Pulmonary Function and Survival in Idiopathic vs Secondary Usual Interstitial Pneumonia

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BACKGROUND: The usual interstitial pneumonia (UIP) pattern of lung injury may occur in the setting of connective tissue disease (CTD), but it is most commonly found in the absence of a known cause, in the clinical context of idiopathic pulmonary fibrosis (IPF). Our objective was to observe and compare longitudinal changes in pulmonary function and survival between patients with biopsy-proven UIP found in the clinical context of either CTD or IPF.

METHODS: We used longitudinal data analytic models to compare groups (IPF [$n = 321$] and CTD-UIP [$n = 56$]) on % predicted FVC (FVC %) or % predicted diffusing capacity of the lung for carbon monoxide (DLCO %), and we used both unadjusted and multivariable techniques to compare survival between these groups.

RESULTS: There were no significant differences between groups in longitudinal changes in FVC % or DLCO % up to diagnosis, or from diagnosis to 10 years beyond (over which time, the mean decrease in FVC % per year [95% CI] was 4.1 [3.4, 4.9] for IPF and 3.5 [1.8, 5.1] for CTD-UIP, $P = .49$ for difference; and the mean decrease in DLCO % per year was 4.7 [4.0, 5.3] for IPF and 4.3 [3.0, 5.6] for CTD-UIP, $P = .60$ for difference). Despite the lack of differences in pulmonary function, subjects with IPF had worse survival in unadjusted (log-rank $P = .003$) and certain multivariable analyses.

CONCLUSIONS: Despite no significant differences in changes in pulmonary function over time, patients with CTD-UIP (at least those with certain classifiable CTDs) live longer than patients with IPF—an observation that we suspect is due to an increased rate of mortal acute exacerbations in patients with IPF.

CHEST 2014; 146(3):775-785

Manuscript received October 11, 2013; revision accepted March 3, 2014; originally published Online First April 3, 2014.

ABBREVIATIONS: AEx = acute exacerbation pulmonary fibrosis; CTD = connective tissue disease; CTD-UIP = connective tissue disease-related usual interstitial pneumonia; DLCO = diffusing capacity of the lung for carbon monoxide; HR = hazard ratio; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NJH = National Jewish Health; PFT = pulmonary function test; RA = rheumatoid arthritis; SSc = systemic sclerosis; UCTD = undifferentiated connective tissue disease; UIP = usual interstitial pneumonia

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FUNDING/SUPPORT: Dr Swigris is supported in part by a Career Development Award from the National Institutes of Health [K23 HL092227].

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DOI: 10.1378/chest.13-2388

The usual interstitial pneumonia (UIP) pattern of lung injury is nonspecific, occurring in a number of clinical contexts, including underlying connective tissue disease (CTD).¹ Idiopathic pulmonary fibrosis (IPF) is diagnosed when, in the absence of a known cause or association, a UIP pattern is confidently identified on high-resolution chest CT scan or surgical lung biopsy.²

Over the last decade, a groundswell of research has advanced understanding of the pathogenesis of UIP.³ Despite these tremendous advances, significant questions and controversies remain: For example, it is unclear whether survival in patients with UIP depends on the underlying clinical context. Equally elusive is a precise understanding of how measures of pulmonary

function change over time in patients with UIP and whether the slopes of these changes vary with the clinical context.

In this study, our objective was to advance our understanding of UIP by testing the following two hypotheses: (1) The slope of decline in pulmonary function parameters, from diagnosis on, among patients with IPF is steeper than those with CTD-related UIP (CTD-UIP); and (2) time from diagnosis to death is shorter among patients with IPF than those with CTD-UIP. For the sake of brevity and to enhance readability, for the remainder of the article we will use “UIP” to mean UIP pattern of lung injury in surgical lung biopsy specimens.

Materials and Methods

Sample Acquisition

We searched our prospectively enrolled, National Jewish Health (NJH) Institutional Review Board-approved interstitial lung disease (ILD) database (NJH Institutional Review Board #HS-1603) for patients evaluated in our program between January 1, 1985, and January 1, 2011, diagnosed with either IPF or CTD-related ILD. We selected patients who had undergone surgical biopsy and were found to have UIP by an NJH pulmonary pathologist using standard criteria. The diagnosis of IPF was made according to available consensus guidelines,^{4,5} and in each case of CTD-UIP, the diagnosis of CTD was made by a board-certified rheumatologist. Pulmonary function was performed as previously described.⁶ FVC and diffusing capacity of the lung for carbon monoxide (DLCO) were expressed and analyzed as percentages of sex-, age- and height-specific predicted values (ie, FVC %⁷ or DLCO %, respectively).

Statistical Approach

All statistical analyses were conducted with SAS, version 9.2 (SAS Institute Inc). We considered $P < .05$ to represent statistical significance. Summary statistics were generated for baseline characteristics. Categorical variables were compared using χ^2 or Fisher exact tests where appropriate.

Pulmonary Function Analyses: FVC % and DLCO % were each modeled over time using linear mixed models, allowing separate fits for the two UIP groups (IPF or CTD-UIP). In other analyses, five groups were analyzed: IPF and four CTD-UIP subgroups (rheumatoid arthritis [RA], systemic sclerosis [SSc], undifferentiated CTD [UCTD], and other [included patients with four other classifiable CTDs]). Initial models were developed using linear and cubic splines to account for nonlinear-

ity of the data; number and location of knots were selected to minimize the Akaike Information Criterion. Subsequent models categorized subjects into groups based on time of last observation in relation to biopsy, for which simple linear trends by time group were determined to be adequate. All models included a random intercept and random slope for time of observation (relative to diagnosis) for subjects to account for the longitudinal data. Some models also included a spatial power covariance structure for repeated measures and/or an additional random term for spline terms if they improved model fits. More detail is included in e-Appendix 1.

Survival Analyses: Kaplan-Meier survival models were fit for life status of subjects as a function of time from biopsy. The log-rank test was used to test for overall differences in survival curves between groups. Vital status was ascertained on October 12, 2012. Subjects were censored on the date of lung transplantation or on October 12, 2012, if their death could not be confirmed in the Social Security Death Index.

Cox proportional hazards models were used to explore time to death between the two (or, in exploratory analyses, five) diagnosis groups, while controlling for potentially influential predictors. Absence of violation of the proportionality assumption was confirmed for the main effect variable with log(–log) plots. The initial Cox models included only the diagnosis group variable. We then built a model that included a priori-selected, potentially influential covariates—sex, age, FVC %, and DLCO %. FVC % and DLCO % were used as time-varying covariates in the survival model, accomplished by using the “counting process style of input.”⁹ An alternative approach determined subject-specific intercept and slope terms for FVC % and DLCO % from the mixed models and used these as separate time-invariant predictors in survival models.

Results

Baseline characteristics of the sample are presented in Table 1. Subjects with IPF were older and more likely to be men than those with CTD-UIP. Physiologic values at diagnosis and median years of follow-up (from diagnosis to vital status ascertainment) did not differ significantly between the two groups.

Pulmonary Function

Figures 1A and 1B show that there were no significant between-group differences in slopes of FVC % or DLCO %. Before the date of diagnosis, the mean decrease in FVC % per year [95% CI] was 5.5 [2.3, 8.8] for IPF and 7.1 [–0.2, 14.4] for CTD-UIP ($P = .71$ for difference); the mean decrease in DLCO % per year was 7.2 [3.7, 10.8] for IPF and 12.8 [4.5, 21.0] for CTD-UIP

TABLE 1] Baseline Characteristics of Subjects

Characteristics	IPF (N = 321)	CTD-Related UIP				
		All (N = 56)	RA (n = 13)	SSc (n = 11)	UCTD (n = 19)	Other (n = 13)
Age, y	66.1 ± 9.1	59.3 ± 11.3	62.9 ± 10.8	59.3 ± 6.9	59.5 ± 12.0	55.4 ± 13.6
Male sex	240 (75)	31 (55)	11 (85)	5 (45)	13 (68)	2 (15)
Ethnicity ^a						
Non-Hispanic	294	54	12	11	18	13
Hispanic	24	2	1	0	1	0
Race ^a						
Asian	4 (1.3)	0	0	1	0	3
Black	1 (0.3)	4 (7)	0	0	0	0
Other	2 (0.6)	0	0	10	19	10
White	311 (97.8)	52 (93)	13			
FVC %	71.4 ± 17.4 (n = 315)	70.6 ± 19.8 (n = 55)	77.3 ± 16.4 (n = 12)	85.5 ± 13.5 (n = 11)	62.6 ± 18.5 (n = 19)	63.6 ± 21.4 (n = 13)
Dlco %	52.3 ± 18.7 (n = 311)	54.6 ± 18.2 (n = 54)	60.7 ± 15.6 (n = 11)	66.2 ± 22.5 (n = 11)	42.6 ± 11.8 (n = 19)	57.0 ± 15.4 (n = 13)
Years follow-up	4.0 (2.1-6.2)	5.1 (2.6-10.2)	5.0 (3.1-11.7)	6.4 (3.3-8.5)	3.8 (2.4-6.7)	7.3 (1.8-11.3)
Died	230 (72)	32 (57)	7 (54)	2 (18)	15 (79)	8 (62)

Entries are mean ± SD, No. (%), or median (first quartile-third quartile). Statistics for FVC % and Dlco % were calculated based on subject measurements closest to diagnosis. Other group contained five subjects with antisynthetase syndrome/dermatomyositis/polymyositis, one with mixed CTD, five with primary Sjögren syndrome, and two with systemic lupus erythematosus. CTD = connective tissue disease; Dlco % = % predicted diffusing capacity of the lung for carbon monoxide; FVC % = % predicted FVC; IPF = idiopathic pulmonary fibrosis; RA = rheumatoid arthritis; SSc = systemic sclerosis; UCTD = undifferentiated connective tissue disease; UIP = usual interstitial pneumonia.

^aThree IPF subjects had unknown ethnicity and race.

Figure 1 – A, B, Change in FVC% (A) or DLCO% (B) over time for sample stratified on clinical context of UIP. Points represent observed values, with fitted (predicted) functions for groups (blue = IPF, red = CTD-UIP) superimposed; predicted means are solid, 95% confidence bands are dashed. Predicted values were obtained using mixed-model fits, using knots (ie, allowing change points) at -0.5 , 0 , 0.5 , 1 , and 2 y from diagnosis. A spatial power covariance structure was included in the model to account for repeated measures within subjects; random effect terms for subjects were also included, as described in e-Appendix 1. There were no significant differences between groups for segments between comparable time points. The plots demonstrate sharper declines near time of diagnosis for both groups. CTD-UIP = connective tissue disease-related usual interstitial pneumonia; DLCO% = % predicted diffusing capacity of the lung for carbon monoxide; FVC% = % predicted FVC; IPF = idiopathic pulmonary fibrosis.

($P = .23$ for difference). After diagnosis, the mean decrease in FVC % per year was 4.1 [$3.4, 4.9$] for IPF and 3.5 [$1.8, 5.1$] for CTD-UIP ($P = .49$ for difference); the mean decrease in DLCO % per year was 4.7 [$4.0, 5.3$] for IPF and 4.3 [$3.0, 5.6$] for CTD-UIP ($P = .60$ for difference). See e-Appendix 1 for more details.

Figure 2 shows spaghetti plots of raw data for within-subject changes in FVC % and DLCO %: It is apparent that some subjects who experienced sharp declines around the time of diagnosis had shorter time of follow up. To systematically assess for the impact of this within-group, differential dropout, we stratified the groups on quartiles of time from diagnosis to last observed pulmonary function test (PFT) and refit models (e-Fig 1); within each quartile of time (< 0.42 years, 0.42 – 1.23 years, 1.24 – 3.33 years, ≥ 3.34 years), the proportions of subjects with IPF vs CTD-UIP, and the predicted mean FVC % at time of diagnosis, between subjects with IPF vs those with CTD-UIP were similar (see e-Appendix 1 for additional details). e-Figure 2 displays graphs of longitudinal changes in FVC % or DLCO % for subjects in the upper quartile of (ie, longest) time from biopsy to last PFT observation.

Nearly one-half of the subjects in each group (IPF or CTD-UIP) had their last PFT obtained < 100 weeks (1.92 years) after diagnosis. Results for additional analyses similar to those previously described for quar-

tiles of follow-up, but using data only from subjects with early (< 100 weeks) or late (≥ 100 weeks) time from diagnosis to last PFT observation, and including analyses on the individual CTD subgroups (eg, RA, SSc, UCTD, other), are displayed in Table 2 and Figure 3. Within groups (or CTD subgroups), subjects with last PFT observations < 100 weeks from biopsy generally had greater declines in lung function than subjects with late last PFT observations; however, significant between-groups differences were not observed. In a logistic regression analysis, while controlling for age, sex, FVC %, and DLCO %, there was no significant difference between any individual CTD subgroup and IPF in the likelihood of last PFT observation ≥ 100 weeks after biopsy (see e-Table 1 for detailed results).

Survival

Among subjects whose last PFT observation was within 100 weeks of diagnosis, there was no significant difference between groups in the proportion of subjects who died (IPF, 74% of 184 vs CTD-UIP, 69% of 29, $P = .63$); however, among those whose last observed PFT was ≥ 100 weeks after diagnosis, there was a difference between groups (IPF, 68% of 132 vs CTD-UIP, 42% of 26, $P = .01$). In the unadjusted analysis, survival was significantly longer in CTD-UIP than IPF (log-rank $P = .003$) (Fig 4). Median survival was 7.1 years (95% CI, 4.6–11.3) for CTD-UIP and 4.4 years (95% CI, 4.1–5.2)

Figure 2 – Spaghetti plots for FVC% or DLCO% by diagnosis group (IPF or CTD-UIP) and last observation (< 100 wk or ≥ 100 wk). See Figure 1 legend for expansion of abbreviations.

for IPF. Among subjects with at least 174 weeks (3.34 years) of follow-up ($n = 92$), there was a trend toward an increased risk of death in the IPF group compared with the CTD-UIP group (IPF, 59% of 76 died vs CTD-UIP, 37% of 16 died, $P = .16$). Figure 5 shows that compared with IPF, survival was longer for the RA-related UIP subgroup (median survival, 5.5 years vs 4.4 years, log-rank $P = .049$) and the SSc-related UIP subgroup (median never reached in the SSc subgroup vs 4.4 years, log-rank $P = .005$); but there was no significant difference in survival between UCTD-related UIP and IPF (median survival 3.8 years vs 4.4 years, log-rank $P = .95$).

In a Cox model that contained only the main effect variable (IPF vs CTD-UIP), IPF was associated with a risk of death during follow-up that was 1.78 times the risk of CTD-UIP (hazard ratio [HR] for IPF = 1.78, $P = .003$). While controlling for potentially influential demographic and pulmonary function predictors in a multi-

variable model, in IPF, the risk of death during the follow-up period was 1.4 times the risk for CTD-UIP (Table 3, e-Fig 3, and for the alternate approach, e-Table 2). The log hazards estimate for the group effect in the model with all covariates was 0.31 (0 indicating no effect), down from 0.58 for the model with group as the only predictor. This suggests that at least one-half of the difference in survival between the IPF and CTD-UIP groups was not accounted for by the demographic and pulmonary variables, but estimates in Table 3 indicate that each of the variables accounted for some of the between-groups survival difference. Also, the HR for the group was 1.68 in the model that included only the group and lung function variables, while the HR for group was 1.54 in the model that included only the group and age variables, indicating that age accounted for more of the group effect than lung function in the unadjusted model (which included group only and its HR was 1.78).

TABLE 2] Intercept and Slope Estimates (With 95% CIs) From Mixed-Model Fits, by Diagnosis Group and Last Time of Follow-up

Statistic	Subjects	IPF	CTD-Related UIP				
			All	RA	SSc	UCTD	Other
FVC %	All	68.0 (66.3, 69.8)	65.6 (61.4, 69.8)	70.5 (61.4, 79.5)	72.7 (63.7, 81.8)	60.7 (53.5, 67.9)	61.4 (52.7, 70.2)
	Intercept, estimated mean FVC % at diagnosis						
	Last follow-up < 100 wk	64.5 (62.3, 66.7)	58.9 (53.3, 64.5)	68.9 (56.9, 81.0)	56.0 (39.6, 72.4)	54.2 (45.1, 63.3)	56.8 (45.8, 67.8)
	Last follow-up ≥ 100 wk	73.5 (70.9, 76.1)	73.1 (67.4, 78.9)	72.0 (59.7, 84.3)	78.7 (68.6, 88.8)	69.9 (58.9, 80.9)	69.5 (56.4, 82.6)
	All	-4.4 (-5.1, -3.6)	-4.2 (-5.9, -2.6)	-3.1 (-6.5, 0.3)	-4.9 (-7.7, -2.1)	-3.7 (-7.0, -0.3)	-4.6 (-8.2, -1.0)
Slope, mean change in FVC % per year							
	Last follow-up < 100 wk	-7.8 (-9.3, -6.3)	-6.5 (-9.9, -3.1)	-1.3 (-8.7, 6.1)	-10.5 (-16.2, -4.8)	-1.4 (-11.0, 8.2)	-7.0 (-13.1, -0.9)
DLco %							
	Last follow-up ≥ 100 wk	-3.3 (-4.1, -2.5)	-3.6 (-5.3, -1.8)	-3.6 (-7.2, -0.1)	-3.4 (-6.4, -0.4)	-3.8 (-7.1, -0.4)	-3.1 (-7.2, 1.1)
DLco %	All	48.3 (46.7, 50.0)	49.5 (45.6, 53.4)	56.7 (48.2, 65.3)	53.5 (45.4, 61.7)	40.6 (34.0, 47.2)	52.8 (44.9, 60.7)
	Intercept, estimated mean DLco % at diagnosis						
	Last follow-up < 100 wk	45.0 (42.9, 47.0)	45.2 (39.9, 50.5)	52.1 (39.8, 64.3)	49.8 (35.1, 64.5)	36.7 (28.2, 45.2)	49.2 (39.3, 59.1)
	Last follow-up ≥ 100 wk	53.4 (51.0, 55.8)	54.3 (49.0, 59.6)	60.6 (49.6, 71.7)	53.5 (44.3, 62.8)	47.5 (37.5, 57.4)	58.7 (46.7, 70.7)
	All	-5.1 (-5.8, -4.5)	-5.3 (-6.8, -3.9)	-6.1 (-9.0, -3.1)	-4.4 (-6.9, -2.0)	-4.9 (-7.8, -2.0)	-6.3 (-9.5, -3.1)
Slope, mean change in DLco % per year							
	Last follow-up < 100 wk	-8.3 (-9.9, -6.8)	-9.7 (-13.0, -6.5)	-4.5 (-12.5, 3.4)	-13.0 (-17.9, -8.1)	-7.6 (-17.8, 2.7)	-8.6 (-13.9, -3.2)
	Last follow-up ≥ 100 wk	-4.4 (-5.1, -3.7)	-4.1 (-5.6, -2.7)	-6.2 (-9.1, -3.4)	-2.0 (-4.4, 0.5)	-4.3 (-7.0, -1.7)	-4.8 (-8.3, -1.3)

Other group contained five subjects with antisynthetase syndrome/dermatomyositis/polymyositis, one with mixed CTD, five with primary Sjögren syndrome, and two with systemic lupus erythematosus. See Table 1 legend for expansion of abbreviations.

Figure 3 – A-B, Estimated mean FVC% (A) and DLCO% (B) by diagnosis group (IPF = blue, CTD-UIP = red) and last time of follow-up (< 100 wk, solid; ≥ 100 wk, dashed) based on linear mixed-model fits. Plots demonstrate that those with earlier last follow-up tended to have steeper declines in lung function. See Figure 1 legend for expansion of abbreviations.

In a Cox model that contained only the group variable (IPF vs each of the four individual CTD categories, with IPF as the reference category), a significant or strong trend toward a protective effect was observed for three CTD subgroups (HR for RA = 0.437, $P = .046$; HR for SSc = 0.175, $P = .014$; HR for other = 0.550, $P = .10$). There was no significant difference in time to death for IPF vs UCTD (e-Fig 4).

Discussion

We identified a cohort of patients who, over a 25-year period, were diagnosed at our center with UIP and met current diagnostic criteria for IPF or rheumatologist-defined CTD. We examined whether pulmonary function over time or survival differed between groups. Interestingly and surprisingly, there were no significant between-group differences in change (decline) over time

Figure 4 – Kaplan-Meier survival curves for sample stratified on clinical context of usual interstitial pneumonia (IPF or CTD-UIP). See Figure 1 legend for expansion of abbreviations.

Figure 5 – Kaplan-Meier survival curves for sample stratified on clinical context for usual interstitial pneumonia, including IPF and CTD-UIP subgroups. Other group contained five subjects with antisynthetase syndrome/dermatomyositis/polymyositis, one with mixed CTD, five with primary Sjögren syndrome, and two with systemic lupus erythematosus. RA = rheumatoid arthritis; SSc = systemic sclerosis; UCTD = undifferentiated connective tissue disease. See Figure 1 legend for expansion of other abbreviations.

in either FVC % or DLCO %, but compared with subjects with CTD-UIP, subjects with IPF had significantly shorter survival. After accounting for age and sex, lung measures only explained (at best) a small amount of group differences in survival; approximately one-half of the between-groups difference in survival remained unexplained after accounting for these variables in the model.

To our knowledge, this is the first study in which longitudinal analytic methods were used to generate rich models for pulmonary function trajectory—from before to long after diagnosis in a large cohort of patients with surgical biopsy-proven UIP. Slopes were steeper among subjects whose last observed PFT was < 100 weeks after biopsy and shallower among subjects whose last observed PFT was later. We had hypothesized and expected—particularly given the results of the survival analysis—that, over the entire observation period, there would be steeper declines in the slopes for pulmonary function in the IPF subgroup than in the CTD-UIP subgroup. Although the aim of our study was different from a study by Brown et al,¹⁰ one finding was similar in both studies: Patients with the longest survival after diagnosis had less severe physiologic impairment at diagnosis.

So, how can we reconcile the survival difference that remained between subjects with IPF and those with CTD-UIP even after accounting for the contributions of age, sex, and pulmonary function? In the absence of

differential dropout between groups, we believe the most likely explanation is that acute exacerbation pulmonary fibrosis (AEx) occurred more frequently (and resulted in more deaths) in the IPF group than in the CTD-UIP group. Only relatively recently has AEx fully grabbed the attention of investigators in the ILD arena.^{11,12} Despite this interest, much about AEx remain poorly understood: Although they are known to occur in ILD of any etiology,¹³⁻¹⁵ based on extremely limited data, they appear most likely to occur in patients with IPF. Unfortunately, in this retrospective study, we were unable to ascertain cause of death, so it was not possible to investigate whether our suspicion—that AEx explains the between-groups survival difference—is true.

In the most frequently cited study of UIP published to date, Park et al¹⁶ examined survival among 239 subjects with surgical biopsy-proven UIP and, like us, found that, compared with the subgroup with CTD-UIP ($n = 36$, 18 with RA), subjects with IPF ($n = 203$) had significantly shorter survival. Controlling for baseline characteristics, subjects with IPF were nearly three times more likely to die during follow-up than subjects with CTD-UIP (HR 2.9, $P = .007$). In a study with similar results, Song et al¹⁷ observed that subjects with IPF had significantly shorter survival than subjects in an RA-dominated CTD-UIP comparator group (median survival for IPF = 40 months vs CTD-UIP = 144 months, $P = .001$). Neither study included estimates for longitudinal changes in pulmonary function.

TABLE 3] HRs (With 95% CIs) From Multivariable Cox Proportional Hazards Models for Survival

Variable	Model							
	1	2	4	3	5	6	7	8
IPF, relative to CTD-UIP	1.78 (1.22, 2.60)	1.73 (1.18, 2.52)	1.54 (1.05, 2.27)	1.48 (1.00, 2.18)	1.68 (1.13, 2.49)	1.45 (0.98, 2.14)	1.46 (0.98, 2.20)	1.37 (0.91, 2.06)
Age, per y increase	...	...	1.02 (1.01, 1.04)	1.02 (1.01, 1.04)	...	1.04 (1.02, 1.05)	1.03 (1.01, 1.04)	1.04 (1.02, 1.05)
Men, relative to women	...	1.32 (1.00, 1.74)	...	1.31 (0.99, 1.74)	...	1.45 (1.09, 1.92)	0.91 (0.67, 1.23)	1.01 (0.74, 1.37)
FVC %, per 10% increase	...	...	...	...	0.87 (0.79, 0.94)	0.72 (0.67, 0.78)	...	0.80 (0.73, 0.88)
DLco %, per 10% increase	...	...	...	...	0.70 (0.63, 0.77)	...	0.65 (0.59, 0.71)	0.72 (0.65, 0.80)

Models show impact of covariates on diagnosis group effect. Model 1 has only the group variable; models 2 through 8 progressively add covariates. HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

The relatively small number of subjects in each CTD subgroup significantly limited our exploratory analyses (particularly those in which the already small CTD subgroups were further divided, as in the < 100 weeks vs ≥ 100 weeks follow-up analyses). Thus, all of those results should be viewed with caution. For SSc, certain existing data suggest the risk for ILD progression is greatest within the first 3 years after diagnosis.¹⁸ Although the extremely small number of subjects in the SSc group precludes our ability to make meaningful inferences, three of 11 subjects with SSc had short follow-up (last observation < 100 weeks from diagnosis); compared with subjects with SSc who had longer follow-up times (≥ 100 weeks), the modeled slopes of decline for both FVC % and DLCO % for the short follow-up subjects were steeper.

Despite the small numbers for the CTD subgroups, the survival analysis results would seem consistent with studies published by other investigators. Like us, neither Vij et al¹⁹ nor Corte et al²⁰ found a difference in survival between subjects with UCTD-ILD (patients Vij et al¹⁹ refer to as having autoimmune-featured ILD) and those with IPF. The question about survival in RA-related UIP vs IPF remains unanswered: Results from different studies are conflicting, and ours were not necessarily intended to solve matters. Clearly, further investigation is required in a larger cohort of patients with RA-UIP.

Our study has limitations. Data from a single center may not be representative of the larger population with IPF or CTD-UIP. The decision about whether and when to perform surgical lung biopsy was made by treating physicians in the context of clinical care. Also, in general, far fewer patients with CTD undergo surgical biopsy. Thus, despite the increased diagnostic certainty gained from surgical biopsy, we cannot discount the possibility that bias was introduced by only including patients who underwent biopsy.

Although we cannot be certain, we strongly suspect that the steeper slopes for FVC % and DLCO % around the time of diagnosis were a reflection of patients getting referred to our tertiary center because they were declining. Indeed, there was a substantial proportion of subjects (in each group) with steep drops in function before and continuing immediately after biopsy; these were the subjects with shorter follow-up, and the ones who were largely responsible for dragging down slopes for FVC % and DLCO % around the time of diagnosis (as demonstrated in Fig 1).

Our database does not contain information on education or socioeconomic status—variables that could have influenced referral and/or its timing to our center. Likewise, our database contains no data on medications; however, during the latter one-half of the 1980s and throughout all of the 1990s, many patients with IPF were treated with immunosuppressive drugs, including prednisone. From 2000 on, some patients with IPF would have enrolled in therapeutic trials, others would have been followed using watchful waiting, and still others would have been treated with a combination regimen including prednisone, azathioprine, and N-acetyl cysteine—which may have altered the slope of their pulmonary function (or survival).²¹ Throughout the entire study period, patients with CTD-UIP would have been more likely than patients with IPF to receive immunosuppressive therapy; we were unable to systematically examine the effects of such therapy, but we cannot discount the possibility that it altered disease course or survival among patients in the CTD-UIP subgroup. Nor were we able to analyze data from high-resolution chest CT scans. Although histologic specimens were not re-reviewed for the purposes of this study, to be included in our database patients' pathologic slides would have been read by one of our program's pulmonary pathologists and

re-read according to updated definitions/criteria in the late 1990s. Some subjects in our study were included in a recently published article in which Solomon et al²² reported the results of a two-center study on survival in patients with RA-UIP. In that study, using the Kaplan-Meier method, the authors found no difference in survival between subjects with RA-UIP and FVC %-matched and DLCO %-matched IPF control subjects. This study extends the results of that study.

Despite these limitations, we have generated novel data on longitudinal disease behavior in patients with UIP and observed that, on balance, the rate of physiologic decline does not differ between groups defined by clinical context, although patients with certain CTDs and UIP live longer than those with IPF. Thus, our data suggest that all UIP may not behave the same across the CTD spectrum. In fact, longitudinal disease behavior and survival among subjects with UCTD-UIP was identical to subjects with IPF, while survival in subjects with SSc, in particular, and RA too, was better than subjects with IPF—findings that underline the importance of investigators in future studies not merging all patients with CTD-UIP into one group for comparison against other UIP groups.

Acknowledgments

Author contributions: J. J. S. guarantees the manuscript and takes responsibility for its data and accuracy. M. J. S. contributed to manuscript preparation and editing, data analysis, and final approval of the manuscript; D. S., G. P. C., E. R. F.-P., S. K. F., T. J. H., A. L. O., J. S., K. K. B., and J. J. S. contributed to study conceptualization, manuscript preparation and editing, data collection, and final approval of the manuscript; and J. S. and K. K. B. contributed to data analysis.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Cosgrove is Chief Medical Officer for the Pulmonary Fibrosis Foundation and has served on an advisory board for InterMune. Drs Strand, Sprunger, Fernandez-Perez, Frankel, Huie, Olson, Solomon, Brown, and Swigris have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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