

# Clinical diagnosis of patients subjected to surgical lung biopsy with a probable usual interstitial pneumonia pattern on high-resolution computed tomography

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## Research

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# Abstract

**Background:** Usual interstitial pneumonia (UIP) can present with a probable pattern on high-resolution computed tomography (HRCT), but the probability of UIP by surgical lung biopsy in such cases remains controversial. We aimed to determine the final clinical diagnosis in patients with a probable UIP pattern on HRCT subjected to surgical lung biopsy.

**Methods:** HRCT images were assessed and categorized by three radiologists, and tissue slides were evaluated by two pathologists, all of whom were blinded to the clinical findings. The final clinical diagnosis was accomplished via a multidisciplinary discussion. Patients with a single layer of honeycombing located outside of the lower lobes on HRCT were not excluded.

**Results:** A total of 50 patients were evaluated. The most common final clinical diagnosis was fibrotic hypersensitivity pneumonitis (38.0%; 95% CI: 24.7% to 52.8%), followed by idiopathic pulmonary fibrosis (24.0%; 95% CI: 13.1% to 38.2%) and interstitial lung disease ascribed to gastroesophageal reflux disease (12.0%; 95% CI: 4.5% to 24.3%) and familial interstitial lung disease (10.0%; 95% CI: 3.3% to 21.8%). In the group without environmental exposure (n = 22), 10 patients had a final clinical diagnosis of idiopathic pulmonary fibrosis (45.5%; 95% CI: 24.4% to 67.8%). Irrespective of the final clinical diagnosis, by multivariate Cox analysis, patients with honeycombing, dyspnoea and the presence of fibroblastic foci on surgical lung biopsy had a high risk of death.

**Conclusions:** The most common disease associated with a probable UIP pattern on HRCT is fibrotic hypersensitivity pneumonitis, followed by idiopathic pulmonary fibrosis and interstitial lung disease ascribed to gastroesophageal reflux disease. In patients without environmental exposure, the frequency of UIP and a final clinical diagnosis of idiopathic pulmonary fibrosis are not sufficiently high to obviate the indication for surgical lung biopsy.

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a fibrosing interstitial lung disease (ILD) of unknown aetiology defined by the presence of usual interstitial pneumonia (UIP) patterns on surgical lung biopsy (SLB).(1) On high-resolution computed tomography (HRCT), the UIP pattern is characterized by predominant basal reticular abnormalities with honeycombing cysts and the absence of inconsistent features and is considered sufficient for diagnosis in the proper clinical context.(1) However, many patients with IPF do not have a UIP pattern on HRCT. Patients with the same findings of the UIP pattern except honeycombing were classified by the ATS/ERS/JTS and ALAT in 2011 as having possible UIP.(1)

Some studies found a high positive predictive value of a possible UIP pattern on HRCT for the diagnosis of UIP on lung biopsy.(2–6) However, these studies included patients with a high prevalence of UIP, which introduces a selection bias and inflates the diagnosis of IPF. A study of individuals with possible UIP pattern on HRCT showed that the positive predictive value is highly dependent on the underlying

prevalence.(5) In that study, the second most common diagnosis was hypersensitivity pneumonitis (HP). In Brazil, HP is a common cause of ILD.(7)

More recently, the Fleischner Society and ATS/ERS/JTS/ALAT guidelines suggested four categories for classifying HRCT patterns of UIP.(8, 9) In the absence of honeycombing and in the appropriate clinical context, a reticular pattern with lower lobe predominance and traction bronchiectasis should be considered not a possible UIP pattern but a probable UIP pattern. According to the Fleischner Society, SLB could be avoided in such cases, but the ATS/ERS/JRS/ALAT made a conditional recommendation for SLB in these cases.(8, 9)

The objective of the present study was to evaluate the frequency of IPF and other ILDs in patients with a probable UIP pattern on HRCT.

## Methods

This study was approved by the Ethics and Research Committee of the Federal University of Sao Paulo (register number 2.180.594). Informed consent was not required, as the data were collected retrospectively and anonymously analysed.

## Study population

Patients were selected retrospectively from ILD reference centres in Brazil. For inclusion in the study, HRCT, histological samples, and clinical data should be available for central review and a multidisciplinary discussion (MDD). All HRCT images were obtained within one year of the biopsy. Consecutive patients were evaluated until 50 filled the criteria for analysis.

## Inclusion criteria

The presence of a probable UIP pattern on HRCT according to ATS/ERS/JRS/ALAT 2018 guidelines.(9)

## Exclusion criteria

Patients with any one of the following HRCT UIP patterns: UIP, indeterminate or alternative diagnosis of UIP, including predominant bronchovascular abnormalities;(9) inadequate HRCT image quality; emphysema with extension greater than 10% on HRCT; diagnosis of connective tissue disease prior to SLB; and a probable UIP pattern on HRCT with exposure to HP and lymphocytosis (> 20%) in bronchoalveolar lavage. Patients with a single layer of honeycombing cysts located outside of the lower lobes on HRCT were not excluded.

## Clinical data

Demographic data were recorded. Dyspnoea was scored as absent, major, moderate, small efforts or at rest.

The gastroesophageal reflux disease (GERD) symptoms investigated included heartburn, regurgitation and dyspepsia. Gastroesophageal reflux disease was evaluated by endoscopy, oesophageal manometry and pH monitoring.(10, 11)

Familial ILD was defined as the diagnosis of an ILD in two or more relatives who share common ancestry. (12)

Predicted values for forced vital capacity (FVC) were those derived from the Brazilian population.(13)

## **HRCT evaluation**

All HRCT scans were reviewed through a protocol by three thoracic radiologists (GSPM, IM and KN) with experience in ILD (18, 22 and 8 years, respectively) without knowledge of the clinical data and final clinical diagnosis. The presence of a probable UIP pattern in each patient was established by a consensus. Patients in which no consensus was reached among radiologists for probable UIP were excluded.

## **Histologic evaluation**

All samples were reviewed independently of each other by two pathologists (RGF and ENAMC) with experience in ILD (35 and 27 years, respectively).

The histological pattern of UIP was characterized according to the criteria proposed for definitive and probable UIP in 2011 by the ATS/ERS/JRS/ALAT.(1)

Bronchiolocentric fibrosis (BF) was defined by predominant involvement centred on the airways associated with inflammation or peribronchiolar metaplasia.(14) The presence of giant cells and granuloma, fibroblastic foci (FF) and microscopic honeycombing was noted. The number of FF was considered relevant if greater than occasional.(15)

Histological findings suggestive of autoimmune disease were characterized by the presence of lymphocytic pleuritis, bronchiolitis, vascular sclerosis, several lymphoid follicles, and intense lymphoplasmacytic infiltrate.(16)

Unclassifiable interstitial lung disease was defined as the presence of overlapping patterns found in a single lobe or multiple lobes or when it was not possible to include the patient in any of the categories proposed for the classification of interstitial pneumonias.(17)

## **Final clinical diagnosis**

The patients were reassessed, and the final clinical diagnosis was established by an MDD with the same pathologists and three pulmonologists experienced in ILD (RCCT, MRS, and CACP). IPF was defined as definitive or probable histological patterns of UIP in the absence of other potential aetiologies.(1) In the presence of environmental exposure, the diagnosis was still defined as IPF in the presence of a UIP pattern in more than one lobe, without any other histological findings suggestive of HP.(18) Fibrotic

hypersensitivity pneumonitis (FHP) was defined as the presence of environmental exposure before the onset of symptoms and by the presence of one of the following histological findings: 1) BF and/or lymphomononuclear infiltrate, bronchiolar poorly defined non-necrotizing granulomas, and/or giant cells and bronchiolitis or 2) BF with or without giant cells or granulomas in the absence of GERD.(19)

For the diagnosis of ILD ascribed to GERD, the patients had to fulfil the following criteria(14) in the presence or absence of symptoms of GERD: histological patterns of BF in the absence of environmental exposure to HP and GERD confirmed through one or more of the following: esophagitis on upper gastrointestinal endoscopy or abnormal oesophageal pH monitoring characterized by a DeMeester score greater than 14.7 or proximal reflux characterized by 1% or more of the total time with a pH less than 4 at the proximal sensor.(10, 11)

The clinical diagnosis of familial ILD was maintained irrespective of the histopathologic findings.(20) Interstitial pneumonia with autoimmune features was characterized as suggested by the ATS/ERS task force.(21)

## **Statistical analysis**

Continuous data are expressed as the mean and standard deviation or as the median and interquartile range. Categorical variables are described as absolute numbers and percentages. The values for the most common final clinical diagnosis and histologic patterns are expressed as the mean percentage and 95% confidence interval of proportions. The comparison between categorical variables was performed using Fisher's exact chi-square test.

The test characteristics of the probable UIP pattern (sensitivity, specificity and positive predictive value) for histopathological UIP were calculated using the prevalence of IPF observed in Brazil (10%) and in other countries with the highest prevalence.(7, 22, 23)

Survival time was calculated from the date of biopsy to death, lung transplantation (n = 1) or loss to follow-up. The survival status was obtained from telephone interviews and/or medical records. The follow-up time was censored on April 30, 2019. All-cause mortality was evaluated.

Univariate Cox analysis was performed to select variables related to survival, and those with p values < 0.20 were entered into a multivariate forward Wald Cox model to select variables predictive of survival. Kaplan-Meier curves were generated to calculate the median survival time and to compare survival between patients with and without the variables of interest.

A p value < 0.05 was considered statistically significant.

Statistical analysis was performed using SPSS software version 21 (IBM, Armonk, NY, USA).

## **Results**

One hundred seventy-seven patients with HRCT images available for re-reading and an SLB sample available for review were selected. After review, 127 patients were excluded (Supplementary Figure S1). Ultimately, 50 patients were included (Supplementary Figure S2). The general characteristics are described in Table 1.

Environmental exposure to HP was reported in 28 patients (56%): mould (n = 10), birds/feathers (n = 11), mould and birds (n = 4), and wood dust (n = 3).

Gastroesophageal reflux disease symptoms were also common and were reported in 22 (44%) patients.

Honeycombing located outside of the lower lobes was recorded in eight patients (16.0%).

Table 1  
General features of 50 patients with a probable usual interstitial pneumonia pattern on HRCT

Characteristic	
Age in years, $\bar{x} \pm SD$	64.0 $\pm$ 7.4
Sex, male, n (%)	32 (64.0)
Duration of symptoms in months, median (Q1-Q3) (n = 47)	15.0 (6.8–36.0)
Smoking history, n (%)	26 (52.0)
Environmental exposure, n (%)	28 (56.0)
Family history, n (%)	5 (10.0)
Dyspnoea, any, n (%)	41 (82.0)
Cough, yes, n (%)	32 (64.0)
Symptoms of GERD, n (%)	22 (44.0)
GERD confirmed, n (%)	16 (32.0)
Velcro crackles, n (%)	34 (68.0)
FVC% predicted, $\bar{x} \pm SD$	80.9 $\pm$ 16.8
FEV <sub>1</sub> % predicted, $\bar{x} \pm SD$	85.6 $\pm$ 17.9
FEV <sub>1</sub> /FVC, $\bar{x} \pm SD$	0.84 $\pm$ 0.08
SpO <sub>2</sub> rest % (n = 44), $\bar{x} \pm SD$	95.0 $\pm$ 1.9
Honeycombing on HRCT*, n (%)	8 (16.0)
* Patients with a single layer of honeycombing cysts located outside of the lower lobes. HRCT: High-resolution computed tomography; GERD: Gastroesophageal reflux disease; FVC: Forced vital capacity; FEV <sub>1</sub> : Forced expiratory volume in the first second; SpO <sub>2</sub> : Peripheral oxygen saturation.	

The histological patterns are described in Table 2. Bronchiolocentric fibrosis was the most commonly observed histological pattern, being observed in 26 (52.0%) patients. The classical histological triad of HP was found in seven (14%) patients, and BF with giant cells and/or granulomas was found in five (10%) patients, two of whom had histological findings of FF and/or microscopic honeycombing. The second most prevalent pattern was UIP (26%). Unclassifiable interstitial lung disease and interstitial pneumonia with autoimmune features were found in two (4%) patients each.

Table 2

Histological patterns of 50 patients with a probable usual interstitial pneumonia pattern on HRCT

<b>Histological pattern</b>	<b>n (%)</b>
Bronchiolocentric fibrosis	26 (52.0)
With fibroblastic foci and/or microscopic honeycombing	14 (28.0)
With giant cell and/or granulomas	3 (6.0)
With fibroblastic foci and/or microscopic honeycombing plus granulomas and/or giant cells	2 (4.0)
Without other findings	7 (14.0)
Usual interstitial pneumonia	13 (26.0)
Classical histological triad of hypersensitivity pneumonitis	7 (14.0)
Unclassifiable interstitial lung disease	2 (4.0)
Interstitial pneumonia with autoimmune features	2 (4.0)

The final clinical diagnoses are described in Table 3. The most frequent diagnosis was FHP, followed by IPF and ILD ascribed to GERD (Supplementary Figures S3, S4 and S5). After excluding patients with environmental exposure (n = 22), 10 (45%) patients were diagnosed with IPF (95% CI: 24.4–67.8%). One patient without apparent exposure but with typical findings on SLB received a final clinical diagnosis of FHP.

Table 3  
Final clinical diagnoses after a multidisciplinary discussion

Final clinical diagnosis	n (%); 95% CI
Fibrotic hypersensitivity pneumonitis	19 (38.0); 24.7–52.8%
Idiopathic pulmonary fibrosis	12 (24.0); 13.1–38.2%
Interstitial lung disease ascribed to GERD	6 (12.0); 4.5–24.3%
Familial interstitial lung disease	5 (10.0); 3.3–21.8%
Unclassifiable interstitial lung disease	2 (4.0); 0.5–13.7%
Fibrotic hypersensitivity pneumonia and/or interstitial lung disease ascribed to GERD	2 (4.0); 0.5–13.7%
Interstitial pneumonia with autoimmune features	2 (4.0); 0.5–13.7%
Idiopathic bronchiolocentric fibrosis	2 (4.0); 0.5–13.7%

In two patients, the final clinical diagnosis was FHP and/or ILD ascribed to GERD due to the presence of BF on histology, relevant environmental exposure and confirmed GERD. In two patients with histological findings of BF, no cause was apparent (idiopathic BF).

After the MDD, the two patients with histological patterns of unclassifiable interstitial lung disease remained without a final clinical diagnosis.

In five patients, there was a familial history of ILD, which was the final clinical diagnosis. These patients presented with the following histological patterns: BF (n = 3), UIP (n = 1) and classical histological triad of HP (n = 1).

Groups of patients with FHP, IPF and the other diagnoses were compared. As expected, the presence of environmental exposure was different between the groups: 20 (95.2%) in the FHP group, two (16.7%) in the IPF group and 11 (64.7%) in the other diagnoses group ( $\chi^2 = 21.8$ ;  $p < 0.001$ ). Confirmed GERD was more frequent in the group with other diagnoses: 11 (64.7%) compared to three (15%) in the FHP group and two (16.7%) in the IPF group ( $\chi^2 = 13.7$ ;  $p = 0.002$ ). The presence of Velcro crackles, FVC%, and peripheral oxygen saturation at rest and at the end of exercise was similar in the three groups (Supplementary Table S1).

In the present study, no patient died in the first month after SLB. The median general survival time was 72.0 (95% CI = 57.5–96.5) months. According to Kaplan-Meier curves, the median survival time was similar when patients with IPF, FHP and other diagnoses were compared (Supplementary Figure S6).

Honeycombing outside of the lower lobes was present in four patients with FHP, one with IPF, and three with other diagnoses. Fibroblastic foci were observed in all 13 patients with IPF, nine patients with FHP

and 10 patients with other diagnoses.

In the univariate Cox analysis, age, dyspnoea score, FVC%, FF and honeycombing on HRCT were selected. In the multivariate Cox analysis honeycombing outside of the lower lobes, dyspnoea score and FF on SLB remained significant (Table 4). When the FVC% was entered in the model instead of dyspnoea, it became significant, with lower values associated with poorer survival ( $p = 0.01$ ).

Table 4  
Multivariate analyses for survival\*

Factor	HR	95% CI	p-value
Honeycombing on HRCT**	11.9	2.9–55.0	0.001
Dyspnoea score	2.9	1.6-6.0	0.004
Fibroblastic foci on SLB	6.2	1.6–24.3	0.009

\*Model containing age, dyspnoea score, % predicted forced vital capacity, fibroblastic foci on SLB, and honeycombing on HRCT. \*\*A single layer of honeycombing cysts located outside of the lower lobes. HRCT: High-resolution chest tomography; SLB: Surgical lung biopsy.

Antifibrotic agents were prescribed for 13 patients, seven with IPF.

After excluding environmental exposure ( $n = 28$ ) as a possible cause of the number of FHP cases diagnosed, a probable UIP pattern on HRCT demonstrated a sensitivity and specificity of 83.3% (95% CI 51.6–97.9%) and 68.4% (95% CI 51.3–82.5%), respectively. The positive predictive value was 22.7% (95% CI 14.7–33.3%) when considering the prevalence of IPF as 10% and 63.7% (95% CI 50.8–74.9%) when considering the prevalence of IPF as 40%.

## Discussion

In the present study, FHP was the most frequent cause of a probable UIP pattern on HRCT. Considering only the patients without a history of environmental exposure, IPF was observed in less than 50% of the sample, with several ILDs diagnosed in the remaining subjects.

In 2011, the ATS proposed a tomographic classification for UIP in three categories.(1) In 2017, the Fleischner Society suggested splitting the possible group from ATS 2011 guidelines into the probable and indeterminate groups.(8) Probable UIP was characterized by the presence of a reticular pattern with peripheral traction bronchiectasis or bronchiolectasis in the absence of honeycombing. A diagnosis of IPF could confidently be made in a patient with a typical clinical context of IPF, with an HRCT pattern of probable UIP. (8)This statement was based on two papers: one had a recognized selection bias(3), and the other included patients with an undefined location of honeycombing on HRCT as a probable UIP pattern.(4)

Similar to the Fleischner Society, in 2018, the ATS/ERS/JRS/ALAT suggested a pattern of “probable UIP”, but the panel emphasized that the decision to perform SLB should be made in the context of an MDD by experienced clinicians.(9)

Criteria for the diagnosis of IPF have been discussed for a long time. Criteria for the diagnosis of FHP have been suggested more recently, but many differences persist.(24–26) Relevant environmental exposure, suggestive HRCT findings, and increased lymphocytes in bronchoalveolar lavage are important for diagnosis but are not helpful in many cases. Histopathologic findings can be typical, but these are absent in many cases of FHP.

In Brazil, HP is more common than IPF as a cause of ILD (24 vs 10%), as shown in a recent multicentre study.(7) However, 53% of all patients with ILD had potential exposure to HP, raising the question of whether other diagnoses can be excluded simply by the presence of environmental antigens. In the present study, only one patient without apparent exposure had a diagnosis of FHP, established by typical findings on biopsy. In contrast, in many studies, the causal agent for HP has not been identified.(25) Indeed, the prevalence of HP can be underestimated. In a study from Spain, almost half of the patients diagnosed with IPF on the basis of the 2011 criteria were subsequently diagnosed with FHP.(27)

Hypersensitivity pneumonitis can present with several histopathologic patterns.(18) In FHP, a typical pattern is characterized by chronic fibrosing pneumonia, airway-centred fibrosis and poorly formed non-necrotizing granulomas. Fibrosing interstitial pneumonia is characterized by architectural distortion; FF and subpleural honeycombing can be present. In airway-centred fibrosis or bronchiolocentric fibrosis, there is also extensive peribronchiolar metaplasia and, in many cases, bridging fibrosis. In FHP, the presence of granulomas and giant cells is uncommon. Another possible presentation for FHP is a pattern of nonspecific interstitial pneumonia.

In the present study, six patients were diagnosed with ILD ascribed to GERD. In these patients, the histological pattern was BF, there was no environmental exposure to HP, and GERD was substantiated. In our opinion, the role of GERD as an aetiological factor of fibrosing ILD, not UIP, has been neglected. (14)

In two patients in the present series with BF, FHP and ILD ascribed to GERD were possible causes. In our opinion, these patients cannot be discriminated by biopsy. In the other two patients, a possible cause for BF was not determined.

Patients with nonspecific interstitial pneumonia were not observed in the present series, probably due to a high frequency of findings inconsistent with UIP on HRCT.

In the present study, five patients had familial ILD. On SLB, three displayed BF with FF and/or microscopic honeycombing, one had a typical PH pattern, and one had an isolated UIP pattern. In a study of 30 patients with familial ILD, diagnostic features of UIP were observed in less than 50% of the samples, but FF was observed in 87%, and multifocal bronchiolocentric fibrosis was observed in 37%.(20) Familial interstitial lung disease presents in many different ways on HRCT and in lung biopsies.(12, 28) Genetic

factors can predispose patients to several ILDs, and diverse pathologic expressions can be found in the same family.(12, 29) The indications for SLB in familial ILD remain controversial. (30, 31)

The likelihood of a histopathological UIP pattern in patients with a probable UIP pattern on HRCT remains undefined.

In a recent paper from Japan, the prevalence of a histopathological UIP pattern was 83% (90 of 109) in patients with a probable UIP pattern on HRCT, but the diagnosis of IPF after the MDD was made in only 66%. (30) The median survival time was 72.1 months for patients with the probable UIP pattern, very similar to that found in our series. This survival time is longer than that found in patients with IPF and suggests that a heterogeneous number of diagnoses are included in the group with a probable UIP pattern. In this study, different clinical diagnoses were not the objective and were not explored. (32)

In the present study, the degree of dyspnoea, the presence of honeycombing not in the lower lobes irrespective of diagnosis, and the presence of FF on SLB were predictive of poor survival. The presence of honeycombing on HRCT in an ILD other than IPF is a predictor of a poor prognosis, but in most cases, honeycombing is present in the lower lobes. (33) Even with a limited sample, we found that honeycombing outside of the lower lobes was associated with poor survival, irrespective of the final diagnosis.

Fibroblastic foci are a major histological feature of UIP in SLB but can be present in other conditions. It has been recognized for a long time that the presence and extent of FF predicts poor survival in patients with IPF as well as in those with FHP. (15, 19, 34, 35)

In the INPULSIS trial, which evaluated the efficacy and safety of nintedanib in the treatment of IPF, subjects enrolled with the possible UIP pattern and traction bronchiectasis showed similar disease progression and treatment responsiveness to subjects enrolled with the IPF HRCT pattern. (36) This was used as an argument supporting these cases as IPF.

The INBUILD trial was a randomized, double-blind, multicentre, parallel group trial performed in 663 patients with a progressive fibrosing ILD other than IPF.(37, 38) Chronic hypersensitivity pneumonitis was diagnosed in 173 patients (26%). Participants were randomly assigned to receive 150 mg nintedanib twice daily or placebo for at least 52 weeks. Nintedanib reduced the rate of ILD progression, as measured by a decline in the FVC, irrespective of the underlying ILD diagnosis. In patients with a UIP-like fibrotic pattern, the adjusted rate of decline in the FVC over the 52-week period was more conspicuous. (38)

These studies raise the question of whether the diagnosis of ILD fibrosing really matters. In FHP, if the antigen is not identified, the prognosis is worse. (39) Otherwise, identification and antigen avoidance, even in FHP, can result in a prolonged survival time. (40) A subset of patients with FHP experience a progressive disease course, even after antigen avoidance, and these patients can be treated with pharmacologic agents, including antifibrotic drugs if necessary.

In patients with fibrotic ILD of indeterminate aetiology, we now indicate transbronchial lung cryobiopsy before entertaining SLB. (41)

Some authors suggest that older age, male sex and smoking could increase the positive predictive value for IPF diagnostics in patients with a possible UIP pattern on HRCT.(2) In the present study, these data were not helpful.

Several limitations to our study should be noted. The sample size was relatively small. This was a retrospective study, and selection bias should be considered. All the patients were reviewed by two expert pathologists in ILD, but the concordance was not evaluated. HRCT in expiration was not performed in all patients, so air trapping was not evaluated; however, this finding has a lower predicted value for separating FHP from IPF in comparison to the mosaic pattern.(42) Treatment was not standardized, making it difficult to evaluate its effect on survival.

## Conclusion

Different ILDs are observed in patients with a probable UIP pattern on HRCT. Even in patients without relevant environmental exposure, IPF should not be presumed as the most common diagnosis. After considering the risks, a biopsy approach should be entertained.

## List Of Abbreviations

ATS/ERS/JRS/ALAT: American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association

BF: Bronchiolocentric fibrosis

FF: Fibroblastic foci

FHP: Fibrotic hypersensitivity pneumonitis

FVC: Forced vital capacity

GERD: Gastroesophageal reflux disease

HP: Hypersensitivity pneumonitis

HRCT: High-resolution computed tomography

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

MDD: Multidisciplinary discussion

SLB: Surgical lung biopsy

UIP: Usual interstitial pneumonia

95% CI: 95% confidence interval

## Declarations

### Ethics approval and consent to participate

This study was approved by the institutional research ethics board, and the requirement for informed consent was waived due to the retrospective nature of the analysis.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional supplemental files.

### Competing interests

The authors declare that they have no competing interests.

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### Author's contributions

RCCT participated in the study design, had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data. MRS participated in the multidisciplinary discussion and helped draft the manuscript. KMS participated in the study design. GSPM, KN and IM collaborated to perform the radiological analysis. ENAMC and RGF collaborated to perform the histological analysis. CACP is the guarantor of the paper and coordinated the study, performed the statistical analysis and helped draft the manuscript. All authors read and approved the final manuscript.

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## References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788–824.
2. Fell CD, Martinez FJ, Liu LX, Murray S, Han MK, Kazerooni EA, et al. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2010;181(8):832–7.
3. Raghu G, Lynch D, Godwin JD, Webb R, Colby TV, Leslie KO, et al. Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial. *Lancet Respir Med*. 2014;2(4):277–84.
4. Chung JH, Chawla A, Peljto AL, Cool CD, Groshong SD, Talbert JL, et al. CT scan findings of probable usual interstitial pneumonitis have a high predictive value for histologic usual interstitial pneumonitis. *Chest*. 2015;147(2):450–9.
5. Brownell R, Moua T, Henry TS, Elicker BM, White D, Vittinghoff E, et al. The use of pretest probability increases the value of high-resolution CT in diagnosing usual interstitial pneumonia. *Thorax*. 2017;72(5):424–9.
6. Salisbury ML, Xia M, Murray S, Bartholmai BJ, Kazerooni EA, Meldrum CA, et al. Predictors of idiopathic pulmonary fibrosis in absence of radiologic honeycombing: A cross sectional analysis in ILD patients undergoing lung tissue sampling. *Respir Med*. 2016;118:88–95.
7. Pereira CAC, Soares MR, Botelho A, Gimenez A, Beraldo B, Fukuda C, et al. Multicenter Registry of Interstitial Lung Diseases in Adults in Brazil. *Am J Respir Crit Care Med*. 2020;201:A3352.
8. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med*. 2018;6(2):138–53.
9. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44–68.
10. Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol*. 1992;87(9):1102–11.
11. Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. *Am J Gastroenterol*. 1993;88(1):25–9.

12. Steele MP, Speer MC, Loyd JE, Brown KK, Herron A, Slifer SH, et al. Clinical and pathologic features of familial interstitial pneumonia. *Am J Respir Crit Care Med*. 2005;172(9):1146–52.
13. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. *J Bras Pneumol*. 2007;33(4):397–406.
14. Kuranishi LT, Leslie KO, Ferreira RG, Coletta EA, Storrer KM, Soares MR, et al. Airway-centered interstitial fibrosis: etiology, clinical findings and prognosis. *Respir Res*. 2015;16:55.
15. Coletta ENAM, Pereira CAC, Ferreira RG, Rubin AS, Vilela LS, Malheiros T, et al. Achados Histopatológicos e sobrevida na fibrose pulmonar idiopática. *J Bras Pneumol*. 2003;29(6):371–8.
16. Adegunsoye A, Oldham JM, Valenzi E, Lee C, Witt LJ, Chen L, et al. Interstitial Pneumonia With Autoimmune Features: Value of Histopathology. *Arch Pathol Lab Med*. 2017;141(7):960–9.
17. Travis WD, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188(6):733–48.
18. Takemura T, Akashi T, Kamiya H, Ikushima S, Ando T, Oritsu M, et al. Pathological differentiation of chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis/usual interstitial pneumonia. *Histopathology*. 2012;61(6):1026–35.
19. Churg A, Bilawich A, Wright JL. Pathology of Chronic Hypersensitivity Pneumonitis What Is It? What Are the Diagnostic Criteria? Why Do We Care? *Arch Pathol Lab Med*. 2018;142(1):109–19.
20. Leslie KO, Cool CD, Sporn TA, Curran-Everett D, Steele MP, Brown KK, et al. Familial idiopathic interstitial pneumonia: histopathology and survival in 30 patients. *Arch Pathol Lab Med*. 2012;136(11):1366–76.
21. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J*. 2015;46(4):976–87.
22. JH F, M K, KA MAJM. J, S S, et al. Baseline Characteristics and Comorbidities in the Canadian Registry for Pulmonary Fibrosis. *BMC pulmonary medicine*. 2019;19(1).
23. BF SS, BB C, JM S, D J. T, S K, et al. Interstitial Lung Disease in India. Results of a Prospective Registry. *American journal of respiratory and critical care medicine*. 2017;195(6).
24. Salisbury ML, Myers JL, Belloli EA, Kazerooni EA, Martinez FJ, Flaherty KR. Diagnosis and Treatment of Fibrotic Hypersensitivity Pneumonia. Where We Stand and Where We Need to Go. *Am J Respir Crit Care Med*. 2017;196(6):690–9.
25. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity Pneumonitis: Perspectives in Diagnosis and Management. *Am J Respir Crit Care Med*. 2017;196(6):680–9.
26. Morisset J, Johansson KA, Jones KD, Wolters PJ, Collard HR, Walsh SLF, et al. Identification of Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis: An International Modified Delphi Survey. *Am J Respir Crit Care Med*. 2018;197(8):1036–44.

27. Morell F, Villar A, Montero M, Muñoz X, Colby TV, Pipvath S, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med*. 2013;1(9):685–94.
28. Lee HY, Seo JB, Steele MP, Schwarz MI, Brown KK, Loyd JE, et al. High-resolution CT scan findings in familial interstitial pneumonia do not conform to those of idiopathic interstitial pneumonia. *Chest*. 2012;142(6):1577–83.
29. Adegunsoye A, Vij R, Noth I. Integrating Genomics Into Management of Fibrotic Interstitial Lung Disease. *Chest*. 2019;155(5):1026–40.
30. Borie R, Kannengiesser C, Sicre de Fontbrune F, Gouya L, Nathan N, Crestani B. Management of suspected monogenic lung fibrosis in a specialised centre. *Eur Respir Rev*. 2017;26(144).
31. Newton CA, Batra K, Torrealba J, Kozlitina J, Glazer CS, Aravena C, et al. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. *Eur Respir J*. 2016;48(6):1710–20.
32. Fukihara J, Kondoh Y, Brown KK, Kimura T, Kataoka K, Matsuda T, et al. Probable usual interstitial pneumonia pattern on chest CT: is it sufficient for a diagnosis of idiopathic pulmonary fibrosis? *Eur Respir J*. 2020;55(4).
33. Adegunsoye A, Oldham JM, Bellam SK, Montner S, Churpek MM, Noth I, et al. Computed Tomography Honeycombing Identifies a Progressive Fibrotic Phenotype with Increased Mortality across Diverse Interstitial Lung Diseases. *Ann Am Thorac Soc*. 2019;16(5):580–8.
34. King TE, Schwarz MI, Brown K, Tooze JA, Colby TV, Waldron JA, et al. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. *Am J Respir Crit Care Med*. 2001;164(6):1025–32.
35. Wang P, Jones KD, Urisman A, Elicker BM, Urbania T, Johannson KA, et al. Pathologic Findings and Prognosis in a Large Prospective Cohort of Chronic Hypersensitivity Pneumonitis. *Chest*. 2017;152(3):502–9.
36. Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, et al. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria. *Am J Respir Crit Care Med*. 2017;195(1):78–85.
37. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med*. 2019;381(18):1718–27.
38. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med*. 2020;8(5):453–60.
39. Fernández Pérez ER, Swigris JJ, Forssén AV, Tourin O, Solomon JJ, Huie TJ, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest*. 2013;144(5):1644–51.

40. Gimenez A, Storrer K, Kuranishi L, Soares MR, Ferreira RG, Pereira CAC. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. *Thorax*. 2018;73(4):391–2.
41. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med*. 2020;8(2):171–81.
42. Barnett J, Molyneaux PL, Rawal B, Abdullah R, Hare SS, Vancheeswaran R, et al. Variable utility of mosaic attenuation to distinguish fibrotic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis. *Eur Respir J*. 2019;54(1).

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