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Idiopathic pulmonary fibrosis: significance of the usual interstitial pneumonia (UIP) CT-scan patterns defined in new international guidelines

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Abstract

Introduction. The new 2018 international guidelines for diagnosing usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF) by CT scan split the old pattern *possible UIP* (2011 IPF guidelines) into two new patterns: *probable UIP* and *indeterminate for UIP*. However, the proportions and prognoses of these new CT-scan patterns are not clear.

Methods. We used a monocentric retrospective cohort of 322 patients suspected of having IPF (University Hospital of Rennes; Competence Center for Rare Lung Diseases; 1 January 2012-31 December 2017). All patients initially diagnosed by CT scan as *possible UIP* were included. The chest CT-scans were then reclassified according to the new 2018 international guidelines by 3 observers. These data were then subjected to survival analysis with multivariate Cox regression using a composite endpoint of death, lung transplantation, a decline of $\geq 10\%$ in forced vital capacity (FVC), or hospitalization.

Results. Of the 89 *possible UIP* patients included, 74 (83%) were reclassified as *probable UIP* and 15 (17%) as *indeterminate for UIP*. *Probable UIP* patients were more likely to meet the composite endpoint (56/74 [75.7%] vs. 5/15 [33%] patients; HR [IC 95%] = 3.12 [1.24 ; 7.83], $p=0.015$). Multivariate analysis indicated that the *probable UIP* pattern was associated with significantly increased risk of reaching the composite endpoint (HR [95% CI] = 2.85[1.00; 8.10], $p=0.049$).

Conclusion. The majority of *possible UIP* diagnoses corresponded to *probable UIP*, which was associated with a significantly worse prognosis than *indeterminate for UIP*. This distinction between these two CT patterns emphasizes the relevance of the new international guidelines for the diagnosis of IPF.

Keywords: interstitial lung disease, computed tomography, prognostic factors, outcomes, nintedanib, pirfenidone

Introduction

Idiopathic pulmonary fibrosis (IPF) is a diffuse interstitial lung disease (ILD) associated with a CT-scan and/or histopathological pattern of usual interstitial pneumonia (UIP) (1) that is chronic, gradually worsens and is incurable (excluding lung transplantation) (2). Some patients experience a slow gradual decline in respiratory function, while in others the disease worsens very rapidly during acute exacerbations or "flare-ups" (2). The median survival of all patients with IPF is 3 years from diagnosis (2). Chest CT-scan is now prominent in the management of those patients, in order to obtain an accurate, early diagnosis needed for treatment with the anti-fibrotic drug that have recently become available (3,4).

The 2011 IPF international guidelines identified three degrees of diagnostic certainty for UIP assessed with a CT-scan: *typical UIP*, *possible UIP*, and *inconsistent with UIP* (5). However, the *possible UIP* pattern was problematic because it included a large proportion of patients, who theoretically had to be subjected to potentially dangerous surgical biopsy (5). The data accumulated over the past 15 years have led to the *possible UIP* CT-scan pattern being divided into *probable UIP* and *indeterminate for UIP*, with biopsy being less frequent in the *probable UIP* patients (6). The Fleischner Society's White Paper and the new IPF international guidelines have established four CT-scan categories: *typical UIP*, *probable UIP*, *indeterminate for UIP* and *alternative diagnosis* (6,7). Chest CT-scans previously classified as *possible UIP* are now classified as *probable UIP* or *indeterminate for UIP*.

However, the frequency of distribution of *probable UIP* and *indeterminate for UIP* within the former *possible UIP* pattern is not known precisely, and only few data are available on the prognoses of these two new CT-scan patterns (8). Therefore, we analyzed retrospectively the clinical, functional, radiological and prognostic differences between the *possible UIP* patients reclassified as *probable UIP* or *indeterminate for UIP*.

Methods

Design and study population.

This retrospective, monocentric cohort study was conducted in the Pulmonology Department of the University Hospital of Rennes (Competences Center for Rare Pulmonary Diseases). It included all patients suspected of having IPF and initially diagnosed by CT-scan as *possible UIP* in multidisciplinary discussion (MDD), between 1 January 2012 and 31 December 2017. Patients with known causes of ILD (occupational or environmental exposure, systemic disease, or drug toxicity) were not eligible. The MDD followed the 2011 IPF international guidelines throughout the inclusion period (5).

The study was approved by the ethics committee of the University Hospital of Rennes (n°19.82).

Data collection.

Demographic (gender, age), clinical (comorbidities, dyspnea, tobacco use, performance of surgical lung biopsy), and functional data at the time of diagnosis were obtained from the hospital computerized medical records. The Charlson comorbidity score was calculated (9). Dyspnea was assessed using the New York Heart Association (NYHA) scale. Pulmonary

functional tests (PFTs) were performed according to international recommendations (10,11). The gender age physiology (GAP) score was calculated as proposed by Ley et al (12).

Prognosis data, including death/lung transplantation, functional decline, hospitalization, were obtained for all patients from the hospital medical records and verified with each patient's general practitioner at the end of the analysis (April 2019). No patients were lost to follow-up.

Radiological evaluation.

The initial chest CT-scans of all patients were analyzed by 2 independent experienced observers (T.D. and L.S.), blinded to all clinical and histological data. All discrepancies were reviewed by a third observer (M.L.) and a consensus was reached. Chest CT-scans were reclassified according to the new international guidelines (7). Briefly, the CT features of the *probable UIP* pattern are subpleural and basal reticulations with peripheral traction bronchiectasis or bronchiolectasis (TB). Mild ground glass opacity might be present. The CT features of the *indeterminate for UIP* pattern are subpleural and basal subtle reticulations ("early UIP pattern") or lung fibrosis that do not suggest any specific etiology ("truly indeterminate") (7). The total disease extent, $\pm 5\%$, was calculated for each patient (13). The presence of peripheral TB and five interstitial features (reticulations, ground glass opacities, honeycombing, condensations, mosaic attenuation) and emphysema, based on the Fleischner Society glossary (14), was assessed (presence/ absence) for each patient.

Statistical analysis.

The quantitative variables normally distributed were reported as N, mean, standard deviation. Groups were compared by Student's *t* test. GAP score was the only quantitative variable not normally distributed. Thus it was reported by N, median, interquartile range. Groups were compared by the non-parametric Mann-Whitney U-test. The number (N) and percentage (%) are given for each modality of qualitative variables. These groups were compared using the χ^2 parametric test or Fisher's non-parametric test.

Survival was analyzed using a composite endpoint: time from initial MDD assessment to the first occurrence of all-cause death, lung transplantation, a decline of $\geq 10\%$ in absolute forced vital capacity (FVC), or all-cause hospitalization (15-17). Patients who did not report events were censored at the end of the analysis (30 April, 2019). Each component of the composite endpoint was evaluated independently using the total number of events observed during follow-up. Kaplan-Meier curves were prepared and compared using a log-rank test. The variables ($p <$

0.20) identified by univariate survival analysis with a Cox model were included in a multivariate model, which was followed by stepwise top-down selection.

All statistical tests (two-tailed $p < 0.05$) were performed with SAS software, version 9.4.

Results

Study population.

Overall, 89 patients were included (mean age 72.8 ± 8.2 years; 72 (80.9%) male) (Figure 1). Their characteristics are summarized in Table 1.

CT-scan Features

Of these 89 patients, 74 (83%) were reclassified with a *probable UIP* pattern (*probable UIP* group), and 15 (17%) with an *indeterminate UIP* pattern (*indeterminate UIP* group) (Table 1) (Figures 2-4). *Probable UIP* patients had more extensive disease and more frequent peripheral TB compared with *indeterminate UIP* patients (44.8% vs. 29.7%, $p=0.006$ and 74/74 [100.0%] vs. 7/15 [46.7%], $p<0.001$, respectively). *Indeterminate UIP* could be divided in 8 “early UIP pattern” and 7 “truly indeterminate”. Emphysema lesions were more common in the *indeterminate UIP* group ($p=0.03$) (Figure 4).

Demographic, clinical and functional characteristics

There was no difference in the age, sex, or Charlson comorbidity score between the groups (Table 1). More patients were smokers in the *indeterminate UIP* group (13/15; 86.7%) than in the *probable UIP* group (38/74; 52.8%) ($p=0.015$). Numerically, more *probable UIP* patients (31/34; 91%) displayed typical or probable UIP pathology than did the *indeterminate UIP* patients (5/7; 71%) ($p=0.196$). In the *indeterminate for UIP* group, alternative pathological diagnoses were possible UIP ($n=1$), hypersensitivity pneumonitis ($n=2$), and organized pneumonia ($n=2$). Impaired pulmonary function was more severe in *probable UIP* patients than in *indeterminate UIP* patients, with greater NYHA dyspnea (2.2 ± 1.1 vs. 1.1 ± 1.0 , $p<0.001$), lower FVC ($85.2 \pm 17.3\%$ vs. $103.7 \pm 18.6\%$, $p<0.001$), lower pulmonary carbon monoxide transfer (TLCO) ($50.3 \pm 16.3\%$ vs. $65.0 \pm 14.0\%$, $p=0.01$) and a higher GAP score (4.0 [3.0; 5.0] vs. 3.0 [2.0; 4.0], $p=0.04$).

Evolution

The mean follow-up period of the *probable UIP* group was 23.7 ± 15.8 months; it was 32.3 ± 20.5 months for the *indeterminate UIP* group ($p=0.071$). More *probable UIP* patients (56/74; 75.7%) met one of the composite endpoint events than did the *indeterminate for UIP* patients (5/15; 33%, HR [IC 95%] = 3.12 [1.24 ; 7.83], $p=0.015$) (Figure 5A). The median composite endpoint-free survival of the *probable UIP* patients was 22.5 months, while that of the *indeterminate UIP* group was not reached (Figure 5A).

Significantly more *probable UIP* patients (32/74; 43.2%) died or had lung transplants than did the *indeterminate UIP* patients (2/15; 13.3%, HR [IC 95%] = 4.66 [1.11; 19.61], $p=0.035$). The median lung transplant-free survival time was 46.2 months in the *probable UIP* group and was not reached by any of the *indeterminate UIP* group (Figure 5B). Significantly more *probable UIP* patients (35/64; 54.7%) demonstrated a $\geq 10\%$ decline in FVC than did those in the *indeterminate UIP* group (2/12; 16.7%, HR [IC 95%] = 4.28 [1.03; 17.84], $p=0.045$) (Figure 5C). No significant difference was seen between the groups for all-cause hospitalizations (38/66; 57.6% and 3/11; 27.3%, HR [IC 95%] = 2.39 [0.74; 7.76], $p=0.145$) (Figure 5D).

Univariate analysis indicated that the parameters significantly associated with the composite endpoint were: FVC % predicted value ($p=0.001$), TLCO % predicted value ($p<0.0001$), GAP score ($p=0.01$), *probable UIP* CT pattern ($p=0.015$), total CT disease extent ($p=0.004$) (Table 2). Multivariate analysis showed that only TLCO (HR [95%CI] = 0.73 [0.61; 0.88], $p<0.001$) and a *probable UIP* CT-scan pattern (HR [95%CI] = 2.85 [1.00; 8.10], $p=0.049$) were significantly associated with the composite endpoint (Table 2).

Discussion

In this study, we reclassified 83% of the patients having an initial *possible UIP* CT pattern (2011 IPF guidelines) (5) as *probable UIP* (2018 IPF guidelines) (7); the remaining 17% were assigned to the *indeterminate for UIP* category (2018 IPF guidelines) (7). The *probable UIP* CT pattern was associated with more severe functional impairment at diagnosis, an increased risk of death, lung transplantation, and a decline in FVC during follow-up than was the *indeterminate for UIP* pattern. The median lung transplant-free survival time of 46.2 months indicated that the prognosis for these *probable UIP* patients appears to be similar to that of *typical UIP* patients (18).

Our results are consistent with those of Putman *et al.* who recently observed that the *typical UIP* and *probable UIP* CT patterns were associated with a greater risk of death than was the *indeterminate for UIP* pattern (8).

The new 2018 international guidelines for CT diagnosis of UIP were developed from several studies that took into account the diagnostic and prognostic value of TB (19-22), together with the presence of signs that can make it difficult to classify ILD, such as the heterogeneous appearance of the CT abnormalities and the absence of geographical predominance (23). However, neither the proportions nor the prognoses of the *probable UIP* and *indeterminate for UIP* patterns were assessed in these studies.

We found a prevalence of pathological UIP of 91% for the *probable UIP* CT pattern and 71% for the *indeterminate UIP* CT pattern. The absence of a statistically significant difference could be explained by the lack of patients undergoing pulmonary biopsies. Nevertheless, these results are consistent with previous studies. Chung *et al.* found a pathological UIP predictive value of 82% for the *probable UIP* pattern and 54% for the *indeterminate for UIP* pattern (21). Brownell *et al.* showed that the probability of pathological UIP was 95-97% in presence of severe and extensive TB on the chest CT-scan (22).

The *probable UIP* pattern was by definition associated with the presence of peripheral TB, but, more specifically in our study, with a more extensive disease on the chest CT-scan, two well-recognized prognostic factors (19,20). The *indeterminate UIP* pattern could also include the presence of peripheral TB when the chest CT-scan showed features of lung fibrosis without any specific etiology (7).

We also identified significantly more smokers with lung emphysema in the *indeterminate UIP* group. Some scans reclassified as *indeterminate for UIP* with emphysema lesions may have been retrospectively related to both *smoking-related interstitial fibrosis (SRIF)* and *airspace enlargement with fibrosis (AEF)* entities (Figure 4) (24,25), which are associated with a slower clinical course than UIP (26). We have not categorized these entities because their diagnostic criteria are not yet sufficiently validated on CT without pathological confirmation. The *indeterminate UIP* pattern remains a grey area that could include all patients without the three other patterns (*typical UIP*, *probable UIP*, and *alternative diagnosis*), thereby covering SRIF/AEF. However, despite a greater proportion of patients with pulmonary emphysema lesions in the *indeterminate UIP* group, we observed more respiratory functional impairment

in the *probable UIP* than in the *indeterminate UIP* group. This point supports the nosological distinction and reinforces the value of the new recommendations (7).

This study has some limitations. First, data were missing from the PFTs and hospitalizations records because of the retrospective cohort design. But in view of the objective of the study (i.e. reclassifying CT scans from an old to a new classification), the design could only be retrospective in nature. We have tried to reduce missing data as much as possible. No patient was lost to follow-up and no data were missing for lung transplant-free survival. We therefore believe that our analyses make sense, despite limitations inherent to the study design. Second, our study involved a single tertiary center, which may limit generalization of these results. However, we strived to select only patients whose diagnosis of *possible UIP* had been validated by MDD. Between 2011 and 2018, there was no substantial change in our institution, either in CT acquisition technique, or in the reading of CT scans. We therefore believe that this MDD reading was reproducible over the 7 years of the study and that such a design is the guarantee of a "real life" study. Finally, only a small number of patients were diagnosed with *indeterminate for UIP* pattern (n=15). This limited sample size does not invalidate the results of the multivariate analysis (because there was only two variables in the final model), but it should lead to some caution in interpreting the results. In addition, this group of *indeterminate UIP* was composed of 8 "early UIP pattern" and 7 "truly indeterminate" patients. Having more than half patients with such a limited disease has undoubtedly accentuated the difference of prognosis with the *probable UIP* patients, and may therefore constitute a bias.

In conclusion, we have shown that the majority of *possible UIP* cases correspond to *probable UIP* while a minority correspond to *indeterminate for UIP* whose prognosis is significantly better. The *probable UIP* CT-scan pattern is a powerful prognostic marker when IPF is suspected. These data provide additional evidence of the relevance of the new international guidelines by confirming the value of separating these two CT entities *probable UIP* and *indeterminate for UIP* (7). However, research efforts in this area must be continued in order to further refine the non-invasive stratification of patients suspected of having IPF.

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Figure 1: Flow chart

IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; CT, CT scan; UIP, usual interstitial pneumonia

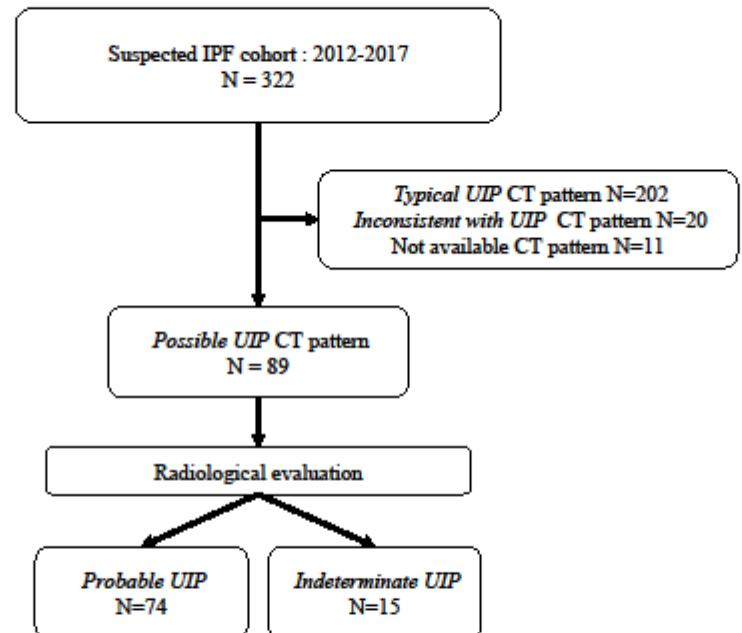


Figure 2: Possible Usual Interstitial Pneumonia (UIP) CT scan (CT) reclassified as Probable UIP.

(A-C) Multiple native axial sections and (D) reconstruction in the sagittal plane, showing reticulations with peripheral traction bronchiolectasis with sub-pleural and basal predominance. Some ground glass opacities are also present in the sub-pleural and basal regions. A UIP was confirmed by surgical lung biopsy. The patient died 30.5 months after diagnosis.

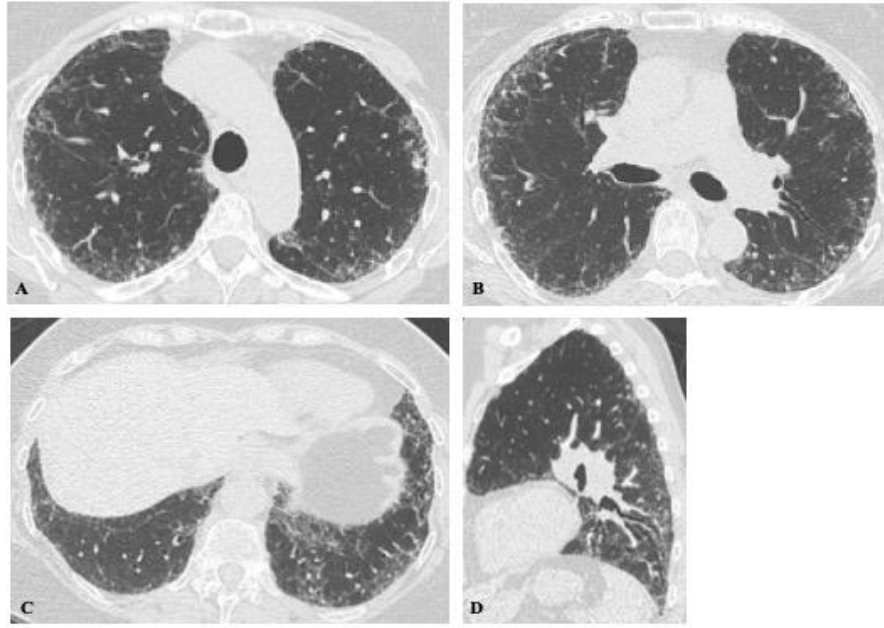


Figure 3: Possible Usual Interstitial Pneumonia (UIP) CT scan (CT) reclassified as indeterminate for UIP.

(A-C) Multiple native axial sections and (D) reconstruction in the sagittal plane, showing reticular opacities with slightly extended ground glass opacities in sub-pleural and basal regions, without peripheral traction bronchiolectasis. A UIP was confirmed by surgical lung biopsy. The patient is still alive 47 months after diagnosis, with no decline in forced vital capacity (FVC) or hospitalization

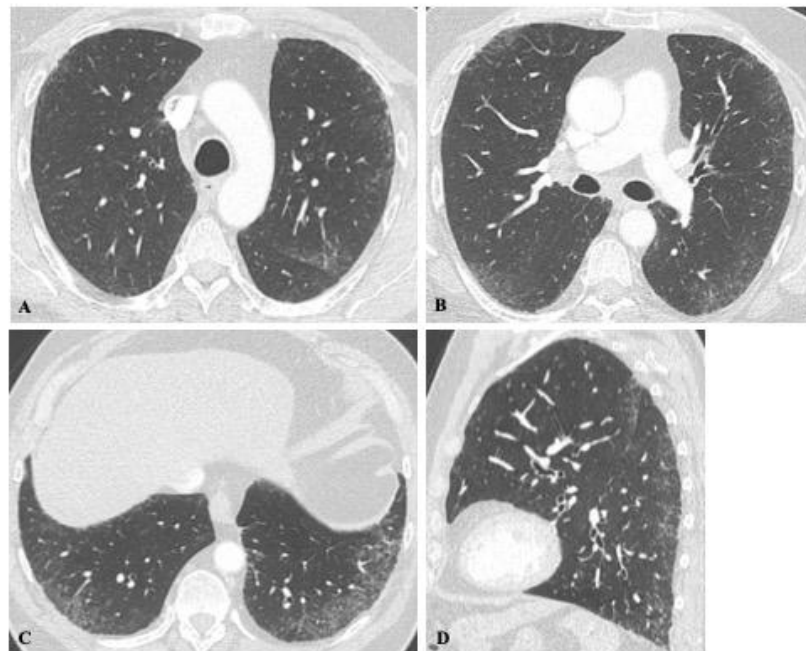


Figure 4: Possible Usual Interstitial Pneumonia (UIP) CT scan (CT) reclassified as indeterminate for UIP.

(A-D) Multiple native axial sections showing mild-to-moderate pulmonary fibrosis with ground glass opacities slightly more extensive than reticular opacities. The presence of clusters of cysts of varying size and

shape, with respect of subpleural areas and little architectural distortion, may suggest *smoking-related interstitial fibrosis/airspace enlargement with fibrosis* (SRIF/AEF) but no surgical lung biopsy was taken. The patient died 58.5 months after diagnosis; progression was slow.

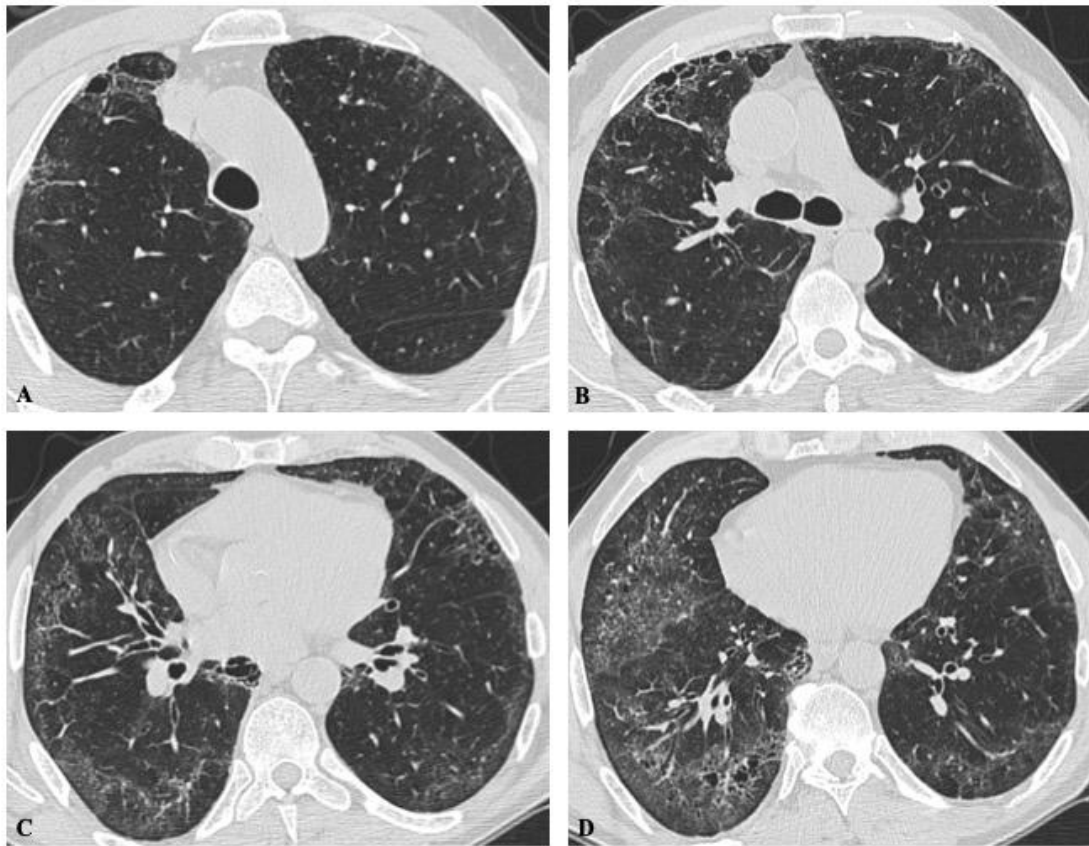


Figure 5: Kaplan-Meier survival curves for composite endpoint (A) and the components: death or lung transplantation (B), decline in FVC \geq 10% (C), hospitalization (D), by CT-scan group.

FVC, forced vital capacity

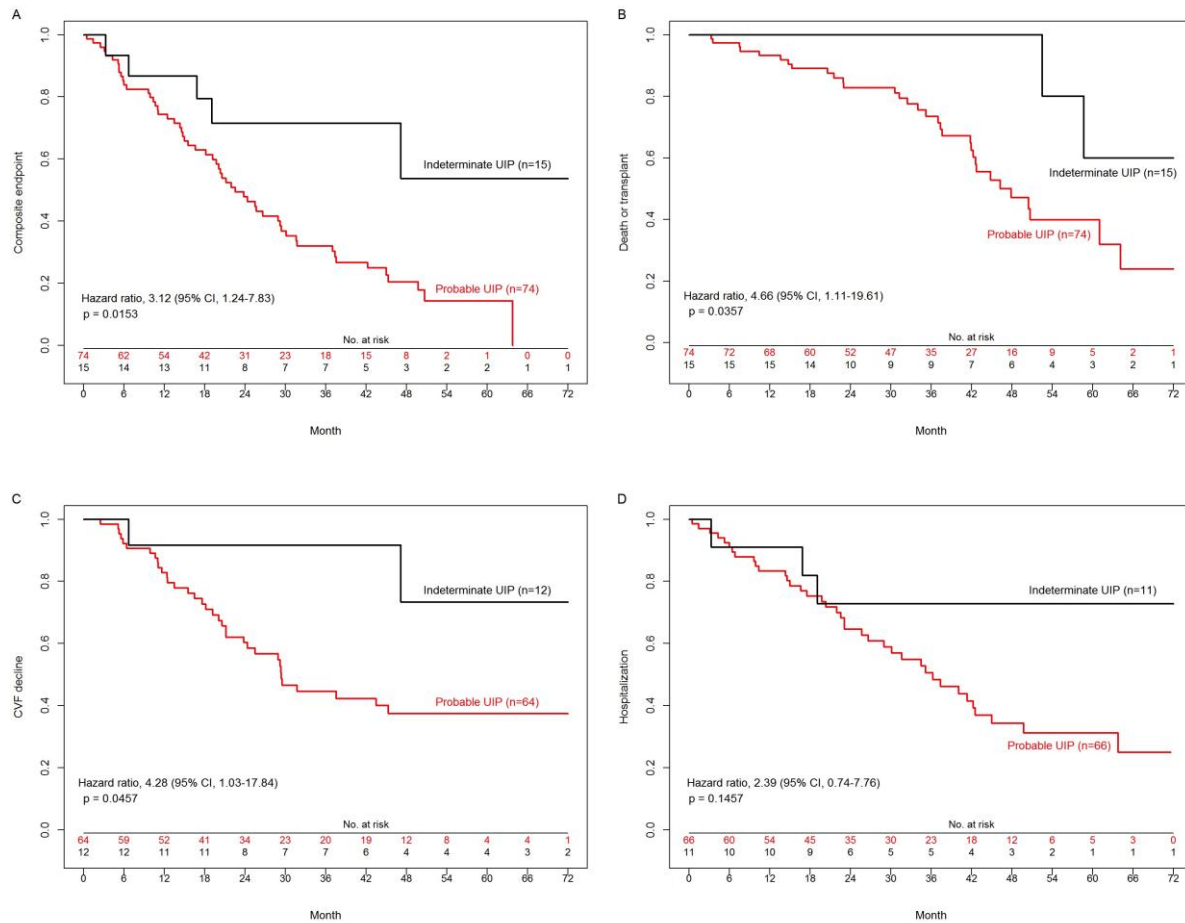


Table 1. Patient characteristics at diagnosis

| Characteristic | All patients (possible UIP) N = 89 | Probable UIP N = 74 | Indeterminate [#] UIP N = 15 | p |
|---------------------------------------|--|------------------------|---|--------|
| Age (years) | 72.8 ± 8.2 | 73.3 ± 8.3 | 70.2 ± 6.9 | 0.178 |
| Sex (male) | 72 (80.9%) | 59 (79.7%) | 13 (86.7%) | 0.726 |
| Tobacco use | 51 (58.6%) | 38 (52.8%) | 13 (86.7%) | 0.015 |
| Charlson comorbidity score | | | | 0.465 |
| 0 | 40 (44.9%) | 33 (44.6%) | 7 (46.7%) | |
| 1 | 26 (29.2%) | 23 (31.1%) | 3 (20.0%) | |
| 2 | 15 (16.9%) | 10 (13.5%) | 5 (33.3%) | |
| 3 | 6 (6.7%) | 6 (8.1%) | 0 (0.0%) | |
| 4 | 1 (1.1%) | 1 (1.4%) | 0 (0.0%) | |
| 5 | 1 (1.1%) | 1 (1.4%) | 0 (0.0%) | |
| Surgical lung biopsy performed | 41 (46.1%) | 34 (45.9%) | 7 (46.7%) | 0.959 |
| Pathological UIP/surgical lung biopsy | 36/41 (87.8%) | 31/34 (91.2%) | 5/7 (71.4%) | 0.196 |
| Dyspnea (NYHA stages) | 2.0 ± 1.2 | 2.2 ± 1.1 | 1.1 ± 1.0 | <0.001 |

| | | | | |
|-------------------------|-----------------|-----------------|----------------|--------|
| FVC % pred | 88.2 ± 18.7 | 85.2 ± 17.3 | 103.7 ± 18.6 | <0.001 |
| TLCO % pred | 52.6 ± 16.7 | 50.3 ± 16.3 | 65.0 ± 14.0 | 0.003 |
| GAP score | 4.0 [3.0 ; 4.0] | 4.0 [3.0 ; 5.0] | 3.0 [2.0; 4.0] | 0.041* |
| CT total disease extent | 42.2 ± 19.9 | 44.8 ± 19.2 | 29.7 ± 18.9 | 0.006 |
| CT features | | | | |
| Peripheral TB | 81 (91.0%) | 74 (100.0%) | 7 (46.7%) | <0.001 |
| Reticulations | 89 (100.0%) | 74 (100.0%) | 15 (100.0%) | NA |
| Ground glass opacity | 77 (86.5%) | 66 (89.2%) | 11 (73.3%) | 0.113 |
| Honeycombing | 0 | 0 | 0 | NA |
| Condensations | 5 (5.6%) | 5 (6.8%) | 0 (0.0%) | 0.584 |
| Mosaic attenuation | 9 (10.1%) | 8 (10.8%) | 1 (6.7%) | 1.000 |
| Emphysema | 19 (21.3%) | 13 (17.6%) | 6 (40.0%) | 0.034 |
| Follow-up time (months) | 25.2 ± 16.9 | 23.7 ± 15.9 | 34.2 ± 20.5 | 0.071 |

[#]*Indeterminate UIP* pattern includes 8 “early UIP pattern” and 7 “truly indeterminate”.

UIP, usual interstitial pneumonia; NYHA, New York Heart Association; FVC, forced vital capacity; % pred, % of predicted value; TLCO, carbon monoxide lung transfer; GAP score, gender/ age/physiology score; CT, CT scan; TB, traction bronchiectasis; NA, not applicable.

Qualitative variables: number (%).

Quantitative variables normally distributed: mean ± standard deviation (Student’s *t* test).

*Quantitative variable not normally distributed: median, interquartile range (Mann-Whitney U-test)

Missing data: Tobacco, n=2; Dyspnea, n=5; FVC, n=1; TLCO, n=4; GAP score, n=4

Table 2. Univariate and multivariate survival analyses for the composite endpoint

HR: hazard ratio; FVC, forced vital capacity; % pred, % of predicted value; TLCO, pulmonary transfer of carbon monoxide; GAP score, gender/age/physiology score; CT, CT scan; UIP, usual interstitial pneumonia; TB, traction bronchiectasis

The following variables were included in the multivariate analysis: Charlson comorbidity score, FVC % pred, TLCO % pred, probable UIP CT pattern, total CT disease extent. A top-down selection was then made.

Missing data: Tobacco, n=2; FVC, n=1; TLCO, n=4; GAP score, n=4

| Variable | Univariate analysis | | Multivariate analysis | |
|-----------------------------------|---------------------|---------|-----------------------|--------|
| | HR [95%CI] | p | HR [95%CI] | p |
| Age (for 1 year) | 0.98 [0.95 ; 1.01] | 0.277 | | |
| Sex male | 1.12 [0.58 ; 2.17] | 0.728 | | |
| Tobacco use | 1.07 [0.64 ; 1.77] | 0.798 | | |
| Charlson comorbidity score | | 0.054 | | |
| 0 | 1 | | | |
| 1 | 2.00 [1.07 ; 3.72] | | | |
| ≥2 | 1.82 [0.98 ; 3.38] | | | |
| FVC % pred (for 10%) | 0.79 [0.68 ; 0.91] | 0.001 | | |
| TLCO % pred (for 10%) | 0.69 [0.58 ; 0.83] | < 0.001 | 0.73 [0.61 ; 0.88] | <0.001 |
| GAP score (for 1 point) | 1.26 [1.06 ; 1.50] | 0.01 | | |
| Probable UIP CT pattern | 3.12 [1.24 ; 7.83] | 0.015 | 2.85 [1.00 ; 8.10] | 0.049 |
| Total CT disease extent (for 10%) | 1.22 [1.06 ; 1.41] | 0.004 | | |
| CT features | | | | |
| Peripheral TB | 1.27 [0.39 ; 4.10] | 0.687 | | |
| Ground glass opacity | 2.68 [0.97 ; 7.40] | 0.057 | | |
| Condensations | 1.08 [0.39 ; 2.98] | 0.882 | | |
| Mosaic attenuation | 0.80 [0.34 ; 1.87] | 0.606 | | |
| Emphysema | 1.21 [0.66 ; 2.20] | 0.542 | | |