



Prevalence and prognosis of unclassifiable interstitial lung disease

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ABSTRACT The aim of this study was to determine the prevalence, characteristics and outcomes of patients with unclassifiable interstitial lung disease (ILD) and to develop a simple method of predicting disease behaviour.

Unclassifiable ILD patients were identified from an ongoing longitudinal cohort. Unclassifiable ILD was diagnosed after a 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 behaviour.

Unclassifiable ILD was diagnosed in 10% of the ILD cohort (132 out 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 physiological features of unclassifiable ILD were intermediate between IPF and non-IPF disease controls. Unclassifiable ILD had longer survival rates when 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 diffusion capacity of the lung for carbon monoxide ($p=0.001$) and a radiological fibrosis score ($p=0.02$).

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



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Unclassifiable ILD has a heterogeneous clinical course that can be predicted using clinical and radiological variables <http://ow.ly/mdjwg>

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Introduction

Proper classification of 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 nonspecific or conflicting clinical, radiological, or histopathological findings, or when patients are unable or unwilling to undergo diagnostic procedures. These patients are generally labelled as having an “unclassifiable ILD”.

The 2002 American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement on 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-behaviour classification, which is predominantly based upon expert opinion aimed at providing guidance on the management and prognosis of patients with unclassifiable ILD (document under revision, personal communication; W.D. Travis, Memorial Sloan Kettering Cancer Center, New York, NY, USA). Our main aim was to provide additional, objective, data that would describe 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 behaviours.

Methods

Study patients

The University of California San Francisco (UCSF) ILD clinic is a specialised ILD centre, 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 (online supplementary fig. E1). Patients with incomplete medical records ($n=39$) were excluded (online supplementary table E1). These patients had a potentially diagnostic test recommended, but no information was available about whether this test had been 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 a 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 fulfilment of established clinical criteria to be confidently diagnosed with idiopathic pulmonary fibrosis (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 the appropriate treatment for that disease, without further diagnostic evaluation. Patients not meeting these criteria were labelled 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, which included a 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. IPF *versus* chronic hypersensitivity pneumonitis (HP) *versus* 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 they 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, sex, number of pack-years, need for long-term oxygen therapy, pre-bronchodilator forced vital capacity (FVC), and the diffusing capacity of the lung for 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 the presence of honeycombing (yes or no) [10]. Fibrosis score was determined by estimating the per cent of reticular change and honeycombing in

three 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 (<http://ssdi.rootsweb.ancestry.com/>).

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 adjustment for age, sex, 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 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 time to death predictors 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 co-linearity 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 (STATA Corporation, College Station, TX, 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 out of 132 patients). Patients with and without an available baseline HRCT 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 unwilling to perform a surgical lung biopsy due to high surgical risk (52%); conflicting clinical, radiological, and histopathological data (18%); mild/stable disease in which the risk of a biopsy was felt to outweigh the likely benefit (9%); insufficient tissue on surgical biopsy (8%); and unwillingness of patient to undergo a surgical biopsy (8%). The characteristics of each of these subgroups are shown in the online supplementary table E2. The most

TABLE 1 Characteristics of the unclassifiable ILD and control patients in the study

Variable	Unclassifiable ILD	IPF controls	p-value	Non-IPF controls	p-value
Patients n	132	244		294	
Age years	67.8 ± 12.9	69.7 ± 8.8	0.09	59.6 ± 11.9	<0.0005
Sex male	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 [#]					
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

Data are presented as mean ± SD or %, unless otherwise stated. ILD: interstitial lung disease; IPF: IPF, idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; [#]: n=129 for unclassifiable patients. The p-values are reported for comparison between unclassifiable ILD and each ILD subtype using Chi-squared test (sex, smoking history and oxygen therapy), t-test (age, FVC, DLCO), or Wilcoxon rank sum test (pack-years).

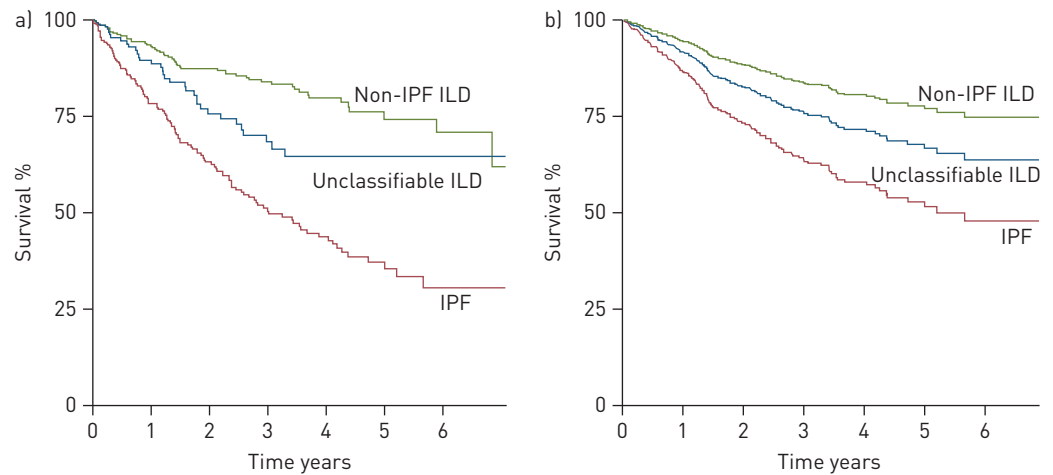


FIGURE 1 Survival analysis (Kaplan–Meier estimates) comparing unclassifiable interstitial lung disease (ILD) to idiopathic pulmonary fibrosis (IPF) and non-IPF ILD controls (connective tissue disease-associated ILD, idiopathic nonspecific interstitial pneumonia or hypersensitivity pneumonitis). a) Shows the unadjusted comparison of unclassifiable ILD with the controls. b) Shows this comparison with adjustment for age, sex, forced vital capacity (FVC), and diffusion capacity of the lung for carbon monoxide ($DLCO$). 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 (hazard ratio 0.49, 95% CI 0.33–0.72; $p < 0.0005$) and worse survival when compared to non-IPF ILD controls (HR 1.67, 95% CI 1.07–2.58; $p = 0.02$) on unadjusted Cox regression analysis. With adjustment, unclassifiable ILD had better survival when compared to IPF controls (HR 0.62, 95% CI 0.40–0.97; $p = 0.04$), but no difference when compared to non-IPF ILD controls (HR 1.54, 95% CI 0.89–2.65; $p = 0.12$).

TABLE 2 Bivariate clinical and radiological predictors of mortality and disease progression in unclassifiable interstitial lung disease

Variable	Patients n (%)	Mortality		Disease progression [#]	
		HR (95% CI)	p-value	OR (95% CI)	p-value
Age years [†]		1.24 [0.92–1.68]	0.16	1.03 [0.67–1.58]	0.91
Sex male %		1.52 [0.76–3.08]	0.21	1.09 [0.40–2.98]	0.87
Smoking history					
Ever smoked %		1.10 [0.98–1.24]	0.11	1.35 [0.48–3.81]	0.57
Pack-years [‡]		1.15 (1.01–1.32)	0.04	1.10 [0.92–1.30]	0.31
Measures of disease severity					
Long-term oxygen therapy %		2.81 [1.35–5.86]	0.006	2.19 [0.64–7.46]	0.21
Pulmonary function	129 [98]				
FVC % pred [†]		0.85 (0.72–1.00)	0.047	0.77 (0.59–1.00)	0.05
$DLCO$ % pred [†]		0.55 (0.42–0.73)	<0.0005	0.66 (0.48–0.91)	0.01
Composite physiologic index		1.07 (1.03–1.10)	<0.0005	1.06 (1.01–1.10)	0.01
HRCT findings	109 [83]				
Fibrosis score ^{†,§}		1.82 [1.30–2.55]	<0.0005	2.16 (1.32–3.56)	0.002
UIP pattern					
Inconsistent with UIP	36 [33]	Reference		Reference	
Possible UIP	54 [50]	2.60 [0.93–7.27]	0.07	4.88 [1.36–17.47]	0.02
UIP	19 [17]	2.92 [0.89–9.61]	0.08	4.33 [0.80–23.49]	0.09
UIP or possible UIP	90 [83]	2.69 (1.00–7.21)	0.049	4.73 (1.42–15.73)	0.01
Honeycombing %	54 [50]	2.81 [1.21–6.55]	0.02	6.57 [1.98–21.78]	0.002

Hazard ratios (HR) and odds ratios (OR) are shown for the bivariate (unadjusted) relationship of each variable with the stated outcome. FVC: forced vital capacity; $DLCO$: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; UIP, usual interstitial pneumonia. [#]: Disease progression was defined as any of the following within 12 months of the initial visit to the University of California San Francisco ILD Clinic: 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: $n = 61$); [†]: HR and OR reported for 10-unit change. [‡]: HR and OR ratios are reported for the square root of pack-years; [§]: mean 20.3.

TABLE 3 Additional bivariate predictors of mortality and disease progression in unclassifiable interstitial lung disease (ILD): impact of multidisciplinary evaluation and reasons for an unclassifiable diagnosis.

Variable	Patients n	Mortality		Disease progression [#]	
		HR (95% CI)	p-value	OR (95% CI)	p-value
Differential diagnoses includes[†]					
Hypersensitivity pneumonitis	91	1.13 (0.54–2.33)	0.75	0.84 (0.28 to 2.53)	0.75
Idiopathic pulmonary fibrosis	86	5.49 (1.91–15.74)	0.002	4.04 (1.28 to 12.75)	0.02
Nonspecific interstitial pneumonia	55	1.08 (0.55–2.15)	0.82	0.97 (0.35 to 2.69)	0.95
Connective tissue ILD	43	0.71 (0.34–1.50)	0.38	1.01 (0.34 to 2.99)	0.99
Reasons for unclassifiable ILD					
Too old or frail for lung biopsy	68	3.22 (1.48–6.97)	0.003	2.39 (0.85–6.70)	0.10
Conflicting clinical, radiological and pathological data	24	0.53 (0.19–1.51)	0.23	0.38 (0.12–1.21)	0.10
Mild or stable disease	12	0.25 (0.03–1.85)	0.18	0.28 (0.03–2.85)	0.28
Insufficient tissue on lung biopsy	11	0.46 (0.06–3.39)	0.45	2.90 (0.28–29.53)	0.37
Declined biopsy	10	0.34 (0.05–2.52)	0.29	1.87 (0.16–21.74)	0.62

Hazard ratio (HR) and odds ratios (OR) 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 visit to the University of California San Francisco ILD Clinic: $\geq 10\%$ decline in forced vital capacity, $\geq 15\%$ decline in the diffusing capacity of the lung for carbon monoxide, 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”.

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 (fig. 1). Patients with unclassifiable ILD had significantly longer survival time compared to IPF on unadjusted analysis (hazard ratio 0.49, 95%CI 0.33–0.72; $p < 0.0005$), and with adjustment for age, sex, FVC, and DLCO (HR 0.62, 95%CI 0.40–0.97; $p = 0.04$). Unclassifiable ILD had worse survival compared to non-IPF ILD controls on unadjusted analysis (HR 1.67, 95%CI 1.07–2.58; $p = 0.02$), which lost significance on adjusted analysis (HR 1.54, 95%CI 0.89–2.65; $p = 0.12$).

Follow-up physiological data was available at 12 months in 61 patients with unclassifiable ILD (46%). There was no difference in baseline clinical, physiological, or radiological features, when comparing patients with and without a 12-month follow-up. Disease progression occurred in 32 (52%) unclassifiable-ILD patients, where follow-up data was 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; the provider’s unwillingness to perform a surgical lung biopsy, due to high surgical risk; and having a differential diagnosis that included IPF (tables 2 and 3, and fig. 2a). Radiological predictors of time to death on bivariate analysis included HRCT fibrosis score, honeycombing on HRCT, and UIP or possible UIP on HRCT (table 2 and fig. 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 (fig. 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 and 3). Multivariate analysis revealed only lower baseline DLCO and higher HRCT fibrosis score as independent predictors of progression (AUROC curve=0.83) (table 4).

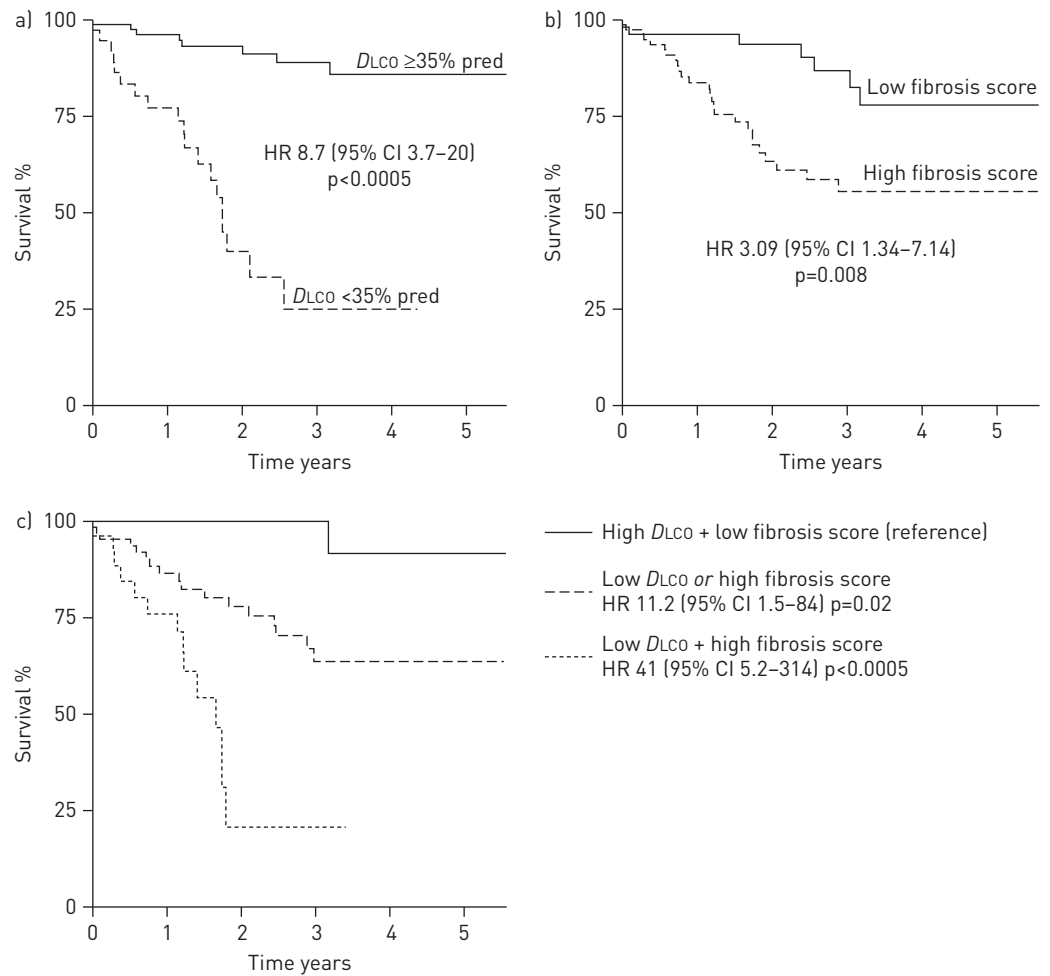


FIGURE 2 Survival of unclassifiable interstitial lung disease (ILD) subgroups. a) Diffusing capacity of the lung for carbon monoxide ($DLCO \geq 35\%$ pred versus $<35\%$ pred). b) Median fibrosis score (median fibrosis score=20%). c) Combination of dichotomized $DLCO$ and fibrosis score using the above thresholds. p-values are for the comparison of unclassifiable-ILD subtypes using Cox proportional hazards analysis.

Discussion

We show in a large, well-described, cohort of patients with ILD that approximately one in 10 patients have an unclassifiable ILD. This makes it the fourth 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

TABLE 4 Multivariate predictors of mortality and disease progression in unclassifiable interstitial lung disease (ILD)

Variable	Mortality		Disease progression [#]	
	HR (95% CI)	p-value	OR (95% CI)	p-value
$DLCO$ % predicted[¶]	0.59 (0.43–0.80)	0.001	0.67 (0.46–0.96)	0.03
HRCT fibrosis score[¶]	1.60 (1.08–2.37)	0.02	2.29 (1.26–4.15)	0.006

Hazard ratios (HR) and odds ratios (OR) are from stepwise regression, using a p-value of 0.05 for inclusion. Diffusing capacity of the lung for carbon monoxide ($DLCO$) and high-resolution computed tomography (HRCT) fibrosis scores were the only variables retained in the multivariate model. [#]: disease progression was defined as any of the following within 12 months of the initial visit to the University of California San Francisco ILD Clinic: 10% decline in forced vital capacity, 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); [¶]: HR reported for 10-unit change.

to IPF, in particular, radiological diagnosis of UIP or possible UIP, HRCT fibrosis score, and the 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 centre, 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 it further.

Unclassifiable ILD is most certainly a heterogeneous collection of ILDs, including IPF and non-IPF conditions, such as chronic HP. Our data suggests that cases with specific clinical features (a low baseline DL_{CO} , 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 behaviour 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. Our results provide additional objective data that support this concept, in particular suggesting that DL_{CO} and HRCT fibrosis score can help guide prognosis 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 DL_{CO} and fibrosis score to illustrate the importance of these variables and their potential application to clinical practice. We chose a cut-off for DL_{CO} of 35% predicted for several reasons. First, there are data suggesting that IPF and NSIP have a similarly poor outcome below this threshold [14]. Secondly, surgical lung biopsy has a higher risk of complication at approximately this threshold [15]. Thirdly, 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 centre. 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 centres. Importantly, inclusion of IPF in the differential diagnosis is dependent on physician expertise, is inherently subjective, and may work differently in less-experienced centres. 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 available progression data, and we believe it is unlikely that the lack of follow-up data could lead to a spurious association of DL_{CO} and fibrosis score with disease progression. Furthermore, the consistent association of DL_{CO} 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 ~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 DL_{CO} 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 categorise 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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