

Clinical Predictors of a Diagnosis of Idiopathic Pulmonary Fibrosis

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Rationale: Idiopathic pulmonary fibrosis (IPF) and other idiopathic interstitial pneumonias (IIPs) have similar clinical and radiographic features, but their histopathology, response to therapy, and natural history differ. A surgical lung biopsy is often required to distinguish between these entities.

Objectives: We sought to determine if clinical variables could predict a histopathologic diagnosis of IPF in patients without honeycomb change on high-resolution computed tomography (HRCT).

Methods: Data from 97 patients with biopsy-proven IPF and 38 patients with other IIPs were examined. Logistic regression models were built to identify the clinical variables that predict histopathologic diagnosis of IPF.

Measurements and Main Results: Increasing age and average total HRCT interstitial score on HRCT scan of the chest may predict a biopsy confirmation of IPF. Sex, pulmonary function, presence of desaturation, or distance walked during a 6-minute walk test did not help discriminate pulmonary fibrosis from other IIPs.

Conclusions: Clinical data may be used to predict a diagnosis of IPF over other IIPs. Validation of these data with a prospective study is needed.

Keywords: idiopathic pulmonary fibrosis; idiopathic interstitial pneumonia; diagnosis; computed tomography of the chest

Idiopathic interstitial pneumonias (IIPs), including idiopathic pulmonary fibrosis (IPF), are characterized by chronic dyspnea, interstitial infiltrates on radiographs, reduced lung volumes, and impaired diffusion capacity of the lung (DL_{CO}) (1). There is considerable overlap in the clinical features (2) of the IIPs, although the histopathologic features differ (1). An accurate diagnosis is critical as the response to treatment and prognosis differs between IIPs, with IPF having the worst prognosis (3–5). Difficulty in diagnostic separation between these entities has been emphasized by several groups (6–8), highlighting the need to optimize the diagnostic evaluation.

The diagnosis of IPF is confirmed when appropriate clinical and radiographic features are seen in combination with a surgical lung biopsy showing a pattern of usual interstitial pneumonia (UIP). In an appropriate clinical setting, a diagnosis of IPF can be made without a surgical lung biopsy when definitive high-resolution computed tomography (HRCT) scan features

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Idiopathic interstitial pneumonias (IIPs), including idiopathic pulmonary fibrosis (IPF), share many clinical and radiographic features. However, their histopathology, response to therapy, and natural history differ. A surgical lung biopsy is often required to differentiate early IPF from other non-IPF IIPs.

What This Study Adds to the Field

Age and total HRCT interstitial score on an HRCT scan of the chest may predict a diagnosis of biopsy-confirmed IPF over non-IPF IIPs. This study provides clinical variables that may be used to predict IPF over non-IPF IIPs, thus saving some patients from a surgical lung biopsy.

are present (8–10). Definitive features of UIP on HRCT include subpleural reticulation with a basal predominance and honeycombing with an absence of extensive ground glass abnormality, micronodules, discrete cysts, mosaic attenuation/air trapping, or consolidation (8–11). Unfortunately, many patients do not have definitive radiographic features of UIP, leaving a wide differential diagnosis and the requirement for a surgical lung biopsy. IPF is ultimately diagnosed in a large proportion of these patients based on the histopathologic finding of UIP (3). Unfortunately, many patients who present with fibrotic lung disease are elderly and have important comorbidities that increase the risk of a surgical lung biopsy (12–15). We hypothesized that a combination of clinical and radiological features could be used to accurately predict a diagnosis of IPF confirmed by surgical lung biopsy. Some of the results of these studies have been previously reported in the form of an abstract (16, 17).

METHODS

This is a retrospective study of 135 patients with biopsy-proven IPF/UIP ($n = 97$) or other IIPs ($n = 38$) from our database who did not have honeycomb change on HRCT. A total of 644 patients with evidence of fibrotic lung disease were enrolled sequentially into protocols investigating the etiology, diagnosis, and treatment of fibrotic lung disease from 1995 to 2006 (Figure 1). Patients without a surgical lung biopsy or in whom there was evidence of underlying connective tissue disease (ie, clinical diagnosis and/or specific serology and/or clear symptoms of connective tissue disease) or other cause of interstitial disease were excluded. Data were extracted for those patients with HRCT, pulmonary function testing (PFT), and 6-minute walk test (6MWT) within 6 months of the lung biopsy. Patients with evidence of pulmonary fibrosis but without honeycombing on HRCT (HRCT interstitial score <2) were then selected for data analysis (see below). A final diagnosis was

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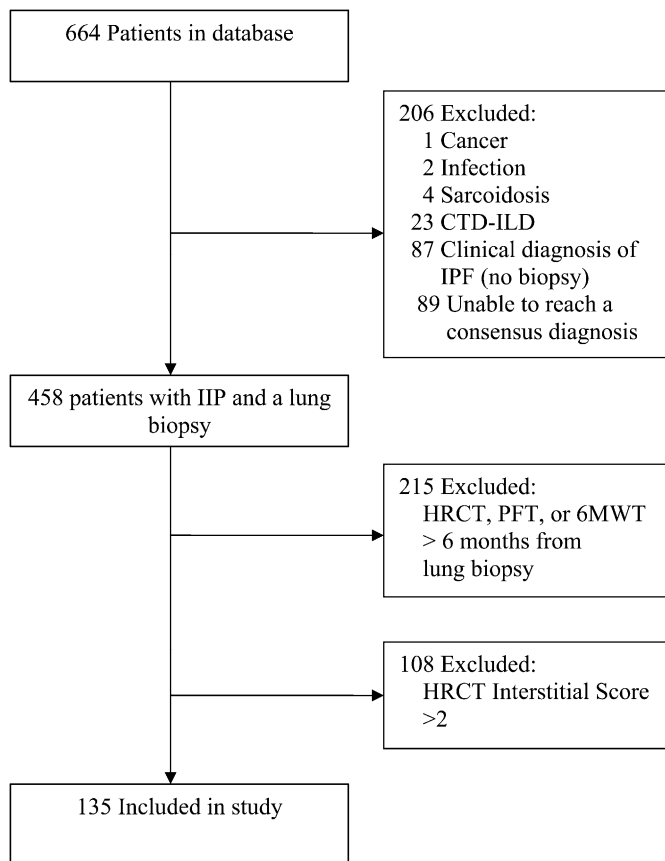


Figure 1. CONSORT diagram illustrating the selection of patients included in the data analysis. CTD-ILD = connective tissue disease–related interstitial lung disease; HRCT = high-resolution computed tomography; IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function tests; 6MWT = 6-minute walk test.

established using a clinical/radiological/pathological diagnostic schema that we have previously described (18).

HRCT scans were scored by two expert thoracic radiologists using a semiquantitative scale that assesses the degree of ground glass attenuation (HRCT alveolar score) and fibrotic change (HRCT interstitial score) (19) (Table 1 and Figure 2). Radiologists were blinded to the diagnosis. Agreement between the radiologists was very good ($\kappa = 0.727$; 95% confidence interval [CI], 0.641–0.813). It is important to recognize that an HRCT interstitial score of less than 2 in all lobes identifies patients without any honeycomb change on HRCT. Pulmonary function studies and 6MWT were performed as described (20, 21). 6MWT data include the distance walked and whether the patient’s oxygen saturation fell below 88% during the test.

Baseline demographic data, pulmonary function, 6MWT, and HRCT scores were compared between patients with IPF and non-IPF IIP using the Student *t* test for continuous variables (22) and the

chi-square test for categorical variables (23), except where indicated. Univariate and multivariate logistic models were constructed to determine which variables predict a diagnosis of IPF. The quality of the prediction models was evaluated using receiver operating characteristics (ROC) analysis with the area under the curve calculated (24). The positive predictive values (PPVs), specificities, sensitivities, and negative predictive values (NPVs) for new patients with different risk profiles were examined based on the final model. Statistical analysis was performed with R 2.8.0 software (<http://www.r-project.org/>).

RESULTS

We examined data from 97 patients with biopsy-proven IPF and 38 patients with other IIPs (nonspecific interstitial pneumonia, 19; hypersensitivity pneumonia, 9; respiratory bronchiolitis interstitial lung disease/desquamative interstitial pneumonia, 9; and cryptogenic organizing pneumonia, 1). Patients with IPF were significantly older, marginally more likely to be female, and had similar smoking histories. They had more fibrosis and less ground glass on HRCT. Pulmonary function and 6MWT results were similar between the groups (Table 2).

Univariate logistic regression models of demographic, HRCT, pulmonary function, and 6MWT variables were generated to determine which variables predict a diagnosis of IPF. Older patient age, lower HRCT alveolar scores, and higher HRCT interstitial scores were significant predictors of an IPF diagnosis (Table 3). Multivariate logistic regression models were used to determine variables that individually contribute toward prediction of IPF. From these analyses, increasing age (OR, 1.09 per year; 95% CI, 1.04–1.14; $P = 0.0007$) and increasing average HRCT interstitial score (OR, 10.44 per unit increase in score; 95% CI, 3.12–34.91; $P = 0.0001$) best predicted a diagnosis of IPF.

Age and HRCT interstitial scores were examined in detail for their ability to predict a diagnosis of IPF. Increasing age was a powerful predictor of IPF. Age of at least 70 years was associated with a PPV for IPF of at least 95% (Table 4). When HRCT interstitial score was combined with age the ability to predict the presence of IPF improved and could be expanded to even younger patients (Table 5). The likelihood ratio for this model is 40.73 ($P < 0.001$). For example, a patient aged 50 years or older with an HRCT interstitial score of at least 0.8 had a PPV of IPF of at least 97%. ROC analyses were performed for the model with age alone and the model with age combined with HRCT interstitial score (data not shown). The areas under the ROC curves were 0.77 and 0.84, respectively, for these two models, with $P < 0.0001$ for improved prediction based on the model including HRCT interstitial score. These data demonstrate the potential clinical usefulness of semiquantitative HRCT scoring in aiding in the diagnosis of IPF.

For user convenience, we provide a probability of IPF score (Table 6), which predicts the PPV, NPV, sensitivity, and specificity of a diagnosis of IPF based on a patient’s age and HRCT interstitial score using the formula:

TABLE 1. HIGH-RESOLUTION COMPUTED TOMOGRAPHY SCORING SYSTEM (19)

Score	Alveolar	Interstitial
0	No alveolar disease	No interstitial disease
1	Ground glass opacity <5% of lobe	Septal thickening but no honeycomb
2	Ground glass opacity <25% of lobe	Honeycomb change <25% of lobe
3	Ground glass opacity 25–49% of lobe	Honeycomb change 25–49% of lobe
4	Ground glass opacity 50–75% of lobe	Honeycomb change 50–75% of lobe
5	Ground glass opacity >75% of lobe	Honeycomb change >75% of lobe

Radiologists score each lobe and then take an average of all the lobes for the final HRCT scores.

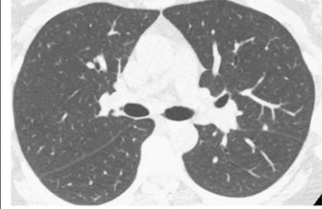



	<u>Panel A</u> RUL 0/0 RLL 0/0 LUL 0/0 LLL 0/0		<u>Panel B</u> RUL 1/1 RLL 1/1 LUL 2/1 LLL 2/1
	<u>Panel C</u> RUL 1/2 RLL 0/1 LUL 1/2 LLL 0/1		<u>Panel D</u> RUL 0/2 RLL 0/3 LUL 0/3 LLL 0/3

Figure 2. Examples of varied high-resolution computed tomography (HRCT) alveolar and HRCT interstitial scores. Each panel is from a different patient. The scores for each panel are for the image that is displayed. Scores are represented as alveolar/interstitial. LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RUL = right upper lobe.

$$\text{probability of IPF score} = [(0.084 \times \text{Age} + 2.346 \times \text{HRCT interstitial score} - 3.31) / 5.856]$$

(truncate negative values as 0; positive values >1 as 1)

The distribution of the probability of IPF scores for patients in this study is shown in Figure 3.

The probability of IPF score can be used to estimate the probability of IPF for an individual patient. For example, if a patient has an average HRCT interstitial score of 0.8 and is 50 years old, the probability of IPF score would be 0.5 corresponding to a PPV of 86% for the presence of IPF. If the same patient is 70 years old, the probability of IPF score would be 0.8 and the PPV for the presence of IPF is 100%.

DISCUSSION

Differentiating between IPF and non-IPF IIPs is clinically relevant and in some cases can be accomplished without a surgical lung biopsy (9, 10). In this study we examined the ability of clinical variables to predict a histopathologic pattern of UIP in a group of patients without a diagnostic HRCT study—patients who traditionally would require a surgical lung

biopsy to obtain a definitive diagnosis. We identified increased age and HRCT interstitial score as important discriminators between IPF and non-IPF IIPs. These data provide practical, important information in the evaluation of patients with suspected IPF. If validated, these data will allow the clinician to estimate the probability that a patient with suspected IPF will have IPF confirmed by surgical lung biopsy by the simple measure of patient's age and average HRCT interstitial score. As older patients often have comorbidities and increased risk of operative morbidity we believe these data will be useful in helping patients and caregivers weigh the risks, benefits, and usefulness of surgical lung biopsy for the diagnosis of suspected IPF or non-IPF IIP. If validated, these data may also allow for a broader inclusion of patients into clinical trials (i.e., those patients unable to tolerate a surgical lung biopsy and with consistent but not definite HRCT criteria for the diagnosis of IPF).

The probability of IPF was increased in older patients consistent with published incidence and prevalence data (25). We extend these data by defining specific test characteristics (sensitivity, specificity, PPV, and NPV) for finding UIP/IPF at biopsy compared with non-IPF IIP for specific age values. Using age as a sole predictor a cutoff of 75 years was associated with

TABLE 2. BASELINE DEMOGRAPHIC AND CLINICAL VARIABLES OF 97 PATIENTS WITH BIOPSY-PROVEN IDIOPATHIC PULMONARY FIBROSIS AND 38 PATIENTS WITH NON-IDIOPATHIC PULMONARY FIBROSIS IDIOPATHIC INTERSTITIAL PNEUMONIA

	IPF (n = 97)	Non-IPF IIP (n = 38)	P Value
Age, yr	62 ± 9	52 ± 9	<0.0001
Sex, male/female	40 (41%)/57 (59%)	22 (58%)/16 (42%)	0.08
Smoking status, never/ever-smoker	32 (35%)/60 (65%)*	15 (41%)/22 (59%)†	
HRCT scores			
HRCT alveolar score	1.72 ± 0.95	2.29 ± 1.32	0.02
HRCT interstitial score	0.91 ± 0.29	0.54 ± 0.39	<0.001
Pulmonary function			
FVC, % predicted	65 ± 16	70 ± 19	0.15
D _{lCO} , % predicted	48 ± 17	50 ± 17	0.57
6MWT			
Distance walked, ft	911 ± 473	895 ± 578	0.92
Desaturation < 88%‡	45 (46%)	6 (16%)	0.47

Definition of abbreviations: D_{lCO} = diffusion capacity for carbon monoxide; HRCT = high-resolution computed tomography; IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; 6MWT = 6-minute walk test.

All patients had an HRCT interstitial score less than 2 in all lobes.

* Missing data for five patients.

† Missing data for one patient.

‡ Number of patients whose oxygen saturation fell below 88% during the 6MWT.

TABLE 3. UNIVARIATE LOGISTIC REGRESSION MODELS OF VARIABLES PREDICTING A DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS

	OR (95% CI)	P Value
Age	1.11 (1.06, 1.16)	<0.0001
Male sex	1.96 (0.92, 4.19)	0.08
Ever smoker	1.28 (0.58, 2.80)	0.54
HRCT score		
HRCT alveolar score	0.61 (0.43, 0.87)	0.007
HRCT interstitial score	17.20 (5.41, 54.70)	<0.0001
Pulmonary function		
FVC % predicted	0.18 (0.02, 1.59)	0.12
DL _{CO} % predicted	0.48 (0.04, 6.01)	0.57
6MWT Variables		
Desaturation <88%	0.63 (0.20, 1.93)	0.41
Distance per 1,000 ft	1.06 (0.35, 3.26)	0.91

Definition of abbreviations: CI = confidence interval; DL_{CO} = diffusion capacity for carbon monoxide; HRCT = high-resolution computed tomography scan of the chest; OR = odds ratio; 6MWT = 6-minute walk test.

a 100% predictive value of confirming IPF by surgical lung biopsy; 70 years was nearly as good, with a PPV of 95%. These findings are consistent with evolving pathobiologic paradigms of IPF as a degenerative disease of aging (26, 27). Our finding that increased age is a strong predictor of IPF in patients with relatively early radiographic manifestations of disease (no honeycomb change) lends some support for this concept.

It is established that HRCT can accurately predict the presence of UIP at biopsy when features of honeycombing in a basilar, peripheral distribution (without a predominance of ground glass or other features to suggest an alternative diagnosis) are present (1, 10, 28, 29). Our data extend these finding by demonstrating that even modest amounts of fibrosis, without honeycombing, can be highly predictive of the presence of IPF when combined with the patient's age.

We were unable to identify any physiologic variables that helped predict the presence of IPF. In aggregate, patients with IPF tend to be older and have more pronounced physiologic derangements (21, 28–30); however, there is a significant overlap between these features between patients with IPF and non-IPF IIP (30). This overlap likely explains the lack of predictive ability for these variables.

We found the best predictive model for finding IPF was an easy-to-calculate probability of IPF score that combined age with the HRCT interstitial score. Using this score, patients 55

TABLE 4. POSITIVE PREDICTIVE VALUE, SPECIFICITY, SENSITIVITY, AND NEGATIVE PREDICTIVE VALUE WHEN CLASSIFYING PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS BASED ON BEING AT LEAST AS OLD AS THE AGE INDICATED

Age (yr)	PPV	Specificity	Sensitivity	NPV
30	72	0	100	NA
35	72	5	99	67
40	74	11	98	67
45	74	16	95	55
50	78	34	92	62
55	83	58	80	54
60	87	76	61	43
65	91	89	43	38
70	95	97	21	32
75	100	100	6	29
80	100	100	1	28

Definition of abbreviations: NA = not applicable; NPV = negative predictive value; PPV = positive predictive value.

Data expressed as percentages.

TABLE 5. POSITIVE PREDICTIVE VALUE, SPECIFICITY, SENSITIVITY, AND NEGATIVE PREDICTIVE VALUE WHEN CLASSIFYING PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS BASED ON BEING AT LEAST AS OLD AS THE AGE INDICATED AND HAVING A HIGH-RESOLUTION COMPUTED TOMOGRAPHY INTERSTITIAL SCORE AT LEAST AS HIGH AS INDICATED

Age	HRCT Interstitial Score	PPV	Specificity	Sensitivity	NPV
30	0.2	72	0	100	NA
	0.4	72	0	100	NA
	0.6	73	5	99	67
	0.8	76	24	97	75
35	1.0	85	61	88	66
	0.2	72	0	100	NA
	0.4	72	0	100	NA
	0.6	74	11	98	67
40	0.8	82	50	92	70
	1.0	90	79	73	54
	0.2	72	0	100	NA
	0.4	72	0	100	NA
45	0.6	76	24	97	75
	0.8	86	66	84	61
	1.0	97	97	32	36
	0.2	72	0	100	NA
50	0.4	73	5	99	65
	0.6	81	42	94	73
	0.8	92	84	70	52
	1.0	100	100	7	30
55	0.2	72	0	100	NA
	0.4	73	8	98	60
	0.6	85	61	88	66
	0.8	97	97	32	36
60	1.0	100	100	1	28
	0.2	72	0	100	NA
	0.4	76	24	97	75
	0.6	92	84	70	52
65	≥0.8	100	100	1	28
	0.2	72	0	100	NA
	0.4	78	32	96	75
	0.6	96	95	45	40
70	≥0.8	100	100	1	28
	0.2	72	0	100	NA
	0.4	82	50	92	70
	0.6	100	100	24	34
75	≥0.8	100	100	1	28
	0.2	72	0	100	NA
	0.4	85	61	88	66
	0.6	100	100	7	30
80	≥0.8	100	100	1	28
	0.2	0	0	100	NA
	0.4	66	66	84	61
	≥0.6	100	100	1	28

Definition of abbreviations: HRCT = high-resolution computed tomography; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value.

Data expressed as percentages.

years of age or older with even modest amounts of fibrosis (average HRCT interstitial scores of 0.8–1.0) were associated with a PPV of 100% for confirming IPF at surgical lung biopsy. Review of the data in Table 6 suggests that a cutoff probability of IPF score could be derived, above which there would be a reasonable PPV and NPV for a diagnosis of IPF based on age and HRCT interstitial score. However, these data should be confirmed with a validation cohort before the probability of IPF

TABLE 6. PROBABILITY OF IDIOPATHIC PULMONARY FIBROSIS SCORES* AND THEIR CORRESPONDING TEST CHARACTERISTICS FOR THE PRESENCE OF IDIOPATHIC PULMONARY FIBROSIS CALCULATED FROM A PATIENT'S AGE AND AVERAGE HIGH-RESOLUTION COMPUTED TOMOGRAPHY INTERSTITIAL SCORE

Score	PPV	Specificity	Sensitivity	NPV
0	72	0	100	NA
0.1	73	5	99	67
0.2	77	26	96	71
0.3	86	65	83	61
0.4	96	95	45	40
0.5	100	100	3	29
≥0.6	100	100	1	28

* Score = $[(0.084 \times \text{Age} + 2.346 \times \text{HRCT interstitial score} - 3.31)/5.856]$ (truncate negative values as 0; positive values >1 as 1)

Definition of abbreviations: NA = not applicable; NPV = negative predictive value; PPV = positive predictive value.

score is used clinically. Until then, patients who do not meet clinical criteria for the diagnosis of IPF following the American Thoracic Society/European Respiratory Society guidelines (28) should undergo an open lung biopsy to establish the diagnosis.

Strengths of this study include the inclusion of a diverse group of patients typical of those who present to the clinician with suspected IIP as well as a detailed clinical, radiographic, and pathologic approach to diagnosis (18). This study is limited by the lack of a validation cohort, by involving only a single center, and by using radiologists who are experienced in the scoring of HRCT studies. The prevalence of IPF in our cohort was 79%, higher than that found in other studies (10, 31). How these data apply to other academic and community practices needs further study. Until emerging genomic and proteomic tools to accurately diagnose IIPS become available, refining current clinical-radiographic-physiologic assessments is needed to improve diagnostic accuracy. This diagnostic accuracy will also be crucial in future clinical trials because the underlying pathogenetic mechanisms and responses to specific treatment modalities are likely to be distinctly different in IPF versus non-IPF IIPs.

In conclusion, we have shown that a higher HRCT interstitial score and older age are predictive of a diagnosis of IPF. In patients without honeycomb change on HRCT, older age and modest amounts of fibrosis are highly predictive of a diagnosis of IPF. Physiological variables, including FVC, DLCO, and 6MWT variables, are not predictive of an IPF diagnosis. Validation of these findings, preferably with a pro-

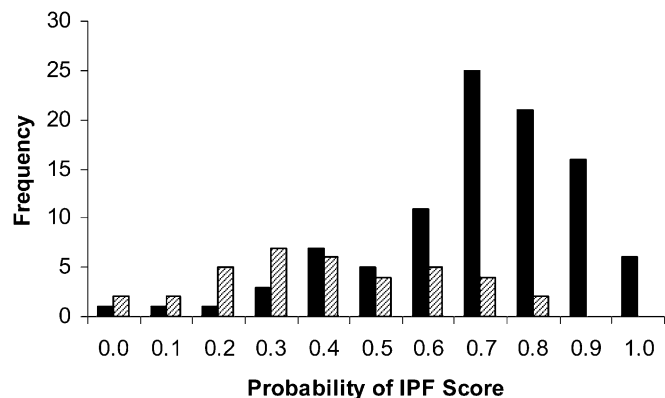


Figure 3. Histogram illustrating the frequency of the probability of idiopathic pulmonary fibrosis (IPF) scores for patients with a biopsy-proven diagnosis of IPF (n = 97) and non-IPF (n = 38). Solid columns, IPF; striped columns, non-IPF.

spective multicentre study, is needed before they can be applied broadly.

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