Histopathology

Histopathology 2024 DOI: 10.1111/his.15179

Presence of focal usual interstitial pneumonia is a key prognostic factor in progressive pulmonary fibrosis

Yukio Tsushima,[1,*] Ethan N Okoshi,[1,*] Sousuke Ishijima,[1] Andrey Bychkov,[2] Kris Lami,[1] Shimpei Morimoto,[3] Yasuhiko Yamano,[4] Kensuke Kataoka,[4] Takeshi Johkoh,[5] Yasuhiro Kondoh[4] & Junya Fukuoka[1]

[1]*Department of Pathology Informatics, Nagasaki University School of Biomedical Sciences, Nagasaki,* [2]*Department of Pathology, Kameda Medical Center, Kamogawa, Chiba,* [3]*Innovation Platform and Office for Precision Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki,* [4]*Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto and* [5]*Department of Radiology, Kansai Rosai Hospital, Amagasaki, Japan*

Date of submission 8 November 2023
Accepted for publication 10 March 2024

Tsushima Y, Okoshi E N, Ishijima S, Bychkov A, Lami K, Morimoto S, Yamano Y, Kataoka K, Johkoh T, Kondoh Y & Fukuoka J

(2024) *Histopathology*. https://doi.org/10.1111/his.15179

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Aims: Progressive pulmonary fibrosis (PPF) is a newly recognised clinical phenotype of interstitial lung diseases in the 2022 interstitial pulmonary fibrosis (IPF) guidelines. This category is based entirely on clinical and radiological factors, and the background histopathology is unknown. Our objective was to investigate the histopathological characteristics of PPF and to examine the correlation between usual interstitial pneumonia (UIP) and prognosis in this new disease type. We hypothesised that the presence of UIP-like fibrosis predicts patients' survival in PPF cases.

Methods and results: We selected 201 cases fulfilling the clinical criteria of PPF from case archives. Cases diagnosed as IPF by a multidisciplinary team were excluded. Whole slide images were evaluated by three pathologists who were blinded to clinical and radiological data. We measured areas of UIP-like fibrosis and calculated what percentage of the total lesion area they occupied. The presence of focal UIP-like fibrosis amounting to 10% or more of the lesion area was seen in 148 (73.6%), 168 (83.6%) and 165 (82.1%) cases for each pathologist, respectively. Agreement of the recognition of UIP-like fibrosis in PPF cases was above $\kappa = 0.6$ between all pairs. Survival analysis showed that the presence of focal UIP-like fibrosis correlated with worsened survival under all parameters tested ($P < 0.001$).

Conclusions: The presence of UIP-like fibrosis is a core pathological feature of clinical PPF, and its presence within diseased areas is associated with poorer prognosis. This study highlights the importance of considering the presence of focal UIP-like fibrosis in the evaluation and management of PPF.

Keywords: 2022 IPF guidelines, PPF histology, progressive pulmonary fibrosis, usual interstitial pneumonia

Introduction

Progressive pulmonary fibrosis (PPF) is a newly defined clinical phenotype of fibrotic interstitial lung disease (ILD).[1] It serves as an update to the former clinical phenotype of progressive fibrosing interstitial lung disease (PF-ILD). Whereas prior clinical practice

Address for correspondence: J Fukuoka, Department of Pathology Informatics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki University Hospital Medical, Dental, and Pharmaceutical Education and Research Building 5F, Sakamoto 1-7-1, Nagasaki 852-8501, Japan. e-mail: fukuokaj@nagasaki-u.ac.jp
*Co-first authors.
Presented at the 112st United States and Canadian Academy of Pathology annual meeting, New Orleans, 11–16 March 2023.

guidelines recommended a period of evaluation of 2 years for PF-ILD, PPF can be identified within a follow-up period of only 1 year, which has benefits in prognostication and treatment.[1,2] PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation in a patient with an ILD other than idiopathic pulmonary fibrosis (IPF): worsening symptoms, radiological progression and physiological progression.[1] However, the histology of PPF has not yet been addressed.

PPF has a similar clinical and radiological presentation and disease progression to that of IPF, a chronic fibrosing interstitial pneumonia of unknown cause.[1,3–5] Clinically, these diseases are characterised by decline in forced vital capacity (FVC), worsening of dyspnoea, reduction in exercise capacity and deterioration in health-related quality of life.[1,5] The diagnostic approach for IPF is radiological and histopathological evaluation for the presence of usual interstitial pneumonia (UIP) pattern. The prevalence and progression of UIP-associated features on computerised tomography (CT) and histology have been shown to predict mortality in patients with IPF.[6–9] While UIP is mainly associated with IPF, UIP can be present in ILDs other than IPF, such as hypersensitivity pneumonitis (HP) and connective tissue disease (CTD).[1,10–16]

The aim of this study was first, to investigate the histopathological characteristics of PPF with a focus on determining the prevalence of UIP pattern or focal UIP-like fibrosis in the pathology of PPF, and secondly to examine the correlation between focal UIP and prognosis in relation to underlying aetiology. Given the clinical and radiological similarities between IPF and PPF, we hypothesised that UIP may constitute a fundamental histological aspect of PPF.

Materials and Methods

PATIENT DATA

A total of 201 cases fulfilling the criteria for PPF as evidenced by pulmonary function tests, patient symptoms or radiological images from 2009 to 2018 were enrolled from a case archive at Tosei General Hospital (Aichi, Japan) and confirmed via multidisciplinary discussion (MDD). Specifically, pulmonary function tests included measuring FVC and DLco over time.[1] We excluded all cases diagnosed as IPF via MDD from our cohort (Figure 1). Clinical data and whole slide images (WSI) of tissue sections derived from surgical lung biopsies (SLB) were collected for each patient (Aperio CS2, ×20 magnification; Leica Biosystems, Wetzlar, Germany). Typically, one biopsy each was taken from segments S5, S8 and S9, and the average number of slides per case was 2.65 (Supporting information, Table S1). This study was conducted at a single institution in compliance with the principles of the Declaration of Helsinki and approved by its institutional review board (IRB no. 14012746, February 3, 2014).

DIGITAL HISTOLOGICAL ANALYSIS

WSIs were evaluated by three pathologists (Y.T., J.F., S.I.) independently, blinded to both clinical and radiological data. The areas of UIP-like fibrosis were demarcated using a digital pen tool (Aperio ImageScope; Leica Biosystems).

Cases were labelled first as 'pathological UIP'-positive or -negative as per the histological criteria presented in the 2010 IPF guidelines[17] for definite, probable or possible UIP, i.e. pathological UIP-positive cases were all cases which fell under the diagnoses of definite, probable or possible UIP. Cases were then labelled 'focal UIP'--positive if the area of UIP-like fibrosis divided by the total lesion area was greater than 10% (Supporting information, Figure S1). This cut-off value was determined by receiver operating characteristic (ROC) analysis (Supporting information, Figure S2). Focal UIP+ cases included all cases that were pathological UIP+.

UIP-like fibrosis was defined as destructive fibrosis/marked distortion which did not necessarily include fibroblastic foci or temporal heterogeneity[1,10,17,18] (Figure 2). Due to the focal nature of the histology being evaluated, there was a high likelihood that areas of UIP lacked patchy involvement of the lung parenchyma or fibroblastic foci; thus, many of our focal UIP+ cohort (UIP-like fibrosis ≥ 10% of disease area) would fall under the diagnosis of probable UIP or possible UIP. To clarify, focal UIP+ cases were cases with 10% or more of the lesion area comprising of destructive fibrosis or marked distortion which did not reach the threshold of NSIP, with or without fibroblastic foci or temporal heterogeneity.

For cases with multiple biopsy specimens, we took the average percentage of UIP-like fibrosis across specimens. In cases where the three pathologists differed on the diagnosis of UIP content, the final diagnosis was made by consensus.

STATISTICAL ANALYSIS

Categorical variables were compared using Pearson's χ^2 test for variables with all expected values ≥ 5 and Fisher's exact test for expected values < 5. Comparisons using continuous variables were performed with the Wilcoxon rank sum test. Agreement between

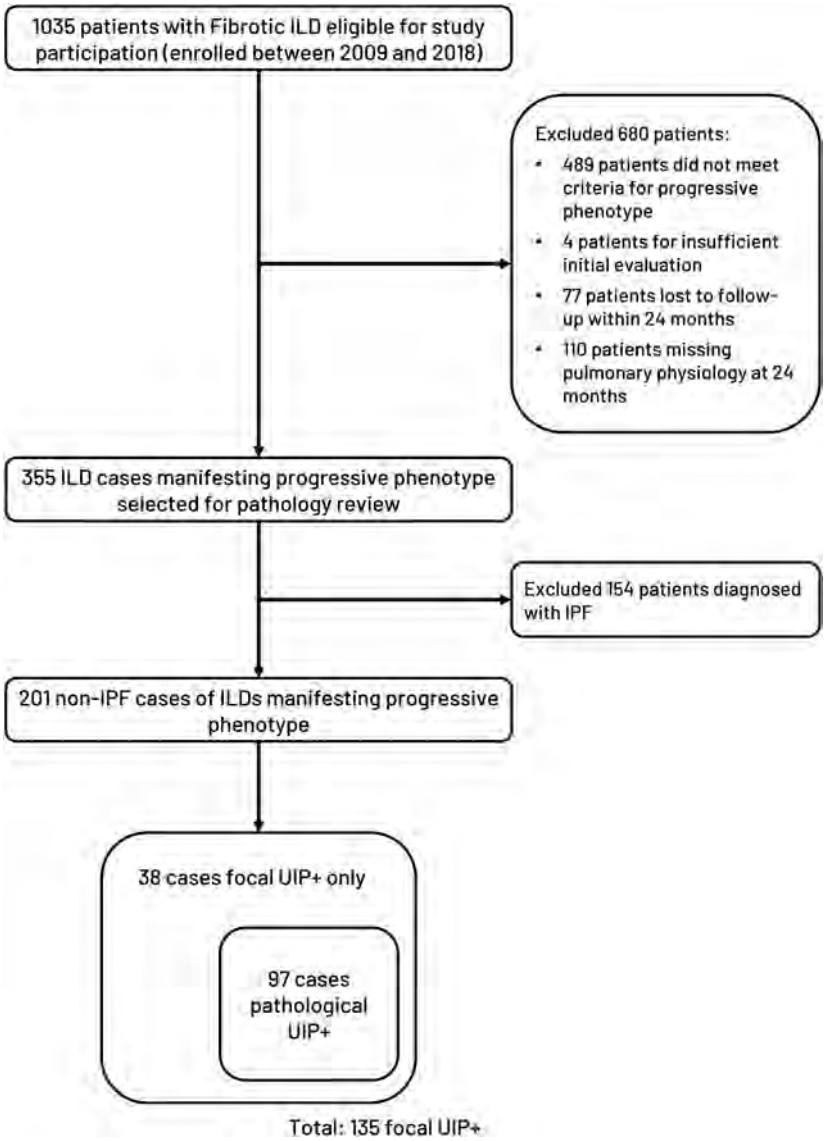

Figure 1. Pipeline diagram describing study cohort. A total of 201 cases of non-IPF ILDs exhibiting progressive phenotype were collected from Tosei General Hospital between 2009 and 2018. These cases were first labelled as pathological UIP+ or pathological UIP−. We then expanded the criteria for UIP positivity, labelling any UIP which was more than 10% of the total disease area as 'focal UIP'. Using the criteria for focal UIP, we labelled an additional 38 cases as focal UIP+ for a total of 135 cases positive for focal UIP. IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia.

pathologists was evaluated using Cohen's kappa. Patient survival data were analysed with the log-rank test and Kaplan–Meier curves. Time-to-event analysis was conducted by fitting multiple univariate Cox proportional hazards models and a multivariate Cox proportional hazards model to our data to investigate time from surgery to either death (n = 50) or lung transplant (n = 5). The patient follow-up data were collected until 31 December 2018, and those who were alive and had not undergone transplant were censored; the follow-up term of the censored patients ranged from 42 to 124 months. All analysis was conducted in R version 4.3.0.

Results

PATIENT POPULATION

Patients' baseline demographic, clinical and physiological characteristics are shown in Table 1. Analysis showed that increased age and %FVC were predictors for pathological UIP positivity. Sex, smoking history

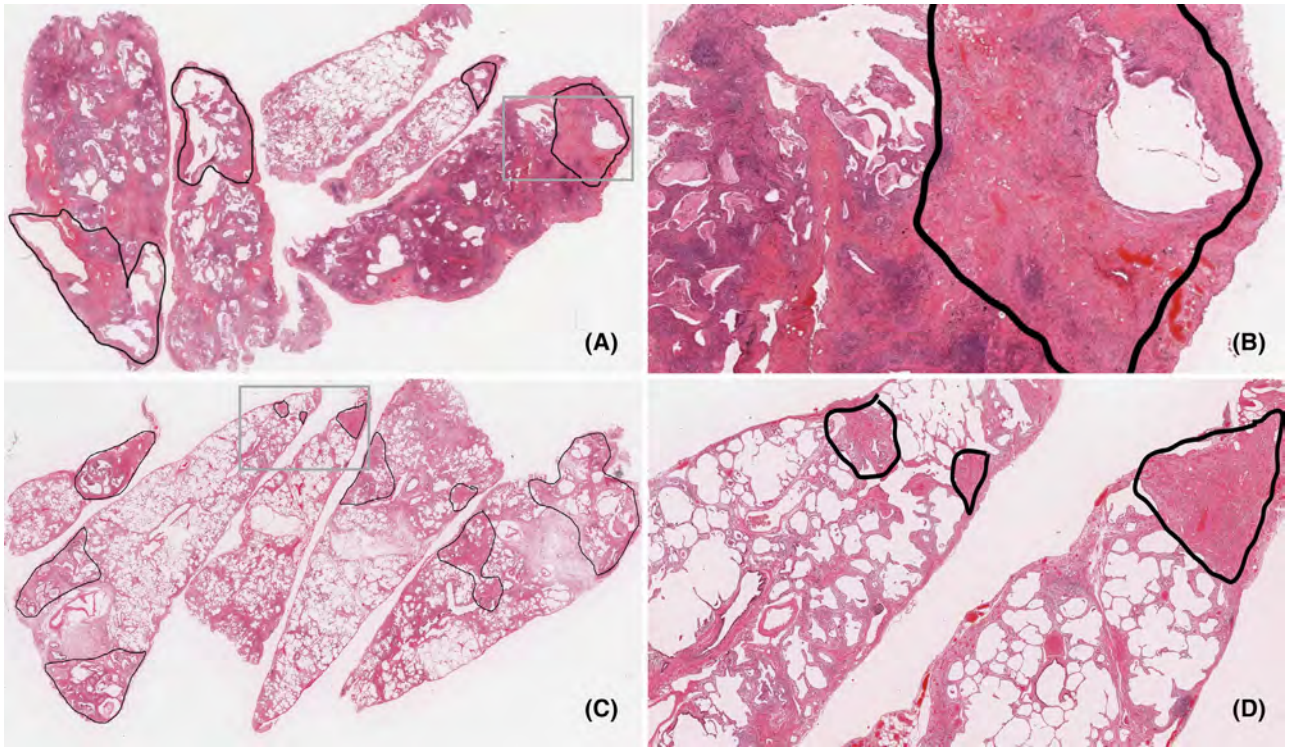

Figure 2. Representative haematoxylin and eosin (H&E) images of areas of UIP. UIP was defined as destructive fibrosis often with honeycombing that did not reach the threshold of NSIP and did not necessarily include fibroblastic foci or temporal heterogeneity, as per the 2010 IPF guidelines. The case depicted in **A** and **B** shows UIP occupying 28.3% of the diseased area, while the case depicted in **C** and **D** shows UIP occupying 17.0% of the diseased area. Annotated areas demarcated with a black line indicate areas of UIP. The grey box indicates areas that were enlarged on the right. UIP, usual interstitial pneumonia.

and FVC were predictors for focal UIP positivity. There was a significant difference in the rates of pathological UIP positivity between the underlying aetiology groups. There was no significant correlation between the number of sampled segments and focal or pathological UIP positivity ($P = 0.6$).

HISTOLOGY

Primary histological findings on analysis of our cohort are described in Table 2. The most frequently identified histological pattern was NSIP, with 38.8% of our cohort exhibiting this pattern. Following that, definite and probable UIP were the next most common findings with 31 cases and 33 cases, respectively (15.4 and 16.4%). There were 13 total separate findings identified in the histology of our cohort, with only four of these findings present in more than 10% of the cohort.

PATHOLOGICAL UIP COHORT

Of the 201 total cases, 97 (48.3%) displayed a histopathological pattern consistent with definite UIP, probable UIP, possible UIP or UIP versus other (Table 3). The mean percentage of UIP pattern within the lesion area was 49.21% among these pathological UIP+ cases. Among all PPF cases, those marked positive for pathological UIP pattern had a poorer prognosis than those that were not marked positive ($P = 0.0005$) (Figure 3).

FOCAL UIP COHORT

To evaluate different cut-off thresholds for focal UIP positivity, a Cox proportional hazards model was univariately fit to cut-off thresholds from 10 to 50%, and a 10% cut-off showed the greatest prognostic value [hazard ratio (HR) = 4.073, $P = 0.000537$] (Supporting information, Figure S2A). ROC analysis showed that the 10% cut-off threshold also had the best trade-off between sensitivity and specificity among all cut-off thresholds ranging from 0 to 100% (Supporting information, Figure S2B).

Among the 201 PPF cases, focal UIP was identified in 148 (73.6%), 165 (82.1%) and 168 (83.6%) cases by the three pathologists, respectively. By consensus,

Table 1. Baseline characteristics in 201 patients with progressive pulmonary fibrosis who underwent surgical lung biopsy

Characteristic	Pathological UIP			Focal UIP			Total
	Negative, *n* = 104*	Positive, *n* = 97*	*P*-value	Negative, *n* = 66*	Positive, *n* = 135*	*P*-value	*N* = 201*
Sex							
Female	63 (58%)	46 (42%)	0.061†	48 (44%)	61 (56%)	< **0.001**†	109 (100%)
Male	41 (45%)	51 (55%)		18 (20%)	74 (80%)		92 (100%)
Age	61 (55, 66.25)	63 (60, 68)	**0.021**‡	62 (55, 67)	62 (58, 67)	0.2‡	62 (57, 67)
Smoking history							
Current	6 (55%)	5 (45%)	0.5†	3 (27%)	8 (73%)	**0.004**§	11 (100%)
Ex-smoker	42 (47%)	47 (53%)		19 (21%)	70 (79%)		89 (100%)
Never	56 (55%)	45 (45%)		44 (44%)	57 (56%)		101 (100%)
FVC	2.21 (1.72–2.72)	2.36 (2.01–3.09)	0.061‡	2.03 (1.67–2.67)	2.41 (1.95–3.09)	**0.004**‡	2.30 (1.82–2.92)
%FVC	81 (69–95)	87 (75–98)	**0.038**‡	79 (69–93)	86 (72–99)	0.052‡	85 (71–97)
Dlco	10.2 (8.5–13.5)	10.6 (8.7–12.5)	0.7‡	9.9 (8.8–11.6)	11.1 (8.5–13.3)	0.3‡	10.4 (8.5–13.0)
Missing	2	0		2	0		2
%Dlco	61 (49–75)	65 (51–77)	0.6‡	62 (49–74)	64 (50–78)	0.7‡	63 (49–76)
Missing	2	0		2	0		2
KL-6	1431 (816–2453)	1102 (663–2159)	0.2‡	1507 (861–2543)	1102 (662–2241)	0.065‡	1204 (726–2380)
Disease							
cHP	5 (36%)	9 (64%)	**0.018**§	4 (29%)	10 (71%)	0.6§	14 (100%)
CTD-ILD	47 (57%)	35 (43%)		30 (37%)	52 (63%)		82 (100%)
iNSIP	15 (79%)	4¶ (21%)		8 (42%)	11 (58%)		19 (100%)
iPPFE	1 (50%)	1 (50%)		0 (0%)	2 (100%)		2 (100%)
UC-ILD	36 (43%)	48 (57%)		24 (29%)	60 (71%)		84 (100%)

Significant *P*-values are highlighted with bold text. Significance was evaluated at $P < 0.05$. Categorical values presented as counts and row-wise frequency. Continuous variables presented as mean ± standard deviation. UIP, usual interstitial pneumonia; cHP, chronic hypersensitive pneumonia; CTD-ILD, connective tissue disease-associated interstitial lung disease; iNSIP, idiopathic non-specific interstitial pneumonia; iPPFE, idiopathic pleuroparenchymal fibroelastosis; UC-ILD, unclassifiable interstitial lung disease; Pathological UIP, definite, possible or probable UIP according to the 2010 IPF guidelines; Focal UIP, UIP-like fibrosis comprises ≥ 10% of disease area.

**n* (%); median (interquartile ratio).

†Pearson's χ^2 test.

‡Wilcoxon rank sum test.

§Fisher's exact test.

¶The pathology of these four cases were difficult to distinguish between UIP and NSIP, but the final diagnosis of NSIP was determined via multidisciplinary discussion (MDD).

135 (67.1%) cases were established to be focal UIP+. Interobserver agreement between each pair of pathologists was 0.61, 0.63 and 0.71. Kaplan–Meier curves for each pathologist's (Figure 4A) and consensus (Figure 4B) diagnoses of focal UIP+/− show that focal UIP+ cases' survival was significantly reduced compared to focal UIP−/− cases.

AETIOLOGY

Finally, we compared the survival of PPF with or without focal UIP in individual ILD aetiologies (Table 1). Separated by aetiology, 64% of chronic hypersensitive pneumonia (cHP) cases, 57% of unclassifiable interstitial lung disease (UC-ILD) cases,

Table 2. Histopathological findings in a 201 patient PPF cohort

Histology	Count	Frequency (%)
NSIP	77	38.8
Definite UIP	31	15.4
Probable UIP	33	16.4
Possible UIP	16	8.0
ALI/DAD	23	11.4
ACIF	8	4.0
OP	3	1.5
PPFE	2	1.0
Small airway disease	2	1.0
DIP	1	0.5
LIP	1	0.5
PAP	1	0.5
IP, NOS	2	1.0

Only primary findings are reported. Values shown as counts and frequency within cohort. NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; ALI, acute lung injury; DAD, diffuse alveolar damage; ACIF, airway-centred interstitial fibrosis; OP, organising pneumonia; PPFE, pleuroparenchymal fibroelastosis; DIP, desquamative interstitial pneumonia; LIP, lymphocytic interstitial pneumonia; PAP, pulmonary alveolar proteinosis; IP, interstitial pneumonia; NOS, not otherwise specified.

43% of connective tissue disease-associated interstitial lung disease (CTD-ILD) cases, 50% of idiopathic pleuroparenchymal fibroelastosis (iPPFE) and 21% of idiopathic non-specific interstitial pneumonia (iNSIP) cases were positive for pathological UIP (Table 3). Regardless of the underlying ILD aetiology of PPF,

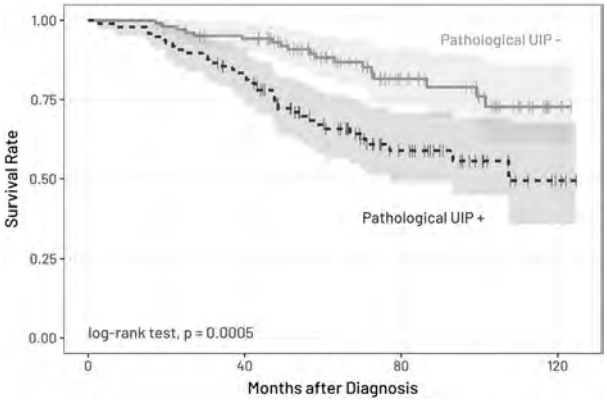

Figure 3. Kaplan–Meier survival curves for pathological UIP+ and pathological UIP− patients. Vertical ticks indicate last follow-up visit. The yellow line indicates pathological UIP− cases (n = 104) and the blue line indicates pathological UIP+ cases (n = 97). UIP, usual interstitial pneumonia; PPF, progressive pulmonary fibrosis.

patients with focal UIP consistently exhibited a poorer prognosis compared to those without, with statistical significance achieved in three of four disease categories tested (CTD-ILD, NSIP and UC-ILD) (Figure 5). Survival analysis for iPPFE was excluded due to the low case count (n = 2). Interestingly, even in cases that were pathological UIP−, the presence of focal UIP fibrosis exceeding 10% tends to result in a worse prognosis (P = 0.0018) (Figure 6).

COX PROPORTIONAL HAZARDS MODEL

We performed univariate and multivariate Cox proportional hazards regression analysis to examine the effect of each clinical variable on patient survival. The multivariate Cox proportional hazards model showed that focal UIP positivity (HR = 6.43, P = 0.00015) and Krebs von den Lungen 6 (KL-6)

Table 3. Diagnosis information for pathological UIP in a 201 patient PPF cohort

Aetiology	*n*	Definite UIP	Probable UIP	Possible UIP	UIP versus other	Percentage UIP+ (%)
iNSIP	19	0	0	0	4	21
cHP	14	5	1	2	1	64
CTD-ILD	82	8	16	3	8	43
iPPFE	2	0	0	0	1	50
UC-ILD	84	13	16	11	8	57

Percentage of UIP+ in this table refers only to pathological UIP cases, not focal UIP cases. iNSIP, idiopathic non-specific interstitial pneumonia; cHP, chronic hypersensitive pneumonia; CTD-ILD, connective tissue disease-associated interstitial lung disease; iPPFE, idiopathic pleuroparenchymal fibroelastosis; UC-ILD, unclassifiable interstitial lung disease; UIP, usual interstitial pneumonia; PPF, progressive pulmonary fibrosis.

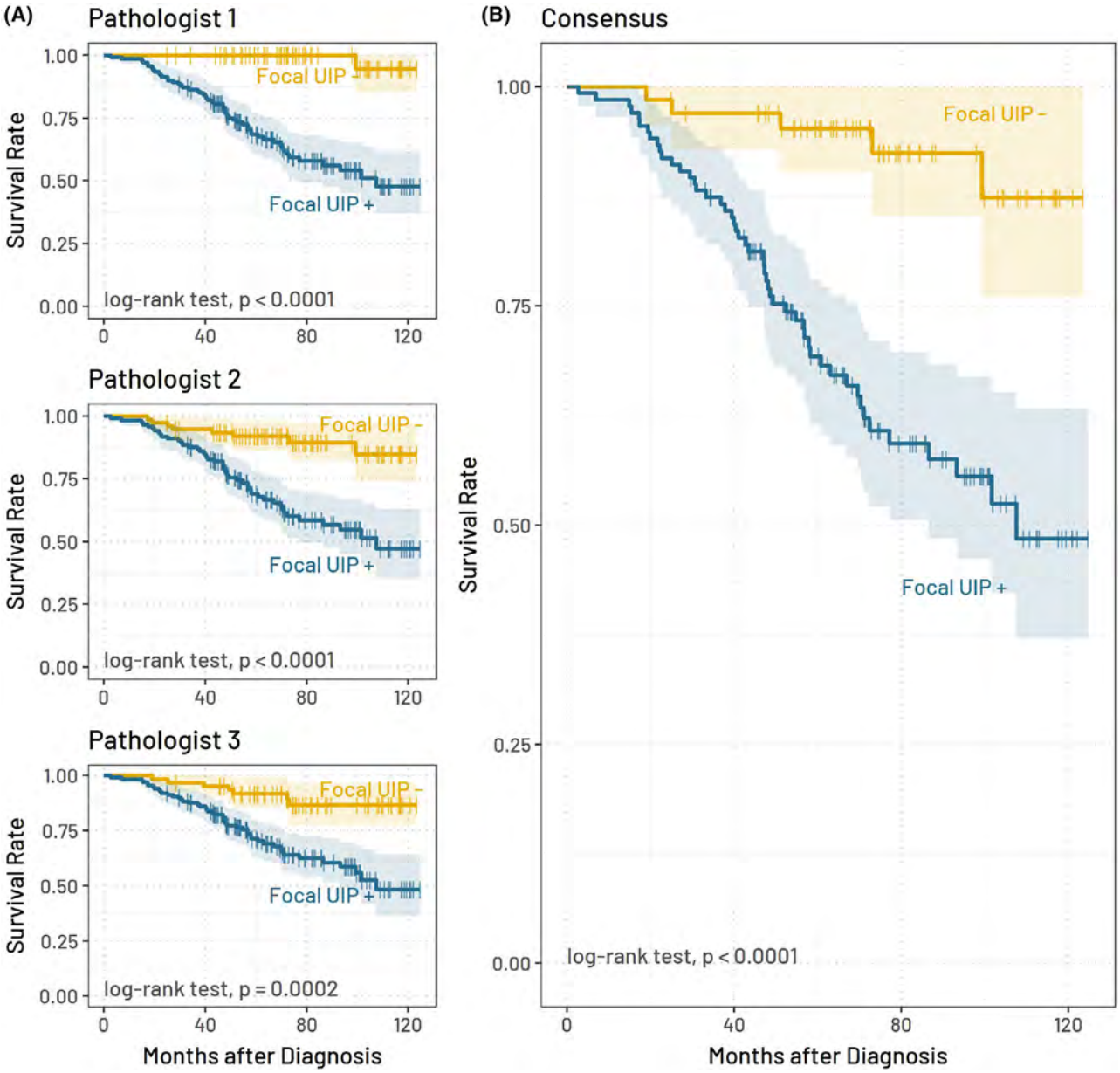

Figure 4. Kaplan–Meier survival curves for focal UIP+ and focal UIP− patients, separated by pathologist (**A**) and by consensus (**B**). Pathological UIP positivity or negativity was not a factor in this analysis—only focal UIP positivity or negativity was considered. Vertical ticks indicate last follow-up visit. The yellow line indicates focal UIP− cases and the blue line indicates focal UIP+ cases. UIP, usual interstitial pneumonia.

value (HR = 0.56, $P = 0.005$) were the only significantly prognostic factors when controlling for all factors (Table 4). Harrel's *C*-index for the model was 0.762 ± 0.036 and the global likelihood ratio test *P*-value was 0.000002. Univariate analysis of each of the above variables individually showed that focal UIP (HR = 6.24, $P = 0.001$) was the sole significantly prognostic factor.

ASSOCIATION BETWEEN FOCAL UIP POSITIVITY AND THE SURVIVAL RATE

The heterogeneity between the disease groups in the association between focal UIP positivity and the HR were shown via referring histograms generated from empirical distributions of the HRs (Figure 7). The result showed that the estimated HRs for focal UIP were significantly larger in the disease groups of cHP

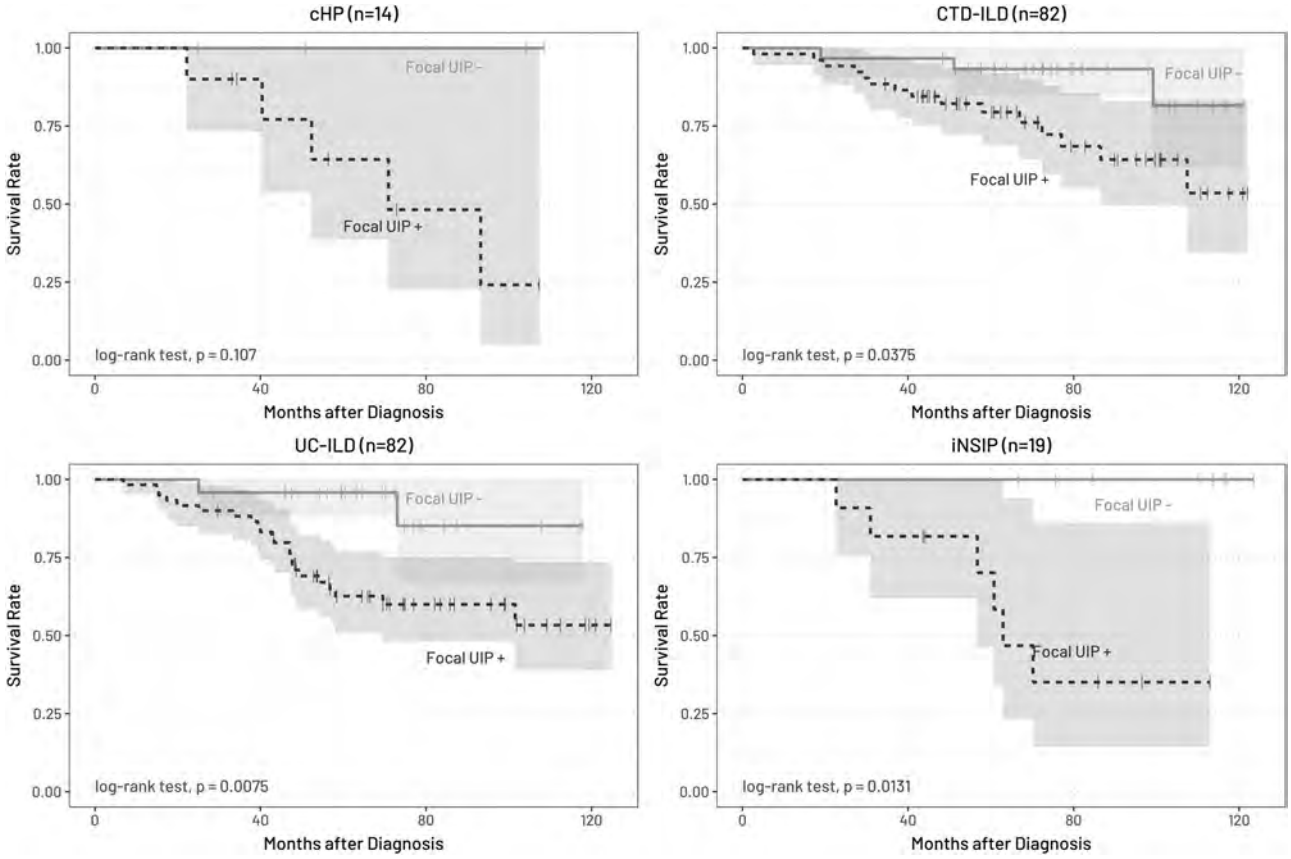

Figure 5. Kaplan–Meier survival curves for focal UIP+ and focal UIP− patients, separated by aetiology. Vertical ticks indicate last follow-up visit. The yellow line indicates focal UIP− cases and the blue line indicates focal UIP+ cases. UIP, usual interstitial pneumonia.

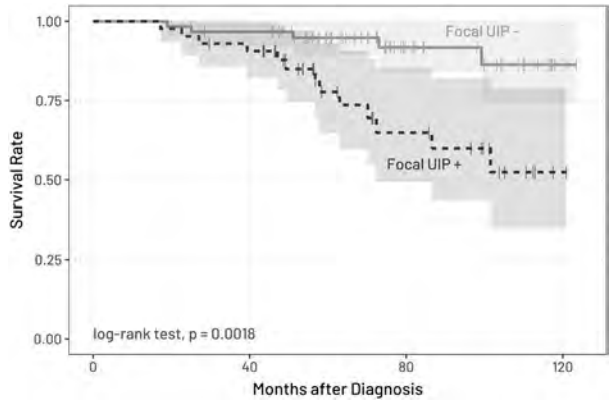

Figure 6. Kaplan–Meier survival curves for focal UIP+ and negative patients within pathological UIP− cases (n = 104). Vertical ticks indicate last follow-up visit. The yellow line indicates focal UIP− cases (n = 66) and the blue line indicates focal UIP+ cases (n = 38). UIP, usual interstitial pneumonia.

and iNSIP than in CTD-ILD and UC-ILD. The HR in the disease group of UC-ILD was the lowest among the disease groups.

Discussion

The 2022 IPF guidelines detailed the clinical and radiological criteria necessary to diagnose PPF in fibrotic ILDs, but omitted histopathological criteria.[1] Identifying the histological features which correlate to disease progression is critical to deepening our understanding of this disorder. Given the similarities between the physiological and radiological criteria of PPF and IPF, we hypothesised that UIP (i.e. the histological marker of IPF) would also hold significance in the histopathology of PPF. Our findings showed that the presence of UIP pattern in ILDs manifesting PPF correlated with worsened survival and had prognostic significance regardless of the underlying aetiology.

While there are many other histologies included in PPF, we believe that focal UIP could function as the core of PPF histology. For most cases in our cohort it was the key to predicting prognosis, and in the future could guide treatment. However, one-third of our PPF cohort did not exhibit UIP reaching the threshold described above, but exhibited progressive fibrotic disease enough to be classified as PPF.

Table 4. Cox proportional hazards regression analysis results

	Univariate			Multivariate	
Characteristic	*n*	HR (95% CI)	*P*-value*	HR (95% CI)	*P*-value†
Focal UIP	201	6.24 (2.49–15.7)	**0.001**	6.43 (2.49–16.6)	< **0.001**
Sex	201	1.86 (1.08–3.19)	0.35	2.94 (0.68–12.7)	0.15
Age	201	1.02 (0.99–1.06)	0.22	1.00 (0.95–1.06)	> 0.9
Smoking history	201				
Current		–		–	
Ex		1.55 (0.37–6.49)	0.55	3.22 (0.71–14.7)	0.13
Never		1.14 (0.27–4.81)	0.86	4.05 (0.78–21.2)	0.10
FVC	201	0.90 (0.64–1.26)	0.53	0.73 (0.12–4.25)	0.7
%FVC	201	0.99 (0.97–1.00)	0.71	0.99 (0.94–1.05)	0.8
Dlco	199	0.92 (0.84–0.99)	0.51	0.88 (0.69–1.13)	0.3
%Dlco	199	0.98 (0.97–1.00)	0.51	0.99 (0.95–1.04)	0.7
KL-6	201	0.84 (0.61–1.15)	0.27	0.56 (0.37–0.84)	**0.005**
Disease	201				
cHP		–		–	
CTD-ILD		0.52 (0.19–1.41)	0.20	0.56 (0.18–1.75)	0.3
iNSIP		0.68 (0.21–2.23)	0.52	0.58 (0.15–2.35)	0.4
iPPFE		2.62 (0.30–22.7)	0.38	5.13 (0.45–58.9)	0.2
UC-ILD		0.79 (0.30–2.06)	0.63	0.75 (0.25–2.31)	0.6

Factors were tested individually with multiple univariate Cox proportional hazards models and also together in a single multivariate Cox proportional hazards model. Two cases had missing DLco data. UIP, usual interstitial pneumonia; cHP, chronic hypersensitive pneumonia; CTD-ILD, connective tissue disease-associated interstitial lung disease; iNSIP, idiopathic non-specific interstitial pneumonia; iPPFE, idiopathic pleuroparenchymal fibroelastosis; UC-ILD, unclassifiable interstitial lung disease; HR, Hazard ratio; CI, Confidence interval.
Note: Bold values indicate significance of $P < 0.05$.
*Wald test with Bonferroni correction.
†Wald test.

The statistically significant differences in UIP positivity by sex and age agrees with widely accepted knowledge on UIP.[19,20] UIP-positive patients would be expected to display a downward trend in FVC, DLco and higher KL-6 values in the diseased population, but our cohort is made up of many different aetiologies, including subacute conditions, and thus the reverse trend in FVC and the lack of significance in DLco and KL-6 was not ultimately surprising.[21,22] The lack of significance in these variables highlights the many confounding factors present in cases of PPF.

Regarding our histological criteria, prior diagnostic guidelines have stated that it is acceptable to apply the label of UIP even when some of its core histological characteristics are missing, especially when there is a lack of features suggestive of an alternative diagnosis.[17,18]

Three of our four disease classifications reached significance in their Kaplan–Meier survival curves. Regarding the one that did not, cHP, it should be noted that the focal UIP− group had a mortality rate of zero and all deaths occurred in the focal UIP+ group. Given the low number of overall cases of cHP in our cohort, statistical tests of this group could be prone to error.

Our finding that different underlying ILD aetiologies did not change the overall negative prognostic effect of UIP could be interpreted as support for the 'UIP bucket' hypothesis.[13] This hypothesis suggests that all ILDs exhibiting UIP make up the same disease—

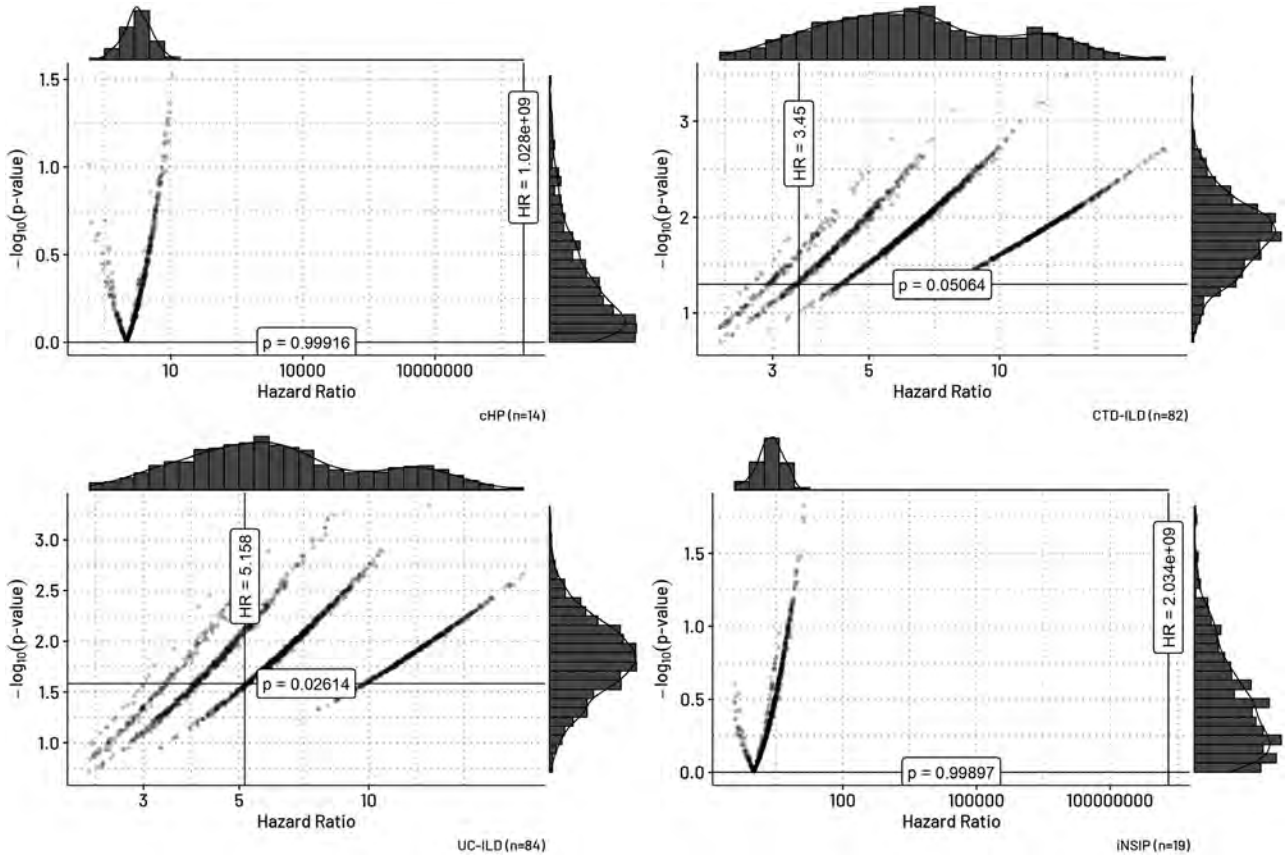

Figure 7. Permutation test results showing the empirical distribution of hazard ratios and *P*-values from 2000 random permutations of the disease type labels in a Cox proportional hazards model, separated by aetiology. The vertical and horizonal lines in each plot show the hazard ratio and *P*-value of the cox proportional hazards model calculated from the real data. The histograms at the top and on the right of each panel show the frequencies of the hazard ratios and the *P*-values obtained from the results of 2000 permutations of the disease labels. iNSIP, idiopathic non-specific interstitial pneumonia; cHP, chronic hypersensitive pneumonia; CTD-ILD, connective tissue disease-associated ILD; iPPFE, idiopathic pleuroparenchymal fibroelastosis; UC-ILD, unclassifiable ILD.

one which eventually progresses to end-stage honeycomb lung as a phenotype, regardless of the initial ILD diagnosis.[23] This could explain why UIP pattern correlates to worsened prognosis in PPF regardless of the diagnosed aetiology. In fact, a prior study has reported that 34% of fibrosing ILDs other than IPF eventually show a progressive phenotype with a prognosis similar to that of IPF.[23] This study also found that UIP was a significant prognostic factor in their 509-patient non-IPF fibrosing ILD cohort.

In terms of clinical suggestions derived from our findings, it is crucial to accurately diagnose PPF cases in which therapeutic agents can have a positive impact. Antifibrotic agents have been proved to be effective in treating patients with PF-ILD.[2,24,25] Although a monitoring period of 1 year is recommended for diagnosing PPF, the presence or absence of UIP can be evaluated from the time of presentation and guide treatment strategies immediately.[26,27] Early identification of pathological or focal UIP pattern is thus valuable for the prompt initiation of treatment, particularly where SLB is widely implemented.[28] Furthermore, for early stage ILDs, when CT is unclear about the presence of UIP, SLB may be an appropriate recommendation to accurately diagnose pathological and focal UIP. For pathologists without access to digital pathology workflows, judgements based on microscopic evaluation of focal UIP presence must be made. We recommend that if a pathologist feels that UIP pattern may exceed 10% of the disease area, they should advise the clinician to pursue intense follow-up.

This study has some limitations. First, it is important to note that this study was conducted at a single institution, and further confirmation from multiple facilities is required to validate these findings. As this study uses SLB as the primary method of biopsy, our results are most helpful to other institutions which use SLB routinely. Additionally, due to the subjective

nature of pathologists' interpretations of the UIP pattern and the potential for other histopathological features to serve as prognostic factors, the use of more objective tools, such as image analysis, empowered by artificial intelligence may be beneficial in determining these factors more objectively and potentially more accurately.

Conversely, the strengths of our study lie in that this is the first paper, to our knowledge, to describe the histology of PPF and relate it to a prognostically significant finding. We also enlisted the expertise of three pulmonary pathologists who blindly evaluated focal UIP, showing high agreement and reproducibility.[29–31]

In conclusion, the histological pattern of UIP in cases of PPF is prognostically meaningful. We hope that this study will spur subsequent research to validate and further explore the connection between the UIP pattern and PPF, and that the histology of PPF may receive more recognition in future updates of the PPF guidelines. Our study highlights the importance of considering the presence of focal UIP-like fibrosis in the evaluation of PPF.

Acknowledgements

Funding provided by the Study Group on Diffuse Lung Disease, Scientific Research/Research on Intractable Diseases in the Ministry of Health, Labour and Welfare, Japan.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author on reasonable request. Code for data cleaning, visualisation and analysis is provided. It is available at https://github.com/eokoshi/PPF.git for review. It can be uploaded to a journal repository on request once the paper has been conditionally accepted.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Illustration of focal UIP label identification methodology. Representative diagrams of surgical lung biopsy specimen. The areas of UIP-like fibrosis were demarcated using a digital pen tool, and the presence of UIP-like fibrosis within the identified interstitial lung disease areas was quantified separately. The area of UIP-like fibrosis (U) and the total area of ILD (L) were measured, excluding normal tissue area in all specimens obtained through surgical lung biopsy. The focal area of UIP-like fibrosis was defined as U/l, and for cases with multiple biopsy specimens, we took the average percentage across specimens. The label of 'focal UIP' was defined as UIP-like fibrosis covering 10% of the total lesion area. UIP, usual interstitial pneumonia.

Figure S2. ROC Curve for evaluating cutoff thresholds for focal UIP diagnosis. (A) Table showing results of individual fits of a univariate Cox proportional hazards model to each cutoff threshold. A 10% area of UIP within the wider diseased area showed the highest separation between prognostic states. 'n Positive' indicates the number of cases positive for focal UIP using that cutoff value. (B) ROC curve showing predictive ability of UIP area percentage for death ($n = 50$) or lung transplant ($n = 5$) occurrence. Data point with the highest distance from the center line is highlighted with a red residual line (sensitivity = 0.873, specificity = 0.38, threshold = 10.05%). HR, hazard ratio.

Table S1. Surgical lung biopsy sampling location data for a 201-patient PPF cohort. Typically, one biopsy each was taken from segments S5, S8, and S9, and the average number of slides per case was 2.65. Values presented as counts.