area of hazy increased attenuation in the lung parenchyma, not associated with obscuration of underlying vessels, is defined as ground-glass opacity (7,8).

HRCT can suggest the underlying pathologic category as summarized by Hwang et al (9), and has been used to distinguish between UIP and NSIP. On HRCT, UIP is characterized by irregular subpleural areas of honeycombing and ground-glass opacity, and NSIP is characterized by patchy, diffuse areas of ground-glass opacity with associated areas of consolidation and irregular septal lines (9). However, reaching a consensus on HRCT categories may be problematic. Flaherty et al reported results in 96 patients with IIP for whom both HRCT and histopathologic data were available (10). The agreement on diagnoses of definite or probable UIP or NSIP between 2 experienced thoracic radiologists was only 35%, which improved to 64% when definite and probable categories were combined. An HRCT diagnosis of definite (n = 16) or probable (n = 11) UIP was associated with a histologic diagnosis of UIP 100% of the time. However, when the HRCT diagnosis was either indeterminate (n = 25), probable NSIP (n = 25), or definite NSIP (n = 19), the histologic diagnosis was UIP in 67% of patients. Patients with an HRCT diagnosis of UIP had a worse prognosis than those with a different HRCT diagnosis, regardless of pathologic diagnosis. An alternative to categorizing ILD into pathologic groups by HRCT is to report fibrosis and alveolar scores (11). A higher fibrosis score is associated with reduced response to therapy and reduced survival in patients with IIP (11). It is thought that patients with CTD-ILD have a better prognosis than patients with IIP (12–14); however, this assertion has been challenged using data from the United Kingdom General Practice Research Database in a cohort dominated by patients with RA (15).

We hypothesized that patients with CTD-ILD would have a better prognosis in comparison with patients with IIP due to earlier diagnosis in the former as a consequence of nonpulmonary manifestations, and due to more aggressive treatment by rheumatologists accustomed to intensive immunomodulatory therapies for other manifestations of CTD. No study to date has compared a large number of patients in the 2 groups using in-depth analysis of the impact of HRCT diagnosis and scoring, different treatment modalities, and the overall disease burden. We compared mortality among a cohort of patients with IIP and CTD-ILD including RA, SSc, PM, DM, systemic lupus erythematosus (SLE), MCTD, and Sjögren's syndrome at a single tertiary care institution. Furthermore, we evaluated these patients to determine factors associated with mortality and disease evolution.

SUBJECTS AND METHODS

Subjects. A case-control study design was used. Controls were defined as individuals with IIP (n = 51) and cases were defined as patients with CTD-ILD (n = 46). Subjects were identified based on International Classification of Diseases, Ninth Revision, Clinical Modification codes for IPF or ILD in conjunction with a CTD diagnosis. A stratified random sample was obtained to yield equivalent-size groups of patients with IIP and CTD-ILD. The study population included individuals with relevant codes who visited the University of Michigan as outpatients or inpatients between July 1, 1998 and June 30, 1999, and who were followed until March 30, 2002. At that time, the diagnosis of IPF was not specific to a histopathologic diagnosis of UIP, as is now the case (3,4). Patients with CTD were diagnosed and followed in the rheumatology clinics at the University of Michigan by the treating rheumatologist. The clinical diagnoses were validated by chart review to confirm that patients met the criteria for IIP and CTD-ILD. The clinical records of each patient were reviewed for demographic data, clinical history, physical examination, radiographic data, and pathologic data. This study was approved by the University of Michigan Institutional Review Board.

Clinical data. Information directly obtained from patient charts included date of birth, sex, race, date of death and/or date lost to followup, onset of ILD, serologic tests (antinuclear antibody titer and pattern, rheumatoid factor, anti-Ro, anti-La, anti-Smith, antineutrophil cytoplasmic antibody titer, anti–Scl-70, anti–Jo-1, and double-stranded DNA antibodies), smoking activity (active, previous, never), pulmonary function tests (diffusing capacity for carbon monoxide [DLCO], forced vital capacity [FVC], forced expiratory volume [FEV_1], and total lung capacity [TLC]), medications and reasons for discontinuation of medicine, and echocardiography for right atrial pressure and right ventricular systolic pressure (RVSP) for cor pulmonale. Other information abstracted from patient records included symptom-years (defined as duration of symptoms from date of symptom onset to diagnosis) and pack per year smoking history. A Charlson comorbidity index (CCI) score was generated for each patient (16). CCI scores provide additive ordinal values to classify the presence and degree of comorbid medical illnesses. The prognostic value of the CCI has also been studied and performed well in predicting mortality and functional decline (17).

HRCT scoring. HRCTs were reviewed independently by the 2 thoracic radiologists, without knowledge of clinical

Table 1. Demographic features of patients with idiopathic interstitial pneumonia (IIP) and connective tissue disease-associated interstitial lung disease (CTD-ILD)*

	No.	Age, years Mean ± SD	Sex F	Race W	Race AA	Race Unknown	Race Asian/Hispanic	CCI scores Mean ± SD	Smoking‡ Active	Smoking‡ Never
IIP	51	63 ± 12	51	78	2	16	4	1.6 ± 0.8	14	31
CTD-ILD	46	51 ± 13†	65	70	24†	4	2	1.8 ± 1.3	17	52
RA	14	58 ± 10	50	86	7	0	7	1.78 ± 1.25	29	29
SSc	11	48 ± 15	73	45	45	9	0	1.8 ± 1.25	9	55
MCTD	6	52 ± 17	83	83	17	0	0	2.8 ± 2.31	17	67
UCTD	1	41 ± NA	100	100	0	0	0	1 ± NA	‡	‡
PM	4	49 ± 10	100	75	0	25	0	1.25 ± 0.5	0	75
DM	5	41 ± 10	40	40	60	0	0	1 ± 0	20	60
SLE	2	47 ± 21	100	50	50	0	0	2 ± 1.41	0	100
SS	2	54 ± 10	50	100	0	0	0	2.5 ± 2.1	0	100
Other	1	41 ± NA	0	100	0	0	0	2 ± NA	100	0

* Unless otherwise indicated, values are percentages. CCI = Charlson Comorbidity Index; F = female; W = white; AA = African American; RA = rheumatoid arthritis; SSc = systemic sclerosis; MCTD = mixed connective tissue disease; UCTD = undifferentiated connective tissue disease; NA = not applicable; PM = polymyositis; DM = dermatomyositis; SLE = systemic lupus erythematosus; SS = Sjögren's syndrome.
† $P < 0.05$
‡ Data is missing/unknown if the sum of active and never is <100%.

diagnosis. HRCTs were available for 70 patients. HRCT examinations were performed using 1.0-mm or 1.5-mm thick collimation at 1-cm intervals throughout both entire lungs during inspiration in the supine position on either a CT HiLite Advantage scanner, HiSpeed Advantage scanner, CTi, LightSpeed, or LightSpeed Ultra (General Electric Medical Systems, Milwaukee, WI) in nonhelical mode at the University of Michigan. Previously validated HRCT scores were used (11). Each lobe was scored on a scale of 0–5 for both alveolar and interstitial abnormality, depending on the percentage of each lobe involved and the type of involvement. Ground-glass opacity and honeycombing represented the alveolar and interstitial findings, respectively. The scores for each lobe were averaged for both readers for the data analysis. Each radiologist provided a diagnosis based on HRCT characteristics. If conflicts regarding the HRCT diagnosis occurred, the HRCTs were re-read by both radiologists and a consensus diagnosis was reached if possible.

Pulmonary function tests. Pulmonary function tests including spirometry, lung volumes, and DLCO of the lungs were performed at the University of Michigan. Data collected from pulmonary function tests included FEV_1, FVC, TLC, and DLCO. Results of the pulmonary function tests were expressed as percentage of predicted (ppd) values for the patient's age, sex, and height. Mean values for each of these pulmonary function test parameters at baseline were compared with the mean of all available values for each patient to evaluate their predictive value.

Statistical analysis. Demographic characteristics were compared between the IIP and CTD groups by 2-sample *t*-tests or chi-square tests, as appropriate for continuous and categorical variables, respectively. Unless otherwise specified, continuous measures are expressed as mean ± SD. One-way analysis of variance was used to compare continuous measures between the CTD-ILD groups. Survival analysis was performed using left-truncated Kaplan-Meier estimates. The left-truncated approach adjusts for survival bias (individuals with longer survival are more likely to be included than those with short survival in prevalence studies). Therefore, we estimated the probability of survival as a function of time since diagnosis, with the risk of death restricted to the observation period, i.e., after July 1, 1998. Similarly, left-truncated univariate and multivariable Cox proportional hazards regression were used to estimate hazard ratios. Testing of the proportional hazards assumption was performed. Survival curves were compared using log-rank tests. Additional Kaplan-Meier estimates comparing the survival functions between patients with IIP and those with CTD-ILD were adjusted for age at diagnosis (standardized to age 40), by calculation of separate Cox regression estimates of the baseline survivor functions for each group.

Pulmonary function tests were modeled in several different ways, due to their time-varying nature and lack of uniformity in the timing of pulmonary function test evaluations in the study population. FVC and FEV_1 were evaluated more frequently than TLC and DLCO, therefore pulmonary function test analyses focused on FVC and FEV_1. An intrapatient mean was computed for each type of pulmonary function test (FVCppd, FEV_1ppd, TLCppd, and DLCOppd). Also, the most recent FVCppd and FEV_1ppd values per patient prior to the end of followup were determined. Data management and analysis were performed using Stata version 8.0 (Stata, College Station, TX).

RESULTS

Demographics. Baseline patient characteristics are summarized in Table 1. A higher proportion of patients with CTD-ILD had never smoked compared with those with IIP (52% versus 31%; $P = 0.062$). Although both groups were predominantly white, the overall racial dis-

Table 2. High resolution computed tomography (HRCT) diagnoses and scores for idiopathic interstitial pneumonia (IIP) and connective tissue disease-associated interstitial lung disease (CTD-ILD) groups*

	HRCT diagnoses						HRCT scores		
	n	Normal	NSIP	UIP	HP	Other†	n	Fibrosis Mean ± SD	Alveolar Mean ± SD
IIP	31	6	32	45	10	6	36	1.5 ± 0.9	1.3 ± 1.1
CTD-ILD	27	0	37	41	4	19‡	34	1.4 ± 1.0	1.2 ± 0.9
RA	9	0	11	56	11	22	11	1.6 ± 1.0	1.2 ± 1.1
SSc	8	0	63	38	0	0	9	1.7 ± 1.0	1.3 ± 1.0
SLE	1	0	0	100	0	0	1	3.8 ± NA	0 ± NA
PM	3	0	67	33	0	0	3	0.7 ± 0.2	1.5 ± 1.1
DM	2	0	100	0	0	0	5	0.8 ± 0.4	1.4 ± 0.6
MCTD	4	0	0	25	0	75	5	0.8 ± 0.7	1.3 ± 1.0

* Unless otherwise indicated, values are percentages. HRCT was not available for patients with Sjögren's Syndrome or undifferentiated connective tissue disease. NSIP = non-specific interstitial pneumonitis; UIP = usual interstitial pneumonitis; HP = hypersensitivity pneumonitis. See Table 1 for additional definitions.
† Includes emphysema.
‡ Includes emphysema, rheumatoid nodules.

tribution differed significantly ($P = 0.002$); 24% of the CTD-ILD group was African American versus 2% in the IIP group. Patients with CTD-ILD were significantly younger than those with IIP (mean ± SD 51 ± 13 years versus 63 ± 12 years; $P < 0.001$). The mean ± SD number of symptom-years was similar (2.1 ± 2.8 years versus 1.6 ± 1.7 years; $P = 0.34$); however, these data were only available for 31 patients with IIP and 36 patients with CTD-ILD. Sex distribution and mean CCI scores were also similar between groups.

High resolution CT. HRCTs were available and scored on 70 patients (36 IIP and 34 CTD-ILD). A consensus HRCT diagnosis was established for 58 patients (83%). Among the 31 patients with IIP, 45% had UIP and 32% had NSIP; and among the 27 patients with CTD-ILD, 41% had UIP and 37% had NSIP (Table 2). Some patients with a clinical diagnosis of ILD also had other HRCT diagnoses, including emphysema in both groups and rheumatoid nodules in the CTD-ILD group. There were no statistically significant differences in the diagnostic categories between IIP and CTD-ILD ($P = 0.356$). In the CTD-ILD group, there was also no significant difference in the HRCT diagnosis by CTD group ($P = 0.114$); however, the patients with SSc were more frequently classified as NSIP (63%) and patients with RA were more frequently classified as UIP (56%).

HRCT fibrotic and alveolar scores were not significantly different between the 2 groups ($P = 0.619$) (Table 2). Among the patients with CTD-ILD, fibrotic scores differed significantly, with average scores being higher among patients with SSc and RA ($P = 0.016$). Alveolar scores did not vary significantly between patients with CTD-ILD ($P = 0.826$). A fibrotic score ≥2 was strongly associated with an HRCT diagnosis of UIP; 76% of patients with UIP had a fibrotic score ≥2, versus 5% of patients with NSIP ($P = 0.000$).

Tests of pulmonary function. Pulmonary function test data were available for 96 patients; FVC and FEV_1 were available for 96 patients, TLC for 55 patients, and DLCO for 62 patients. There was no statistical difference in mean functional measures between the IIP and CTD-ILD groups (Table 3). FVCppd or FEV_1ppd were not correlated with interstitial score. Mean FVCppd was negatively correlated with alveolar score ($r = -0.316$, $P < 0.008$), but FEV_1ppd was not.

Mortality. One patient was excluded from the survival estimates because the date of diagnosis was unavailable. The total followup time was 204.8 person-years, with a median of 4.4 person-years (interquartile range 2.0–8.9 person-years). The 5-year survival for both groups was 48.9% (95% confidence interval [95% CI] 33.5–62.6). Five-year survival in the IIP group was 51.9% (95% CI 30.8–69.4) compared with 43.4% (95% CI 21.1–63.9) in the entire CTD-ILD group. The overall survival between groups appears to be similar, though formal significance testing is not applicable because the survival curves cross at approximately 7.2 years after diagnosis (Figure 1A). Because the CTD-ILD group was significantly younger, Kaplan-Meier estimates were also adjusted for age at diagnosis (Figure 1B); although survival appears to improve in the IIP group relative to the CTD-ILD group when adjusted for age, the apparent difference is not significant ($P = 0.267$). There was also no correlation of RVSP or histopathologic diagnosis with mortality, although this analysis was limited due to the few number of patients with this data available.

HRCT fibrotic score was a useful discriminator (Figure 2). An interstitial (fibrotic) score ≥2 predicted mortality among the entire group ($P = 0.059$ by log rank test). A similar trend was seen among the CTD-ILD group, though significance was not tested because the curves crossed at 2.3 years. There was a trend towards decreased survival corresponding to an HRCT diagnosis of UIP compared with NSIP in both groups; however, because this analysis was restricted to the 45 patients with either UIP or NSIP, there was insufficient power to reach statistical significance ($P = 0.228$). Also, recalling that a fibrotic score ≥2 was strongly associated with an HRCT diagnosis of UIP,

Table 3. Predicted percentage for pulmonary function tests for idiopathic interstitial pneumonia (IIP) and connective tissue disease-associated interstitial lung disease (CTD-ILD) groups*

		Pulmonary function test			
	No.	**FVC**	**FEV1**	**TLC**	**DLCO**
IIP	50	65 ± 19	73 ± 19	77 ± 18	43 ± 17
CTD-ILD	46	64 ± 18	69 ± 19	77 ± 18	47 ± 19
RA	14	67 ± 11	74 ± 11	79 ± 15	40 ± 16
SSc	11	64 ± 17	69 ± 18	74 ± 15	41 ± 17
SLE	2	48 ± 4	53 ± 6	62 ± 0	22 ± 16
PM	4	51 ± 17	54 ± 17	72 ± 5	60 ± 13
DM	5	59 ± 24	62 ± 25	70 ± 19	57 ± 24
SS	2	53 ± 17	54 ± 20	71 ± 11	56 ± 0
MCTD	6	69 ± 19	75 ± 18	85 ± 24	58 ± 16
UCTD	1	120 ± NA	122 ± NA	132 ± NA	81 ± NA
Other	1	49.9 ± NA	51.4 ± NA	58 ± NA	43.4 ± NA

* Values are mean ± SD. FVC = forced vital capacity; FEV_1 = forced expiratory volume; TLC = total lung capacity; DLCO = diffusing capacity for carbon monoxide. See Table 1 for additional definitions.

the relationship between fibrotic score and survival may be confounded by HRCT diagnosis. It is not feasible to examine their independent effects in a multivariable Cox model due to the small size of the subset where an HRCT consensus diagnosis of NSIP or UIP could be reached.

The univariate and multivariable Cox models showed that the age at diagnosis was found to be a significant predictor of mortality; the hazard of death increased by 4% for every 1-year increase in age ($P = 0.027$). The most recent values of FVCppd and FEV_1ppd were shown to be inversely related with hazard of death; both demonstrated a 2% decrease in hazard for every unit increase of FVCppd or FEV_1ppd. Age at diagnosis and most recent FVC remained significant in the multivariable model including IIP and CTD-ILD diagnosis, sex, and interstitial score ≥2. Because of the high degree of collinearity between FVC and FEV_1, these variables were not included in the same model. However, results were similar when FEV_1 was substituted for FVC. There was no evidence for interactions between variables included in the multivariable model.

Treatment effect. The various treatment modalities received by each of the groups were compared (Table 4). There was a significantly greater use of cyclophosphamide, methotrexate, and intravenous corticosteroids in the CTD-ILD group. Prednisone use and dose was not significantly different between the 2 groups. Survival was not associated with treatment with cyclophosphamide, methotrexate, or corticosteroids. Azathioprine use was significantly higher in the IIP group versus the CTD-ILD group (67% versus 41%; $P = 0.029$), though mean daily dose among those taking azathioprine was similar (124 ± 34 mg/day versus 118 ± 43 mg/day). Furthermore, azathioprine use was associated with nonsignificant improvement in survival among the total group ($P = 0.078$); when stratified by IIP versus CTD-ILD, the improved survival persisted among the CTD-ILD group ($P = 0.084$), but not the IIP group ($P = 0.636$). However, because of confounding by indication (i.e., disease features such as severity impacting choice of pharmacologic intervention), caution must be applied when interpreting the associations between treatment and survival.

DISCUSSION

ILD remains difficult to treat and is a significant cause of mortality in patients with CTD. This study confirms the poor prognosis in ILD and reveals that a CTD diagnosis does not confer a survival benefit compared with idiopathic disease. Our data suggest that the survival rate in the CTD-ILD group is in fact worse, when adjusting for age. Our study also demonstrates that an HRCT fibrosis score ≥2 is associated with increased mortality in patients with IIP and CTD-ILD.

HRCT is now commonly used to diagnose and follow ILD. As in the present study, an HRCT diagnosis of UIP and a fibrosis score ≥2 in patients with IIP were previously demonstrated to be associated with increased mortality (10,11). The usefulness of a fibrosis score rather than reliance on an HRCT diagnosis is demonstrated by the fact that a consensus diagnosis between 2 experienced radiologists could only be reached for 83% of patients. Our study relied on HRCT due to the absence of confirmatory pathologic diagnoses in most patients. However, even with lung biopsies available, there can be interlobar and intralobar histologic variability, and patients with an HRCT diagnosis of NSIP often have a histopathologic diagnosis of UIP (5). It has also been shown that patients with a typical HRCT appearance of UIP experience the highest rate of mortality when compared with patients with NSIP and those with histopathologically proven UIP that do not have the typical HRCT characteristics of UIP (10). A histopathologic diagnosis of UIP nevertheless has important implications, as the 5-year survival in IIP was 20–40% in patients with UIP compared with 70–85% in patients with NSIP (18).

Other studies examining the HRCT or histopathologic patterns of patients with CTD as predictors of survival were different from the present study in design, likely accounting for differing conclusions. A previous study of

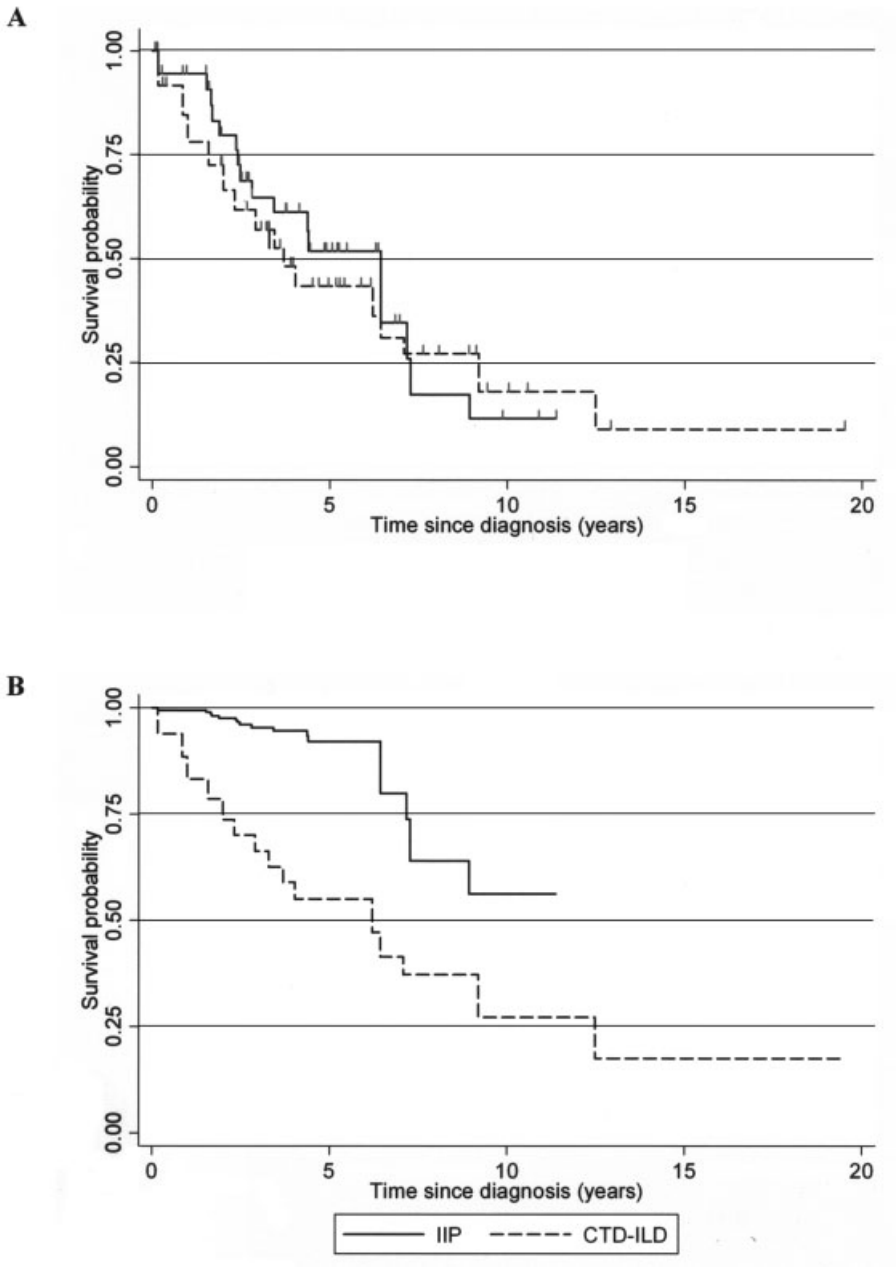

Figure 1. A, Kaplan-Meier estimates comparing survival between patients with idiopathic interstitial pneumonia (IIP) (n = 50) and connective tissue disease-related interstitial lung disease (CTD-ILD) (n = 46) groups. Each tick mark corresponds to a time of patient censoring. **B,** Comparison of survival rates between IIP and CTD-ILD groups when adjusted for age at diagnosis ($P = 0.267$ based on bivariate Cox regression model).

patients with SSc showed that NSIP was the most frequent histopathologic pattern; however, there was no survival difference between NSIP and UIP, and outcome was linked more strongly to DLco trends than to histopathologic diagnosis (19). A recent study of patients with PM/DM also demonstrated a higher prevalence of NSIP (80%) and an absence of honeycombing on HRCT (14). These patients had a much better survival rate than historical controls with IIP. In another study of PM/DM, patients with histopathologic UIP had reduced survival (20). In our CTD-ILD sample, 20% of the patients had PM/DM. We did not find a survival difference between individual diagnostic groups and the group as a whole, but we likely did not have sufficient numbers of patients with each CTD diagnosis to find small survival differences. In agreement with the present study, another recent study challenged the assertion that patients with CTD-ILD have a better outcome than those with idiopathic disease (15). Based on data from the United Kingdom General Practice Research Database, Hubbard and Venn found that the median survival time was 2.4 years for patients with CTD-ILD versus 2.6 years for patients with IIP (15). The predominant CTD

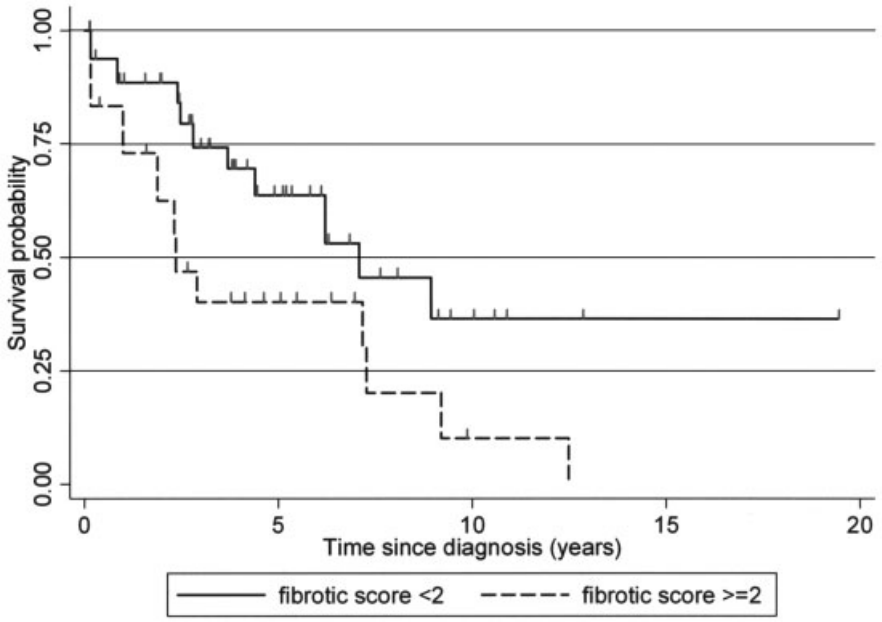

Figure 2. Kaplan-Meier estimates comparing survival by high resolution computed tomography fibrotic score among 70 patients with idiopathic interstitial pneumonia and connective tissue disease-related interstitial lung disease ($P = 0.059$). Each tick mark corresponds to a time of patient censoring.

in this study was RA (80%) rather than SSc, PM, or DM, and the extent to which the category of ILD impacted overall outcome was unclear.

Our study also demonstrated clinical utility for pulmonary function testing. The most recent values of FVCppd and FEV_1ppd demonstrated a 2% decrease in hazard for every unit increase of FVCppd or FEV_1ppd. The univariate and multivariable Cox models demonstrated that the age at diagnosis and most recent FVC were significant predictors of mortality. The hazard of death increased by 4% for every 1-year increase in age, and 4% for every unit decrease of FVCppd, when adjusted for diagnosis of IIP versus CTD-ILD, sex, and interstitial score. It has previously been shown that among patients with SSc, former smokers are at a very high risk for rapid deterioration of pulmonary function and have significantly greater rates of loss of FVC and DLco than either nonsmokers or current smokers (21). In our study, we observed a greater number of patients in the CTD-ILD group who had never smoked, though there was no difference in mean values for pulmonary function tests. We were unable to correlate HRCT scores with pulmonary function test in this study, likely due to the retrospective design. A prospective study with paired HRCT and pulmonary function test evaluations may demonstrate a closer relationship between these measures.

As this and other studies have shown, fibrosis is predictive of poor clinical outcome. Histologically, fibroblastic foci are seen in UIP, and Flaherty et al showed that patients with UIP associated with CTD have fewer fibroblastic foci and improved survival compared with those with idiopathic UIP (22). In that study, however, there were only 9 patients with CTD in comparison with 99 patients with idiopathic UIP, which could account for the different results compared with the present study. The improved survival in patients with CTD could also be confounded by lead time bias accounting for the difference.

There were no significant survival differences between the groups based on treatment modalities, including cyto-

Table 4. Treatment modalities for idiopathic interstitial pneumonia (IIP) and connective tissue disease-associated interstitial lung disease (CTD-ILD) groups*

	IIP (n = 51)	CTD-ILD (n = 46)	*P*
Oral prednisone	34 (66.7)	38 (82.6)	NS
IV corticosteroids	2 (3.9)	11 (23.9)	0.015
Cyclophosphamide	2 (3.9)	15 (32.6)	0.000
Cyclophosphamide oral dosage†	125 ± 35 mg/day	96.9 ± 28 mg/day	NS
Methotrexate	0 (0%)	15 (32.6%)	0.000
Azathioprine	34 (66.7%)	19 (41.3%)	0.029
Azathioprine dosage†	124 ± 34 mg/day	118 ± 43 mg/day	NS

* Unless otherwise indicated, values are frequency (percentage) or mean ± SD. NS = not shown; IV = intravenous.
† Mean dosage among those taking the medication.

toxic agents. This could reflect the lack of available agents for optimal management of ILD, or it could reflect diagnosis at a time when intervention with the currently used immunosuppressive agents is no longer useful. There are few randomized, controlled studies of patients with IIP demonstrating efficacy of treatment. Antiinflammatory agents, including corticosteroids, cytotoxic agents, and antifibrotic agents such as colchicine, have not demonstrated efficacy in patients with IPF (23). A prospective, double-blind, randomized, placebo-controlled trial suggested that azathioprine and corticosteroids may improve lung function tests and have a potential survival advantage in IIP (24).

In the CTD-ILD group, early treatment with cytotoxic agents in the patients with active alveolitis is suggested in RA, SSc, SLE, and MCTD, and less so in Sjögren's-related ILD (25). Corticosteroids used in the early stages improve pulmonary function tests and alveolitis, and there is promising evidence for the successful treatment of alveolitis with cyclophosphamide (25); however, prospective, randomized trials are required for better evaluations of these treatment modalities (26). Retrospective studies of patients with SSc-related ILD have shown significant improvement in pulmonary function tests with either oral or intravenous cyclophosphamide (27,28), and randomized, double-blind, placebo-controlled trials with oral cyclophosphamide are currently ongoing. Uncontrolled studies of patients with RA-related ILD have used methotrexate (29), azathioprine (30), and cyclosporine (31), either alone or in combination with steroids, and have suggested improvement in pulmonary function tests. Case reports in RA-related ILD indicated a beneficial effect of infliximab over 1 year and resulted in improvement in dyspnea, cough, exercise intolerance, and stabilized pulmonary function tests (32). Prospective, randomized, controlled trials are required to determine the optimal management of CTD-ILD. Our data suggest that patients with an HRCT fibrosis score <2 may have a better prognosis, and patients with ILD could be stratified based on the fibrotic score. Study designs should consider this in the randomization scheme or as a covariate in the analysis.

There are a number of limitations to this study, a major one being the retrospective nature of the data collection, which impacted the uniformity of the data available for evaluation. For example, patients with IIP may have features of CTD that could be identified with specific serologic tests that were not routinely collected, making it possible that some patients were misclassified. The cause of death was also not determined in either the IIP or in the CTD-ILD group, and we cannot be certain that the cause of death was always associated with lung disease. However, the fact that specific features of the pulmonary process were predictors of mortality in both groups suggests that lung disease played an important role in mortality. We also were not able to systematically assess the hemodynamic parameters and ascertain if pulmonary hypertension affected the survival data in the CTD-ILD group due to the retrospective nature of the study. The onset of symptoms in the 2 groups also could not be accurately determined from the patient's history. We also acknowledge the fact that there is a lack of data studying the effects of targeted biologic therapy, such as the effect of tumor necrosis factor α inhibitors on the mortality differences in the CTD-ILD group. We hope to conduct prospective studies in the future to determine if there would be significant survival differences when these agents are used.

In summary, patients with either IIP or CTD-ILD have a poor prognosis and similar mortality rate. This appears to be irrespective of the CTD diagnoses or treatment modalities. However, in each subset of CTD-ILD there are limited numbers of patients to draw conclusions between each CTD diagnosis. Our data support the notion that the most important factor contributing to poor outcome in patients with CTD is the presence of fibrosis. Therefore, it is imperative for rheumatologists to have screening guidelines for ILD with the goal of diagnosing patients with CTD-ILD before fibrosis occurs. We suggest that HRCTs obtained while screening for CTD patients with respiratory symptoms should be scored for fibrosis because an HRCT fibrosis score ≥ 2 predicts a subset of CTD patients with a worse prognosis, regardless of the HRCT diagnostic category. It could also be suggested that an HRCT diagnosis of UIP or high HRCT fibrosis scores could identify these patients with poor prognosis without confirmatory biopsies. Further research and prospective studies to compare the 2 groups with HRCT scoring, pulmonary function tests, clinical parameters, and treatment modalities will better delineate ILD and the prognostic implications in the optimal patient management of ILD in patients with CTD-ILD.

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