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Prevalence and Prognosis of Unclassifiable Interstitial Lung Disease

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ABSTRACT

Objectives: To determine the prevalence, characteristics, and outcomes of patients with unclassifiable interstitial lung disease (ILD) and develop a simple method of predicting disease behavior.

Methods: Unclassifiable ILD patients were identified from an ongoing longitudinal cohort. Unclassifiable ILD was diagnosed when multidisciplinary review did not secure a specific ILD diagnosis. Clinical characteristics and outcomes were compared with idiopathic pulmonary fibrosis (IPF) and non-IPF ILDs. Independent predictors of mortality were determined using Cox proportional hazards analysis to identify subgroups with distinct disease behavior.

Measurements and Main Results: Unclassifiable ILD was diagnosed in 10% of the ILD cohort (132 of 1370 patients). The most common reason for being unclassifiable was missing histopathological assessment due to a high risk of surgical lung biopsy. Demographic and physiologic features of unclassifiable ILD were intermediate between IPF and non-IPF disease controls. Unclassifiable ILD had longer survival compared to IPF on adjusted analysis (hazard ratio 0.62, $p=0.04$) and similar survival compared to non-IPF ILDs (hazard ratio 1.54, $p=0.12$). Independent predictors of survival in unclassifiable ILD included DLCO ($p=0.001$) and radiological fibrosis score ($p=0.02$).

Conclusions: Unclassifiable ILD represents approximately 10% of ILD cases and has a heterogeneous clinical course that can be predicted using clinical and radiological variables.

INTRODUCTION

Proper classification of the interstitial lung diseases (ILDs) requires multidisciplinary expertise with input from pulmonologists, thoracic radiologists, and lung pathologists.[1-3] Despite this coordinated effort, some patients cannot be confidently classified with a specific ILD subtype. This can occur when there are non-specific or conflicting clinical, radiological, or histopathological findings, or when patients are unable or unwilling to undergo diagnostic procedures. These patients are generally labeled as having an “unclassifiable ILD”.

The 2002 ATS/ERS consensus statement on the idiopathic interstitial pneumonias (IIPs) identified unclassifiable ILD as an area requiring further study, but resisted the creation of a formal disease category.[2] Indeed, little is known about the prevalence, characteristics, and outcomes of patients with unclassifiable ILD. The forthcoming ATS/ERS IIP classification update proposes a disease behavior classification, predominantly based upon expert opinion, that aims to provide guidance on the management and prognosis of patients with unclassifiable ILD (document under revision; personal communication - W. D. Travis Sept 17, 2012). Our main objective was to provide additional objective data describing the characteristics and outcomes of this population. Specifically, we sought to determine the prevalence of and reasons for unclassifiable ILD, describe the characteristics and outcomes of these patients, and investigate whether there are easily identifiable subgroups of unclassifiable ILD that have distinct and predictable clinical behaviors.

METHODS

Study Patients

The University of California San Francisco (UCSF) ILD Clinic is a specialized ILD center with most referrals originating from community pulmonologists. All consenting patients are included in the UCSF ILD Database regardless of diagnosis. We identified 1409 ILD patients in the UCSF ILD Database seen between January 2000 and April 2011 (**Figure E1 in the online data supplement**). Patients with incomplete medical records (n=39) were excluded (**Table E1 in the online data supplement**). These patients had a potentially diagnostic test recommended, but no information was available about whether this test was performed or the results of this test. Thus the available study population of 1370 patients represents 97.2% of the overall UCSF ILD cohort.

Patients were considered to have unclassifiable ILD if prospective review of clinical, radiological, and pathological data did not reveal a specific diagnosis following multidisciplinary discussion, according to standard criteria where available.[1-5] Patients required fulfillment of established clinical criteria to be confidently diagnosed with IPF.[3] For other diagnoses, we required a level of diagnostic certainty that would allow a clinician to confidently label a patient with a given ILD and move forward with appropriate treatment for that disease without further diagnostic evaluation. Patients not meeting these criteria were labeled as unclassifiable ILD. Clinical, radiological, and pathological data of patients with unclassifiable ILD were re-reviewed to identify the reason that the ILD could not be classified as a specific ILD subtype, including review of follow-up data. Patients with unclassifiable ILD had up to three suspected diagnoses recorded prospectively during multidisciplinary discussion as a “differential diagnosis”

(e.g. idiopathic pulmonary fibrosis (IPF) vs. chronic hypersensitivity pneumonitis (HP) vs. connective tissue disease-associated ILD (CT-ILD)).[3-5]

Patients with a multidisciplinary diagnosis of IPF, CT-ILD, idiopathic nonspecific interstitial pneumonia (NSIP), or HP were used as ILD controls.[3-5] These control groups were selected because these are the most frequently considered differential diagnoses in our unclassifiable population. CT-ILD, idiopathic NSIP and HP were reported together as a non-IPF ILD control group since baseline characteristics and outcomes were similar among these diagnoses. The UCSF Committee on Human Research approved this project and all patients provided written informed consent.

Measurements

Baseline data included age, gender, number of pack-years, need for long-term oxygen therapy, pre-bronchodilator forced vital capacity (FVC), and diffusing capacity of carbon monoxide (DLCO).[6, 7] The Composite Physiologic Index (CPI) was calculated as previously reported.[8] Follow-up FVC and DLCO were collected at 12 (+/- 3) months when available. High-resolution computed tomography (HRCT) scans were re-reviewed for this study by an experienced thoracic radiologist blinded to patient data for all unclassifiable patients that had a baseline HRCT in the 12 months preceding their initial clinic visit. Radiological variables included HRCT fibrosis score,[9] presence of a usual interstitial pneumonia (UIP) pattern (UIP, possible UIP, or inconsistent with UIP),[3] and presence of honeycombing (yes or no).[10] Fibrosis score was determined by estimating the percent of reticular change and honeycombing in 3 regions of each lung, and averaging these scores to produce a total fibrosis score. Date of lung transplantation or

death was verified for all patients using database records and the United States Death Registry Index.

Statistical Analysis

Baseline features of unclassifiable ILD patients were compared pair-wise to IPF and non-IPF controls using a Chi-squared test, t-test, or Wilcoxon rank sum test. Fine-Gray competing-risks regression analysis was used to evaluate the relationship of baseline features with risk of death, treating lung transplantation as a competing risk.[11]

Comparison of unclassifiable ILD with control groups was made in a similar manner, including with adjustment for age, gender, baseline FVC, and baseline DLCO. Time to death or lung transplantation was illustrated using Kaplan-Meier curves. Assumption of proportional hazards was assessed using Schoenfeld's residuals.[12] Disease progression was defined as any of the following within 12 months of the baseline visit: $\geq 10\%$ relative decline in FVC, $\geq 15\%$ relative decline in DLCO, lung transplantation, or death.

Frequency of disease progression was compared with controls using a Chi-squared test and logistic regression for unadjusted and adjusted analyses, respectively.

Independent predictors of time to death were identified using backward selection, forward selection and the Akaike Information Criterion.[13] Predictors with bivariate $p < 0.10$ were evaluated for their independent association with time to death. Predictor variables were transformed to approximate a normal distribution if necessary. Included variables were assessed for collinearity and interactions. Model accuracy was described using the c-statistic for the prediction of time to death and area under the receiver

operating characteristic (AUROC) curve for prediction of disease progression. All data analysis was performed using STATA 11.0 (StataCorp, Texas, USA).

RESULTS

Prevalence and Clinical Characteristics

Demographic and clinical characteristics of the 132 patients with unclassifiable ILD (10% of the total ILD population) and the 538 control patients are shown in **Table 1**. Patients with unclassifiable ILD had a mean age of 68 years, were equally male and female, and 64% were former smokers. A baseline HRCT was available for re-review in 83% of the unclassifiable patients (109 of 132 patients). Patients with and without a baseline HRCT available had no difference in baseline characteristics. “UIP pattern” on HRCT was present in 17% of unclassifiable ILD patients and “possible UIP pattern” was present in 50%. A slight majority (55%) of patients with unclassifiable ILD had received treatment for their ILD. The most common treatment was prednisone (48%), followed by azathioprine (9%).

Patients had five main reasons for being called unclassifiable ILD: provider unwillingness to perform surgical lung biopsy due to high surgical risk (52%); conflicting clinical, radiological, and histopathological data (18%); mild/stable disease in which the risks of biopsy were felt to outweigh the likely benefit (9%); insufficient tissue on surgical biopsy (8%); and patient unwillingness to undergo surgical biopsy (8%). The characteristics of each of these subgroups are shown in **Table E2 in the online data supplement**. The most commonly listed conditions in the differential diagnoses of

unclassifiable ILD patients were HP (68%), IPF (64%), NSIP (41%), CT-ILD (32%), drug-induced ILD (9%), and sarcoidosis (8%).

Outcomes in unclassifiable ILD

There were 33 deaths and no lung transplantations in the 132 patients with unclassifiable ILD. One, two, and five-year mortality rates were 10.6%, 23.8%, and 31.1% respectively (**Figure 1**). Patients with unclassifiable ILD had significantly longer survival time compared to IPF on unadjusted analysis (HR 0.49, 95%CI 0.33 to 0.72, $p<0.0005$), and with adjustment for age, gender, FVC, and DLCO (HR 0.62, 95%CI 0.40 to 0.97, $p=0.04$). Unclassifiable ILD had worse survival compared to non-IPF ILD controls on unadjusted analysis (HR 1.67, 95%CI 0.107 to 2.58, $p=0.02$), which lost significance on adjusted analysis (HR 1.54, 95%CI 0.89 to 2.65, $p=0.12$).

Follow-up physiologic data was available at 12 months in 61 patients with unclassifiable ILD (46%). There was no difference in baseline clinical, physiologic, or radiological features comparing patients with and without 12-month follow-up. Disease progression occurred in 32 (52%) unclassifiable patients with follow-up data available, compared to 63% of patients with IPF ($p=0.16$) and 45% of patients with other fibrotic ILDs ($p=0.38$). Death in the first year after baseline assessment was the most common criteria for disease progression in unclassifiable ILD patients (41%), followed by decline in FVC (25%), decline in both FVC and DLCO (22%), and DLCO alone (13%).

Predictors of mortality

Clinical predictors of time to death on bivariate analysis in unclassifiable ILD patients included the need for long-term oxygen therapy, baseline FVC, baseline DLCO, the CPI, provider unwillingness to perform surgical lung biopsy due to high surgical risk, and having a differential diagnosis that included IPF (**Table 2, Table 3 & Figure 2A**). Radiological predictors of time to death on bivariate analysis included HRCT fibrosis score, honeycombing on HRCT, and UIP/possible UIP on HRCT (**Table 2 & Figure 2B**). Multivariate analysis revealed only baseline DLCO and HRCT fibrosis score as independent predictors of time to death, with a c-statistic of 0.81 (**Table 4**). A combination of DLCO (dichotomized at 35%-predicted) and fibrosis score (dichotomized at the median fibrosis score of 20%) identified patients at low, intermediate, and high risk of mortality (**Figure 2C**).

Predictors of disease progression

Predictors of disease progression in unclassifiable ILD patients using bivariate analysis were similar to predictors of time to death (**Tables 2 & 3**). Multivariate analysis revealed only lower baseline DLCO and higher HRCT fibrosis score as independent predictors of progression (AUROC curve = 0.83; **Table 4**).

DISCUSSION

We show in a large, well-described cohort of patients with ILD that approximately 1 in 10 patients have an unclassifiable ILD. This makes it the 4th most common classification in our cohort behind IPF (21%), HP (15%) and sarcoidosis (14%). Unclassifiable ILD is associated with clinical characteristics and a prognosis intermediate between IPF and non-IPF ILDs. The risk of disease progression or death in subjects with unclassifiable

ILD aligns closely with the presence of baseline clinical and radiological features similar to IPF, in particular, radiologic diagnosis of UIP or possible UIP, HRCT fibrosis score, and presence of honeycombing.

The 2002 ATS / ERS consensus classification document did not include an unclassifiable ILD disease category because it was felt that this would not be helpful to clinicians.[2] Our finding that 10% of patients with ILD remain unclassifiable following an extensive multidisciplinary evaluation in an ILD referral center argues that unclassifiable ILD is a common problem in a sizable number of patients who still require disease management, and therefore is helpful to identify and describe further.

Unclassifiable ILD is most certainly a heterogeneous collection of ILDs, including IPF and non-IPF conditions such as chronic HP. Our data suggest that cases with specific clinical features (a low baseline DLCO, high surgical risk precluding lung biopsy, cases in which a diagnosis of IPF is suspected in the differential diagnosis), and with HRCT features suggesting fibrosis (high HRCT fibrosis score, the presence of honeycombing, or the presence of UIP or possible UIP pattern) have a poor prognosis similar to patients with IPF. Whether these cases actually represent patients with IPF, or remain a heterogeneous collection of conditions, is unknown.

The concept of a disease behavior pattern, in which the ILD phenotype is used to guide management and estimate prognosis, is particularly relevant in unclassifiable ILD, and is a key addition to the forthcoming ATS/ERS IIP classification update (document under revision; personal communication - W. D. Travis Sept 17, 2012). Our results provide

additional objective data that support this concept, in particular suggesting that DLCO and HRCT fibrosis score can help guide prognostication in this patient population.

Potential management implications of this risk stratification approach (e.g. the use of anti-fibrotic or anti-inflammatory agents, the timing of lung transplantation evaluation) are beyond the scope of this paper and require further study.

We provide a simple dichotomization of DLCO and fibrosis score to illustrate the importance of these variables and their potential application to clinical practice. We chose a cut-off for DLCO of 35%-predicted for several reasons. First, there are data suggesting that IPF and NSIP have a similarly poor outcome below this threshold.[14] Second, surgical lung biopsy has a higher risk of complication at approximately this threshold.[15] Third, this threshold is an appropriate time at which to refer a patient with progressive disease for lung transplantation.[16] Finally, this threshold is commonly used as an enrolment criterion (i.e. >35%) for IPF trials. We stratified fibrosis score at the median value for our cohort, as there is no data to support the use of any specific threshold.

The reported prevalence of unclassifiable ILD may be influenced by this study being performed in an ILD referral center. In addition, although we followed established criteria for the diagnosis of IPF and other ILDs, our threshold for assigning a diagnosis of unclassifiable ILD may differ from other academic centers. Importantly, inclusion of IPF in the differential diagnosis is dependent on physician expertise, is inherently subjective, and may work differently in less-experienced centers. A baseline HRCT was not available for re-review in 17% of unclassifiable patients however there were no

differences in characteristics for those with versus without a baseline HRCT available, suggesting that these missing data did not result in substantial bias. Disease progression data was not available in the majority of study subjects. Baseline characteristics were similar in patients with and without progression data available, and we believe it is unlikely that the lack of follow-up data could lead to a spurious association of DLCO and fibrosis score with disease progression. Furthermore, the consistent association of DLCO and fibrosis score with survival in the complete cohort suggests that the relationship of these variables with disease progression is valid. Finally, we did not have sufficient data to directly evaluate the prevalence or impact of pulmonary hypertension and emphysema in patients with unclassifiable ILD.

In summary, we show that unclassifiable ILD represents approximately 10% of ILD cases and has a heterogeneous clinical course that can be predicted using clinical and radiological variables. We believe that unclassifiable ILD is a clinically relevant disease classification for patients with ILD that requires further study. We propose that risk stratification using clinical and radiological features (in particular DLCO and HRCT fibrosis score) may have an important role in the management of patients with unclassifiable ILD. An important area for future research is the evaluation of new and/or improved diagnostic modalities (e.g. serum biomarkers) that can accurately categorize unclassifiable ILD cases into established and distinct disease entities.[17-21] In the absence of serum biomarkers or other biological methods to reclassify unclassifiable ILD cases, stratification by simple clinical and radiological variables may be useful.

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Conflict of interest: The authors have no conflicts of interest to disclose.

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FIGURE LEGENDS

Figure 1. Survival analysis (Kaplan-Meier estimates) comparing unclassifiable interstitial lung disease (ILD) to idiopathic pulmonary fibrosis (IPF) and non-IPF ILD controls (CT-ILD, idiopathic NSIP, or HP). Panel (A) shows the unadjusted comparison of unclassifiable ILD to controls. Panel (B) shows this comparison with adjustment for age, gender, FVC, and DLCO. Adjusted curves are displayed for the average male patient possessing a mean value for age, FVC, and DLCO. Unclassifiable ILD had better survival compared to IPF controls (HR 0.49, 95%CI 0.33 to 0.72, $p < 0.0005$) and worse survival compared to non-IPF ILD controls (HR 1.67, 95%CI 1.07 to 2.58, $p = 0.02$) on unadjusted Cox regression analysis. With adjustment, unclassifiable ILD had better survival compared to IPF controls (HR 0.62, 95%CI 0.40 to 0.97, $p = 0.04$), but no difference compared to non-IPF ILD controls (HR 1.54, 95%CI 0.89 to 2.65, $p = 0.12$).

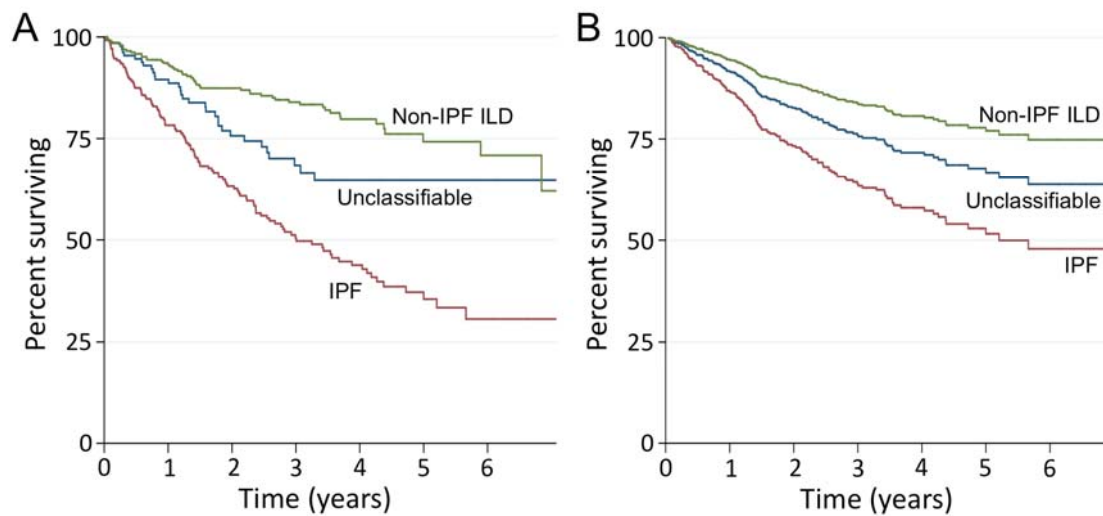
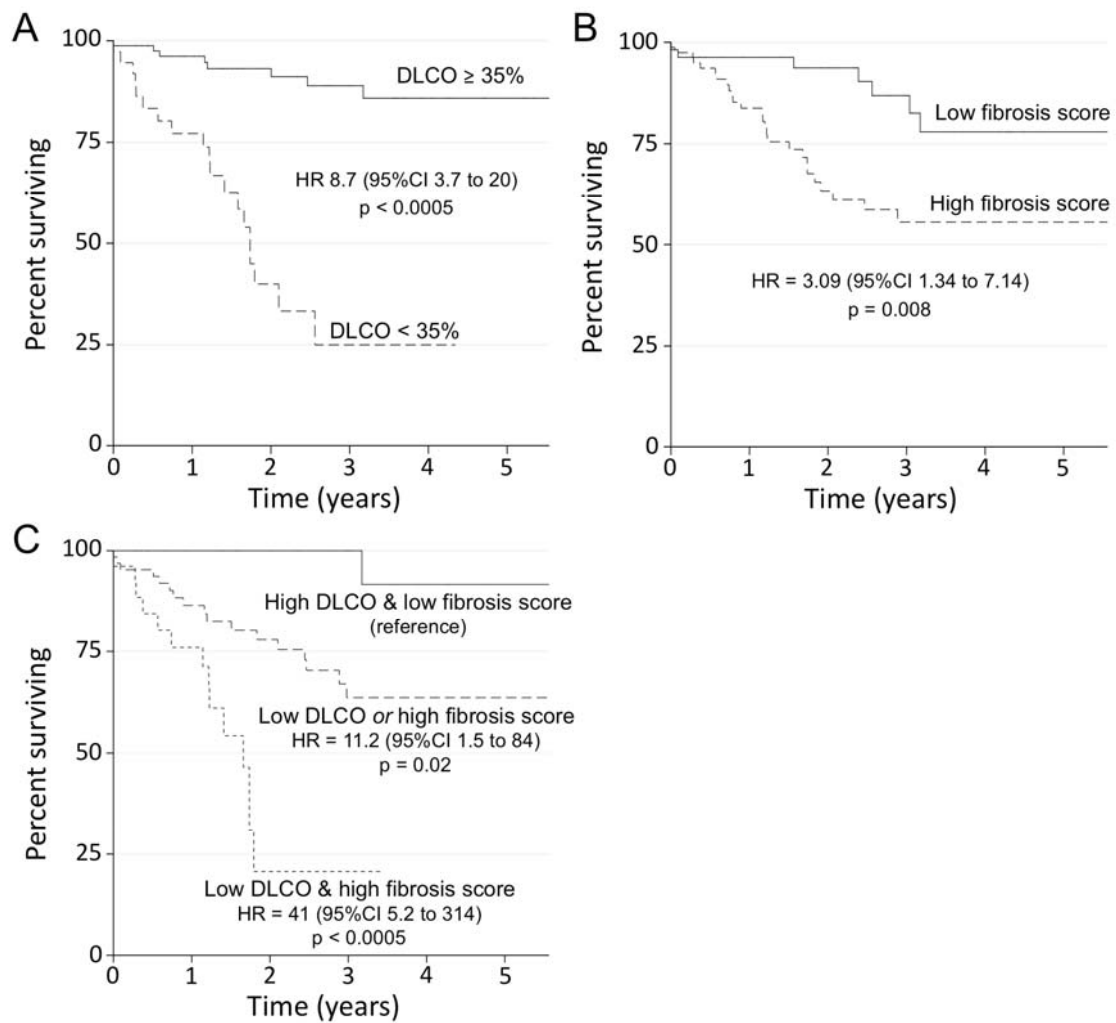


Figure 2. Survival of unclassifiable interstitial lung disease (ILD) subgroups. Stratified by (A) DLCO %-predicted $\geq 35\%$ vs $< 35\%$; (B) median fibrosis score (median fibrosis score = 20%); (C) combination of dichotomized DLCO and fibrosis score using the above thresholds. P values are for the comparison of unclassifiable ILD subtypes using Cox proportional hazards analysis.



TABLES

Table 1. Patient characteristics

Variable	Unclassifiable (n=132)	IPF	p value	Non-IPF	p value
		Controls (n=244)		Controls (n=294)	
Age, years	67.8 (12.9)	69.7 (8.8)	0.09	59.6 (11.9)	<0.0005
Male sex, %	53.0%	72.8%	<0.0005	32.3%	<0.0005
Smoking history					
Ever smoked, %	63.6%	75.8%	0.01	46.1%	0.001
Pack-years	16.0 (23.9)	23.3 (25.2)	<0.0005	8.5 (14.9)	0.001
Measures of disease severity					
Long-term oxygen therapy, %	21.9%	24.7%	0.54	16.8%	0.26
Pulmonary function (n=129)					
FVC, % predicted	69.0 (22.1)	69.1 (17.8)	0.97	68.7 (20.3)	0.89
DLCO, % predicted	47.6 (19.7)	44.0 (16.4)	0.08	48.5 (20.2)	0.66

Values are reported as mean (standard deviation) or percent. P values are reported for comparison between unclassifiable ILD and each ILD subtype using Chi-squared test (gender, smoking history, oxygen therapy), t-test (age, FVC, DLCO), or Wilcoxon rank sum test (pack-years).

Abbreviations: DLCO, diffusion capacity of carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis

Table 2. Bivariate clinical and radiological predictors of mortality and disease progression in unclassifiable ILD

Variable	Mortality		Disease progression*	
	Hazard ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, years [†]	1.24 (0.92 to 1.68)	0.16	1.03 (0.67 to 1.58)	0.91
Male sex, %	1.52 (0.76 to 3.08)	0.21	1.09 (0.40 to 2.98)	0.87
Smoking history				
Ever smoked, %	1.10 (0.98 to 1.24)	0.11	1.35 (0.48 to 3.81)	0.57
Pack-years [‡]	1.15 (1.01 to 1.32)	0.04	1.10 (0.92 to 1.30)	0.31
Measures of disease severity				
Long-term oxygen therapy, %	2.81 (1.35 to 5.86)	0.006	2.19 (0.64 to 7.46)	0.21
Pulmonary function (n=129)				
FVC, % predicted [†]	0.85 (0.72 to 1.00)	0.047	0.77 (0.59 to 1.00)	0.05
DLCO, % predicted [†]	0.55 (0.42 to 0.73)	< 0.0005	0.66 (0.48 to 0.91)	0.01
Composite Physiologic Index	1.07 (1.03 to 1.10)	< 0.0005	1.06 (1.01 to 1.10)	0.01
HRCT findings (n=109)				

Fibrosis score [†] (mean 20.3)	1.82	< 0.0005	2.16	0.002
	(1.30 to 2.55)		(1.32 to 3.56)	
UIP pattern				
Inconsistent with UIP (n=36, 33%)	reference		reference	
Possible UIP (n=54, 50%)	2.60	0.07	4.88	0.02
	(0.93 to 7.27)		(1.36 to 17.47)	
UIP (n=19, 17%)	2.92	0.08	4.33	0.09
	(0.89 to 9.61)		(0.80 to 23.49)	
UIP or possible UIP (n=90, 83%)	2.69	0.049	4.73	0.01
	(1.00 to 7.21)		(1.42 to 15.73)	
Honeycombing, % (n=54, 50%)	2.81	0.02	6.57	0.002
	(1.21 to 6.55)		(1.98 to 21.78)	

Hazard and odds ratios are shown for the bivariate (unadjusted) relationship of each variable with the stated outcome.

* Disease progression was defined as any of the following within 12 months of the initial UCSF ILD Clinic visit: 10% decline in FVC, 15% decline in DLCO, lung transplantation, or death due to any cause. This was only assessable in a subgroup of patients with complete follow up data (n = 61).

[†] Hazard and odds ratios reported for 10-unit change.

[‡] Hazard and odds ratios reported for square root of pack years

Abbreviations: CI, confidence interval; DLCO, diffusion capacity of carbon monoxide; FVC, forced vital capacity; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

Table 3. Additional bivariate predictors of mortality and disease progression in unclassifiable ILD: Impact of multidisciplinary evaluation and reasons for an unclassifiable diagnosis.

Variable	Mortality		Disease progression*	
	Hazard ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Differential diagnoses [†]				
DDx included HP (n=91)	1.13 (0.54 to 2.33)	0.75	0.84 (0.28 to 2.53)	0.75
DDx included IPF (n=86)	5.49 (1.91 to 15.74)	0.002	4.04 (1.28 to 12.75)	0.02
DDx included NSIP (n=55)	1.08 (0.55 to 2.15)	0.82	0.97 (0.35 to 2.69)	0.95
DDx included CT-ILD (n=43)	0.71 (0.34 to 1.50)	0.38	1.01 (0.34 to 2.99)	0.99
Reasons for unclassifiable ILD				
Too old or frail for lung biopsy (n=68)	3.22 (1.48 to 6.97)	0.003	2.39 (0.85 to 6.70)	0.10
Conflicting CRP data (n=24)	0.53 (0.19 to 1.51)	0.23	0.38 (0.12 to 1.21)	0.10
Mild or stable disease (n=12)	0.25 (0.03 to 1.85)	0.18	0.28 (0.03 to 2.85)	0.28
Insufficient tissue on lung biopsy (n=11)	0.46 (0.06 to 3.39)	0.45	2.90 (0.28 to 29.53)	0.37
Declined biopsy (n=10)	0.34 (0.05 to 2.52)	0.29	1.87 (0.16 to 21.74)	0.62

Hazard and odds ratios are shown for the bivariate (unadjusted) relationship of each variable with the stated outcome.

* Disease progression was defined as any of the following within 12 months of the initial ILD Clinic visit: $\geq 10\%$ decline in FVC, $\geq 15\%$ decline in DLCO, lung transplantation, or death due to any cause. This was only assessable in a subgroup of patients with complete follow up data (n = 66).

[†] All patients with unclassifiable ILD had up to three suspected diagnoses recorded prospectively during multidisciplinary discussion as a “differential diagnosis”

Abbreviations: CI, confidence interval; CRP, clinical, radiological and pathological; CT, connective tissue; DDx, differential diagnosis; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia.

Table 4. Multivariate predictors of mortality and disease progression in unclassifiable ILD

Variable	Mortality		Disease progression*	
	Hazard ratio (95% CI)	P value	Odds ratio (95% CI)	P value
DLCO, % predicted [†]	0.59 (0.43 to 0.80)	0.001	0.67 (0.46 to 0.96)	0.03
HRCT fibrosis score [†]	1.60 (1.08 to 2.37)	0.02	2.29 (1.26 to 4.15)	0.006

Hazard and odds ratios are from stepwise regression, using a p value of 0.05 for inclusion. DLCO and HRCT fibrosis score were the only variables retained in the multivariate model.

* Disease progression was defined as any of the following within 12 months of the initial UCSF ILD Clinic visit: 10% decline in FVC, 15% decline in DLCO, lung transplantation, or death due to any cause. This was only assessable in a subgroup of patients with complete follow up data (n = 61).

[†] Hazard ratio reported for 10-unit change.

Abbreviations: CI, confidence interval; DLCO, diffusion capacity of carbon monoxide; HRCT, high resolution computed tomography.