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Implications of the diagnostic criteria of idiopathic pulmonary fibrosis in clinical practice: Analysis from the Australian Idiopathic Pulmonary Fibrosis Registry

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Summary at a glance

In clinical practice, physicians may assign a diagnosis of IPF in patients who are sufficiently similar in their presentation to IPF but who do not strictly fulfill IPF diagnostic criteria. Our study shows that these patients demonstrate identical disease progression and survival to those who fulfill diagnostic criteria.

ABSTRACT

Background and objective: Current guidelines for the diagnosis of idiopathic pulmonary fibrosis (IPF) provide specific criteria for diagnosis in the setting of multidisciplinary discussion (MDD). We evaluate the utility and reproducibility of these diagnostic guidelines, using clinical data from the Australian IPF Registry.

Methods: All patients enrolled in the Registry undergo a diagnostic review whereby international IPF guidelines are applied via a Registry MDD. We investigated the clinical applicability of these guidelines with regard to: 1. Adherence to guidelines; 2. Natural history of IPF diagnostic categories; and 3. Concordance for diagnostic features.

Results: 417 participants (69% male, 70.6±8.0years) with a clinical diagnosis of IPF underwent MDD. The 23% of participants who did not meet IPF diagnostic criteria, displayed identical disease behaviour to those with confirmed IPF. Honeycombing on radiology was associated with a worse prognosis and this translated into poorer prognosis in the 'definite' IPF group. While there was moderate agreement for IPF diagnostic categories, agreement for specific radiological features, other than honeycombing, was poor.

Conclusion: In clinical practice, physicians do not always follow IPF diagnostic guidelines. We demonstrate a cohort of IPF patients who do not meet IPF diagnostic guideline criteria, based largely on their radiology and lack of lung biopsy, but who have outcomes identical to those with IPF.

Key words: Idiopathic Pulmonary Fibrosis, Multidisciplinary, Registry, Honeycombing.

Short Title (40 characters): Implications of IPF Diagnostic Criteria

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF), the most prevalent of the idiopathic interstitial pneumonias (IIP), is a relentlessly progressive disease with a median survival of only 2-5 years[1-3]. Two landmark studies in 2014[4, 5] showed, for the first time, that antifibrotic therapies slow disease progression. These findings have prompted a renewed and global focus on ensuring an accurate diagnosis of IPF[6, 7].

In 2011, the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Latin American Thoracic Association (ATS/ERS/JRS/ALAT), developed evidence based guidelines for the diagnosis of IPF[1]. Central to these guidelines is a multidisciplinary evaluation whereby clinicians, radiologists and histopathologists reach a consensus diagnosis[8, 9]. The multidisciplinary diagnosis of IPF relies heavily on the presence of a definite usual interstitial pneumonia (UIP) pattern on high resolution computed tomography (HRCT). However, the agreement of experienced radiologists using the ATS/ERS/JRS/ALAT criteria is only moderate[10]. In cases where definite UIP is not present radiologically, the guidelines call for a surgical lung biopsy for confirmation of diagnosis.

A rigorous diagnostic approach is appropriate for selecting homogenous, well-characterised cohorts of IPF patients to enhance the uniform recruitment for clinical trials. However, it is increasingly evident that in real-world clinical practice, not all IPF patients fulfill these criteria and physicians rely on other clinically relevant criteria not reflected in the guidelines[11, 12]. In this study, we evaluate the clinical application of the ATS/ERS/JRS/ALAT guidelines in Australia, using our national IPF Registry cohort.

The Australian IPF Registry (AIPFR) recruits patients referred from across Australia with a diagnosis of IPF made by their referring respiratory physician. This diagnosis is then re-

evaluated at a centralised multidisciplinary diagnostic (MDD) review using the 2011 ATS/ERS/JRS/ALAT guidelines[13]. As previously highlighted, this is a process unique to the Australian IPF Registry. In evaluating the clinical application of the IPF diagnostic guidelines, we explored the adherence by Australian respiratory physicians to the guideline diagnostic criteria. Secondly, we investigated prognostic implications of guideline-defined IPF diagnostic categories assigned by our Registry MDD panel. Finally, we evaluated the reproducibility of the guidelines by assessing the concordance of the diagnostic categories and specific UIP features between our multidisciplinary panel members.

METHODS

Study population

The AIPFR is a nationwide collaboration initiated in 2012 and administered by the Lung Foundation of Australia, collating data on incident and prevalent cases of IPF.

The Registry has ethics approval to operate in every State and Territory of Australia. This study has ethical approval from the Sydney Local Health District (protocol no. X14-0264). State based coordinators consent participants and collect baseline and longitudinal information from patients and their referring physicians. Investigations collected are those performed as part of the patient's routine management only, thereby creating a real-world longitudinal cohort. Details regarding the structure and data collected in the Registry have been published previously[14].

Registry Multidisciplinary Diagnosis

Participants in the AIPFR undergo a multidisciplinary central diagnostic review or 'Registry MDD' (Supplementary Figure S1) at which the current ATS/ERS/JRS/ALAT criteria are applied[1]. The most recent HRCT scan is reviewed by one of two parallel Registry radiology review panels. Each radiology panel consists of three experienced pulmonary radiologists who independently review each participant's HRCT. In a similar manner, the histopathology of all participants who have undergone a surgical lung biopsy is reviewed at three independent specialist centers by expert histopathologists. The pattern is reported according to the consensus guidelines (Supplementary Table S1). A consensus result for each panel is then achieved on the basis of the individual reports, or if no consensus is reached, cases are reviewed at a meeting with all panel members.

The above information is synthesized with clinical information by a panel of three respiratory physicians who then designate a Registry MDD diagnosis: 'definite', 'probable', 'possible', and 'inconsistent' with IPF in accordance with the guidelines. A consensus Registry MDD diagnosis is achieved when 2 or more respiratory physicians agree on the classification. In the cases where there is no majority, diagnosis is established after discussion between all clinical panel members. Importantly, an IPF category is assigned for cases that are not definite IPF based on HRCT and clinical findings, even in cases where a lung biopsy is not performed.

Statistical analysis

Baseline comparisons between diagnostic IPF categories were performed using chi squared, Students' t-test, ANOVA or Kruskal Wallis tests as appropriate. Linear mixed models for FVC %predicted were fitted with random intercepts and slopes. We tested differences between

diagnosis categories using an interaction term between diagnosis category and time since Registry consent. The model included age, sex, smoking status and IPF diagnosis category.

Survival curves were estimated using the Kaplan-Meier method. Cox proportional models were used to assess overall survival, with patients who received lung transplantation censored at the date of transplant. In all multivariable models, adjustments for age, gender, smoking status and baseline FVC %predicted were made. In cases where data was incomplete, only cases with complete datasets were used for analysis.

The concordance of inter-observer UIP categories and key radiological and histopathological features was assessed using linear weighted kappa analysis[15]. In the case of radiology, features were reported as present or absent. In histopathology, features were either absent, present or prominent.

All results with a p value <0.05 were reported as significant. All statistical analysis was performed using STATA version 14 (StataCorp, College Station, Texas).

RESULTS

Baseline characteristics by Registry Diagnosis

417 AIPFR participants have undergone central Registry MDD. There was no significant difference in the baseline characteristics of all participants who had completed MDD (n=417), compared to those who are awaiting MDD (n= 230; Supplementary Table S2 and Figure S2). All results below are for the MDD cohort.

Median follow-up time was 2.18 years (range 6 months to 4.5 years) with a total of 960 person years follow-up. In total, there have been 126/417 deaths (30.2%). Mortality at one, two, three and four year follow-up was 4.9%, 23.1%, 35.7% and 41.8% respectively. Of the 417 patients, only 63 patients (15%) had a surgical lung biopsy for review.

Baseline characteristics, categorised by diagnostic classification, are shown in Table 1. Participants with 'definite IPF' were more commonly male. Those with 'possible/probable IPF' were older and had milder disease characterised by higher FVC and DLco% predicted. However, those participants who did not meet diagnostic criteria for IPF had more severe physiological impairment, with lower FVC and DLco % predicted.

Classification of IPF using current ATS/ERS guidelines

The majority of the 417 participants undergoing diagnostic review at Registry MDD had their IPF diagnosis confirmed ('guideline adherent IPF'; n=322; 77%) with most of them having 'definite IPF' (n=202, 48%). There were few participants diagnosed with 'probable IPF' (n= 28, 7%) with a larger number diagnosed with 'possible IPF' (n=92, 22%). Ninety-five participants (23%) did not meet the diagnostic criteria for IPF and so were classified as 'inconsistent with IPF' (Figure 1). None of the participants with histopathology had features inconsistent with UIP.

The main reason participants were considered to be 'inconsistent with IPF' according to diagnostic guidelines was on the basis of radiological features inconsistent with UIP, which were present in 69/95 (73%) participants. These features included ground glass changes, upper lobe predominance and mosaic attenuation present in 59%, 32% and 20% of the HRCTs, with some HRCTs having multiple inconsistent features (Table 2). The other major basis for 'inconsistent' categorisation was the presence of an underlying connective tissue

disease, self-reported on questionnaires in 26 of the 95 (27%) participants (Rheumatoid Arthritis n=22; Scleroderma n=1; other n=3). The majority of these participants had definite UIP on HRCT (n=16) with only 1 participant having a HRCT pattern inconsistent with UIP. Three participants did not have a diagnostic HRCT and IPF diagnosis was made based on histopathology and clinical features.

Natural history of patients in the AIPFR

Annual change in FVC% predicted

There was no significant difference between the annual change in FVC% predicted between participants with 'guideline adherent IPF' and those with 'inconsistent with IPF' (4.2%/year, 95%CI 3.2-5.2% and 4.8%/year, 95%CI 2.6-6.9%, respectively; p=0.65).

In participants with 'definite IPF', the decline in FVC% predicted was 4.9%/year, 95%CI 3.8-6.1%, while in those with 'possible/probable IPF' the decline was 3.2%/year, 95%CI 1.5-4.8%. The apparent trend towards faster decline in FVC% predicted in 'definite IPF' was not statistically significant (p=0.08).

Overall survival

Participants with 'guideline adherent IPF' and those with an 'inconsistent with IPF' diagnosis had identical outcomes on univariable Cox analysis for overall survival (HR 0.91, 95%CI 0.61-1.38; p=0.67) (Figure 2a). The presence of honeycombing on HRCT was associated with increased mortality (HR 1.90, 95%CI 1.29-2.78; p<0.001) (Figure 2b) and this translated to higher mortality within the 'definite IPF' subgroup (HR 1.79 95%CI 1.13-2.84; p=0.013).

Older age, lower BMI and lower baseline lung function were all also associated with increased mortality (Table 3).

These above results were unchanged following multivariable Cox regression analysis, including age, gender, smoking status and baseline FVC %predicted (Supplementary Table S3).

Concordance of diagnostic categories and specific UIP features

Radiology Concordance

The overall concordance for the diagnostic categories for UIP on HRCT was moderate (κ_w=0.51, 95%CI 0.44-0.59 and κ_w=0.43, 95%CI 0.35-0.52). There was higher concordance for the presence of honeycombing (κ_w=0.56, 95%CI 0.48-0.65 and κ_w=0.54, 95%CI 0.45-0.64). The concordance in other diagnostic features of UIP was moderate to fair only (Table 4).

The concordance for the presence of 'any inconsistent feature' was also only moderate to fair. The concordance for the presence of ground glass change, a commonly cited inconsistent feature in our cohort, was fair at best (κ_w=0.37, 95%CI 0.24-0.51 and κ_w=0.27, 95%CI 0.14-0.41), as was the presence of mosaic attenuation (κ_w=0.34, 95%CI 0.08-0.62 and κ_w=0.35, 95%CI 0.16-0.55). Concordance for other specific inconsistent features was fair to poor (Table 5).

Histopathology Concordance

The analysis of inter-observer agreement in histopathology showed moderate overall concordance. Concordance for the presence of specific features however was poor with concordance of only κ_w=0.06 (95%CI -0.05-0.18) for fibroblastic foci, a key histopathological feature of UIP (Table 5). This very low kappa however, reflects the high frequency with which fibroblast foci was reported as present and thus high expected concordance (95% by 2 reviewers and 71% by the other reviewer). Of the inconsistent features, concordance regarding the presence of granulomas was highest but concordance regarding other inconsistent features was fair to poor.

Clinical Concordance

The overall concordance of Registry MDD diagnosis by clinicians after radiological and histopathological review was high, κ_w=0.86 (95%CI 0.82-0.89). This was strongly influenced by the consensus radiological diagnosis with interdisciplinary agreement of κ_w=0.78 (95%CI 0.73-0.83) between consensus radiological and clinical diagnosis. This is unsurprising as most patients did not have histopathology for review.

DISCUSSION

In our national IPF cohort, twenty-three percent of patients diagnosed with IPF in clinical practice did not meet IPF diagnostic criteria, mostly due to the presence of inconsistent radiological features in the absence of a surgical lung biopsy. However, these patients demonstrated no difference in disease progression or overall survival when compared with the guideline adherent group, suggesting that they may indeed have IPF despite not fulfilling the diagnostic criteria. Concordance for the UIP pattern and specific features on radiology

and histopathology were modest at best, with honeycombing having the best overall concordance. These findings highlight the presence of a cohort of patients considered to have IPF by their treating respiratory physician, who behave like IPF, but do not meet criteria for IPF diagnosis.

The Australian IPF Registry includes IPF patients from diverse geographical locations and clinical settings in Australia, including tertiary ILD centers as well as regional pulmonology practices. Given the diversity of referring respiratory physicians, we applied the ATS/ERS/JRS/ALAT guidelines through our Registry MDD to assess the rate of adherence to diagnostic guidelines. While our findings were largely based on the radiology as only 15% of patients had lung biopsy, we found that overall adherence to guidelines was high with 77% of patients meeting guideline criteria for IPF (definite, probable or possible IPF). 23% were 'inconsistent with IPF', largely due to radiology features inconsistent with UIP in patients who did not undergo biopsy. While it is possible that these patients did not have IPF, it is also possible that clinicians may be using other factors including age, gender and disease behavior in their clinical judgment when making a clinical IPF diagnosis[11, 12, 16].

Our findings support growing evidence that in patients where there is a high clinical suspicion of IPF, an atypical scan does not exclude IPF. In a study by Brownell *et al*. a possible UIP pattern on HRCT had high specificity for UIP on biopsy, but an inconsistent with UIP pattern had poor positive predictive value. This study was performed in a general ILD cohort where only about 25% of patients had IPF[16]. In populations where IPF is highly prevalent like ours, a HRCT inconsistent with UIP has been associated with rates of UIP on histopathology as high as 94.7%[17] with other studies showing rates of 62%[18] and 82%[19]. As with our population where overall survival was unaffected by inconsistent UIP features, in a

study of 98 patients with histopathological UIP by Sumikawa *et al*., there was also no difference in survival based on the HRCT UIP classification (definite, possible or inconsistent). Instead, specific radiological features including traction bronchiectasis and fibrosis score were the most significant predictors of survival[20].

Our study demonstrated no difference in the annual FVC decline between 'definite IPF' and 'possible/probable' IPF groups. Interestingly, in a post-hoc analysis of pooled data from the INPULSIS trials by Raghu *et al*.[21] there was no difference in the adjusted annual rate of decline in FVC in patients with definite UIP compared with possible UIP with traction bronchiectasis, although survival data was limited due to the shorter duration of this study. Raghu *et al*. also showed that there was no difference in the efficacy of nintedanib between possible and definite UIP groups, suggesting broad efficacy of nintedanib in IPF[21]. While it is not possible to extrapolate these results to our Registry participants, it does raise the question as to whether patients who are considered to have IPF by their treating physicians, but who do not fulfill the IPF diagnostic criteria would benefit from receiving antifibrotic therapy? In some countries, including Australia, antifibrotic therapy is restricted to patients with a confirmed diagnosis of IPF at ILD multidisciplinary meeting. We suggest that this group of patients who behave clinically like IPF, but who do not fulfill radiological and/or histological criteria for IPF may benefit from a trial of antifibrotic therapy.

Our study also shows that specific radiological features predict survival, with the presence of honeycombing being associated with poorer prognosis. This has been shown in other studies[22] and has also been demonstrated for other radiological features including extent of fibrosis and traction bronchiectasis[20, 23-25]. The increased mortality associated with the 'definite' IPF group compared with 'possible/probable' IPF in our study is likely influenced by the presence of honeycombing, the key defining feature separating these two groups.

In our study, the concordance for honeycombing on radiology was moderate (κ_w=0.54-0.56) and had the highest concordance amongst UIP features, similar to other concordance studies[10]. Concordance for features inconsistent with UIP was only fair at best: ground glass change (κ_w=0.27-0.37); mosaic attenuation (κ_w= 0.34-0.35) and peribronchovascular distribution (κ_w= 0.09-0.18). While in an ideal world, these patients would have a surgical lung biopsy to confirm their diagnosis, many patients are unwilling or unable to undergo this procedure as it can be associated with significant morbidity and mortality in this older population with frequent comorbidities[26-28]. Thus, it is possible that patients may be excluded from an IPF diagnosis based on features that are inconsistently reported. It is also important to note that even when clinical, as well as histopathological data is taken into account, several studies have shown only moderate concordance for IPF diagnosis between physicians[29] as well as between multidisciplinary meetings[30].

Our study has several limitations. Firstly, as this is a real-world Registry, variation in the investigations and monitoring undertaken was present, as this was determined by the treating respiratory physician. Every effort was made however, to ensure that all data regarding the participant was captured; the large number and diversity of participants allowed us to explore the natural history of IPF within these limitations. Of note, the rate of lung biopsy in patients with possible or inconsistent UIP was low. For the purposes of our analysis, these patients were pragmatically given a diagnosis based on radiology and clinical features. Secondly, it must also be noted that the 'Registry MDD' is a virtual MDD where all reviewers assess participants independently and not at the same time and location. However, the final clinical reviewers did have the comprehensive data from the radiology and histopathology reviews available to them.

Finally, while we can demonstrate the natural history, we cannot make any assumptions about the pathobiology or corresponding potential response of different IPF groups to treatment, particularly those with 'inconsistent with IPF' diagnosis, as this group have been largely excluded from clinical trials[4, 5, 31, 32]. Finally, 26 of the 95 (27%) participants were considered to have 'inconsistent with IPF' diagnosis due to the presence of a concomitant CTD. Given the potential lack of reliability of patient reported diagnoses, we performed sensitivity analysis excluding these patients, and there remained no difference for the outcomes demonstrated (Supplementary Table S4).

In summary, our findings have important implications for the clinical application of IPF diagnostic guidelines. The guidelines have been instrumental in advancing our knowledge of IPF and providing homogenous cohorts for clinical trials. However, in clinical practice, we demonstrate a cohort of patients who are sufficiently similar in their presentation to IPF, that their treating clinicians assign them an IPF diagnosis although they do not, strictly-speaking, fulfill IPF diagnostic criteria. While their radiology is inconsistent with IPF and lung biopsy has not been performed, we show that these participants demonstrate identical longitudinal disease behavior to participants with radiology and/or pathology consistent with IPF. Further study of this cohort is crucial, as the decision to assign an IPF diagnosis to a patient has major implications with regard to prognosis and indeed management.

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REFERNCES

1 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Jr., Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ, Fibrosis AEJACoIP. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American journal of respiratory and critical care medicine. 2011; **183**: 788-824.

2 Flaherty KR, Toews GB, Travis WD, Colby TV, Kazerooni EA, Gross BH, Jain A, Strawderman RL, 3rd, Paine R, Flint A, Lynch JP, 3rd, Martinez FJ. Clinical significance of histological classification of idiopathic interstitial pneumonia. The European respiratory journal. 2002; **19**: 275-83.

3 Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. American journal of respiratory and critical care medicine. 2000; **162**: 2213-7.

4 King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW, Group AS. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. The New England journal of medicine. 2014; **370**: 2083-92.

5 Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR, Investigators IT. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. The New England journal of medicine. 2014; **370**: 2071-82.

6 Jones MG, Walsh SLF, Jones KD, Richeldi L. Idiopathic pulmonary fibrosis: securing a confident diagnosis for every patient. European Respiratory Journal. 2016; **47**: 1057-9.

7 Brownell R, Kaminski N, Woodruff PG, Bradford WZ, Richeldi L, Martinez FJ, Collard HR. Precision Medicine: The New Frontier in Idiopathic Pulmonary Fibrosis. American journal of respiratory and critical care medicine. 2016; **193**: 1213-8.

8 Flaherty KR, King TE, Jr., Raghu G, Lynch JP, 3rd, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, Murray S, Lama VN, Gay SE, Martinez FJ. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? American journal of respiratory and critical care medicine. 2004; **170**: 904-10.

9 Flaherty KR, Andrei AC, King TE, Jr., Raghu G, Colby TV, Wells A, Bassily N, Brown K, du Bois R, Flint A, Gay SE, Gross BH, Kazerooni EA, Knapp R, Louvar E, Lynch D, Nicholson AG, Quick J, Thannickal VJ, Travis WD, Vyskocil J, Wadenstorer FA, Wilt J, Toews GB, Murray S, Martinez FJ. Idiopathic interstitial pneumonia: do community and academic physicians agree on diagnosis? American journal of respiratory and critical care medicine. 2007; **175**: 1054-60.

10 Walsh SLF, Calandriello L, Sverzellati N, Wells AU, Hansell DM. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. Thorax. 2015.
11 Wells AU. "Any fool can make a rule and any fool will mind it". BMC medicine. 2016; **14**: 23.
12 Fell CD, Martinez FJ, Liu LX, Murray S, Han MK, Kazerooni EA, Gross BH, Myers J, Travis WD, Colby TV, Toews GB, Flaherty KR. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine. 2010; **181**: 832-7.
13 Kreuter M, Cottin V. The yin and yang of idiopathic pulmonary fibrosis. European Respiratory Journal. 2017; **49**.
14 Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, Reynolds PN, Chapman S, Walters EH, Zappala C, Allan H, Keir GJ, Hayen A, Cooper WA, Mahar AM, Ellis S, Macansh S, Corte TJ. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. The European respiratory journal. 2017; **49**.
15 Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. Bmj. 1992; **304**: 1491-4.
16 Brownell R, Moua T, Henry TS, Elicker BM, White D, Vittinghoff E, Jones KD, Urisman A, Aravena C, Johannson KA, Golden JA, King TE, Wolters PJ, Collard HR, Ley B. The use of pretest probability increases the value of high-resolution CT in diagnosing usual interstitial pneumonia. Thorax. 2017.
17 Yagihashi K, Huckleberry J, Colby TV, Tazelaar HD, Zach J, Sundaram B, Pipavath S, Schwarz MI, Lynch DA. Radiologic-pathologic discordance in biopsy-proven usual interstitial pneumonia. The European respiratory journal. 2016; **47**: 1189-97.
18 Sverzellati N, Wells AU, Tomassetti S, Desai SR, Copley SJ, Aziz ZA, Zompatori M, Chilosi M, Nicholson AG, Poletti V, Hansell DM. Biopsy-proved idiopathic pulmonary fibrosis: spectrum of nondiagnostic thin-section CT diagnoses. Radiology. 2010; **254**: 957-64.
19 Raghu G, Lynch D, Godwin JD, Webb R, Colby TV, Leslie KO, Behr J, Brown KK, Egan JJ, Flaherty KR, Martinez FJ, Wells AU, Shao L, Zhou H, Pedersen PS, Sood R, Montgomery AB, O'Riordan TG. 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. The Lancet Respiratory medicine. 2014; **2**: 277-84.
20 Sumikawa H, Johkoh T, Colby TV, Ichikado K, Suga M, Taniguchi H, Kondoh Y, Ogura T, Arakawa H, Fujimoto K, Inoue A, Mihara N, Honda O, Tomiyama N, Nakamura H, Muller NL. Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. American journal of respiratory and critical care medicine. 2008; **177**: 433-9.
21 Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, Stowasser S, Schlenker-Herceg R, Hansell DM. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria. American journal of respiratory and critical care medicine. 2016.

22 Lynch DA, Godwin JD, Safrin S, Starko KM, Hormel P, Brown KK, Raghu G, King TE, Jr., Bradford WZ, Schwartz DA, Richard Webb W. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. American journal of respiratory and critical care medicine. 2005; **172**: 488-93.
23 Best AC, Meng J, Lynch AM, Bozic CM, Miller D, Grunwald GK, Lynch DA. Idiopathic pulmonary fibrosis: physiologic tests, quantitative CT indexes, and CT visual scores as predictors of mortality. Radiology. 2008; **246**: 935-40.
24 Shin KM, Lee KS, Chung MP, Han J, Bae YA, Kim TS, Chung MJ. Prognostic determinants among clinical, thin-section CT, and histopathologic findings for fibrotic idiopathic interstitial pneumonias: tertiary hospital study. Radiology. 2008; **249**: 328-37.
25 Hansell DM, Goldin JG, King Jr TE, Lynch DA, Richeldi L, Wells AU. CT staging and monitoring of fibrotic interstitial lung diseases in clinical practice and treatment trials: a Position Paper from the Fleischner society. The Lancet Respiratory Medicine. 2015; **3**: 483-96.
26 Hutchinson JP, McKeever TM, Fogarty AW, Navaratnam V, Hubbard RB. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008. European Respiratory Journal. 2016; **48**: 1453-61.
27 Park JH, Kim DK, Kim DS, Koh Y, Lee S-D, Kim WS, Kim WD, Park SI. Mortality and risk factors for surgical lung biopsy in patients with idiopathic interstitial pneumonia. European Journal of Cardio-thoracic Surgery. 2007; **31**: 1115-9.
28 Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, Dubini A, Tantalocco P, Sanna S, Negri E, Tramacere I, Ventura VA, Cavazza A, Rossi A, Chilosi M, La Vecchia C, Gasparini S, Poletti V. Safety and Diagnostic Yield of Transbronchial Lung Cryobiopsy in Diffuse Parenchymal Lung Diseases: A Comparative Study versus Video-Assisted Thoracoscopic Lung Biopsy and a Systematic Review of the Literature. Respiration; international review of thoracic diseases. 2016; **91**: 215-27.
29 Walsh SLF, Maher TM, Kolb M, Poletti V, Nusser R, Richeldi L, Vancheri C, Wilsher ML, Antoniou KM, Behr J, Bendstrup E, Brown K, Calandriello L, Corte TJ, Cottin V, Crestani B, Flaherty K, Glaspole I, Grutters J, Inoue Y, Kokosi M, Kondoh Y, Kouranos V, Kreuter M, Johannson K, Judge E, Ley B, Margaritopoulos G, Martinez FJ, Molina-Molina M, Morais A, Nunes H, Raghu G, Ryerson CJ, Selman M, Spagnolo P, Taniguchi H, Tomassetti S, Valeyre D, Wijsenbeek M, Wuyts W, Hansell D, Wells A. Diagnostic accuracy of a clinical diagnosis of idiopathic pulmonary fibrosis: an international case–cohort study. European Respiratory Journal. 2017; **50**.
30 Walsh SLF, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, Nunes H, Valeyre D, Brillet PY, Kambouchner M, Morais A, Pereira JM, Moura CS, Grutters JC, van den Heuvel DA, van Es HW, van Oosterhout MF, Seldenrijk CA, Bendstrup E, Rasmussen F, Madsen LB, Gooptu B, Pomplun S, Taniguchi H, Fukuoka J, Johkoh T, Nicholson AG, Sayer C, Edmunds L, Jacob J, Kokosi MA, Myers JL, Flaherty KR, Hansell DM. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. The Lancet Respiratory medicine. 2016; **4**: 557-65.

31 Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Kluglich M, du Bois RM. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. The New England journal of medicine. 2011; **365**: 1079-87.

32 Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE, Jr., Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM, Group CS. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011; **377**: 1760-9.

Table 1. Baseline characteristics by Registry MDD IPF categories.

	Definite IPF*§	Probable/ possible IPF†§	Inconsistent with IPF‡	P value
n	202	120	95	
Age, years mean (SD)	69.9 (7.2)	72.2 (7.7)	70.2 (9.6)	**0.037**
Male Sex, n (%)	151 (74.8%)	82 (68.3%)	55 (57.9%)	**0.013**
Ever Smoker, n (%)	152 (75.3%)	88 (73.3%)	62 (65.3%)	0.193
BMI, kg/m^2, mean (SD)	28.2 (4.7)	29.9 (4.3)	28.6 (4.4)	**0.013**
Pulmonary Function Tests, mean (SD) ll				
FVC, L	2.71 (0.72)	2.66 (0.79)	2.32 (0.65)	**<0.001**
FVC, %predicted	81.5 (20.0)	82.3 (20.2)	76.9 (25.7)	**0.047**
FEV_1/FVC	83.4 (9.1)	81.8 (8.8)	82.6 (6.4)	0.656
DLco, %predicted	47.9 (16.8)	53.5 (15.0)	46.5 (19.6)	**0.011**

* participants with a consensus Registry MDD diagnosis of definite IPF
† participants with a consensus Registry MDD diagnosis of possible or probable IPF
‡ participants with a consensus Registry MDD diagnosis which is inconsistent with IPF
§ These two groups constitute guideline adherent IPF.
ll Kruskal Wallis test performed

Table 2. Prevalence of radiological features inconsistent with UIP in patients excluded from IPF diagnosis based on radiology.

Inconsistent feature (n=69)	Prevalence (n)*	%
Ground glass	41	59%
Upper lobe predominance	22	32%
Mosaic attenuation	14	20%
Peribronchovascular predominance	8	12%
Consolidation	6	9%
Cysts	3	4%
micronodules	2	3%

*Some high resolution computed tomography scans had multiple inconsistent features.

Table 3. Univariable Cox analysis for Overall Survival

Variable	n*	HR	95%CI	P
Demographics:				
Age	416	1.04	1.01 - 1.06	<0.002
Male	417	1.48	0.99 - 2.21	0.058
smoking	417	1.48	0.98 - 2.24	0.061
BMI	329	0.91	0.86 - 0.96	<0.001
IPF diagnosis:				
Guideline adherent	417	0.91	0.61 - 1.38	0.671
IPF†				
Definite IPF‡	322	1.79	1.13 - 2.84	0.013
Pulmonary Function Tests:				
FVC, L	338	0.54	0.40 - 0.74	<0·001
FVC, %predicted§	338	0.71	0.63 - 0.80	<0·001
DLco, %predicted§	298	0.53	0.44 - 0.62	<0.001
Radiological Features:				
Honeycombing	414	1.90	1.29 - 2.78	<0.001
Subpleural location	414	1.11	0.65 - 1.87	0.709
Reticulation/traction	414	0.76	0.31 - 1.87	0.551

*Number of participants with data available for calculation. † All patients with Registry MDD diagnosis of IPF (definite, probable, possible) compared with Registry MDD diagnosis of inconsistent with IPF. ‡Patients with Registry MDD diagnosis of definite IPF compared with possible/probable IPF. §HR given for difference of 10 units.

Table 4. Concordance of UIP category and UIP specific features on HRCT

Feature	*Panel 1 (κ_w) n = 214	95%CI	*Panel 2 (κ_w) n = 185	95%CI
Diagnosis	0.51	0.44 - 0.59	0.43	0.35, 0.52
Features of UIP				
Honeycombing	0.56	0.48 - 0.65	0.54	0.45 - 0.64
Subpleural, basal predominance	0.38	0.24 - 0.52	0.29	0.17 - 0.40
Reticular abnormality	0.22	-0.22, 0.72	0.32	-0.01 - 0.70
Features inconsistent with UIP				
Any Inconsistent features	0.42	0.30 - 0.54	0.37	0.26 - 0.48
Ground glass	0.37	0.24 - 0.51	0.27	0.14 - 0.41
Upper lobe predominance	0.38	0.14 - 0.64	0.26	0.12 - 0.41
Mosaic attenuation	0.34	0.08 - 0.62	0.35	0.16 - 0.55
Peribronchovascular predominance	0.18	0.01 - 0.37	0.09	-0.10 - 0.30
Consolidation	0.19	-0.03 - 0.44	0.19	-0.18 - 0.67
Cysts	0.25	-0.21 - 0.87	0.13	-0.15 - 0.46
micronodules	0.40	0.16 - 0.70	N/A†	N/A†

*two parallel registry radiology review panels reviewing HRCTs with 3 members in each panel. †Too few with micronodules (n=1) reported for accurate κ_w calculation.

Table 5. Concordance of UIP category and UIP specific features on surgical lung biopsy

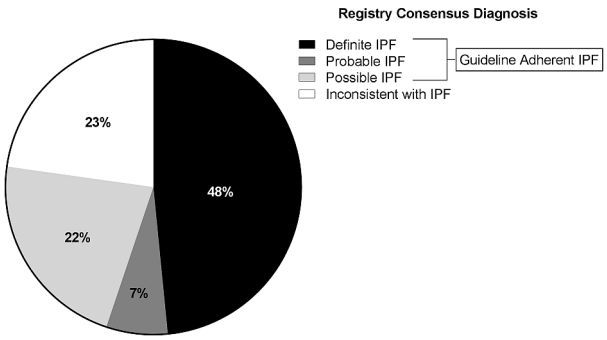
Feature	κ_w (N= 63)	95%CI
Overall diagnosis	0.44	0.30 - 0.59
Features of UIP		
Honeycombing	0.14	-0.02 - 0.32
Fibroblastic foci	0.06	-0.05 - 0.18
Features inconsistent with UIP		
Hyaline membranes	0.02	-0.01 - 0.04
Organizing pneumonia	0.29	0.08 - 0.52
Granulomas	0.39	0.10 - 0.73
Airway inflammation	0.13	-0.08 - 0.36
Airway fibrosis	0.19	0.04 - 0.34

Figure Legends

Figure 1. Classification of Registry MDD IPF diagnosis in the AIPFR

Figure 2. Kaplan-Meier plot for survival by IPF categories

a) Guideline adherent (solid line) compared with inconsistent with IPF category (dashed line) log rank test, p=0.671.
b) Honeycombing present (solid line) compared with honeycombing absent (dashed line) log rank test, p<0.001.



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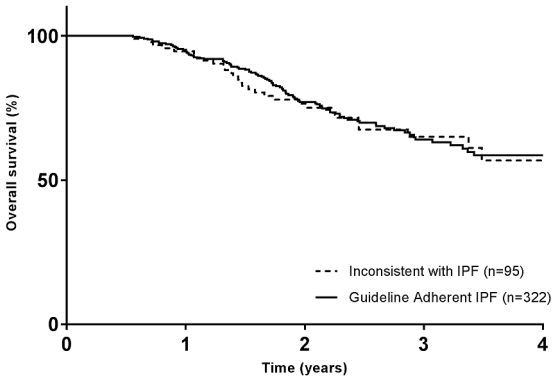
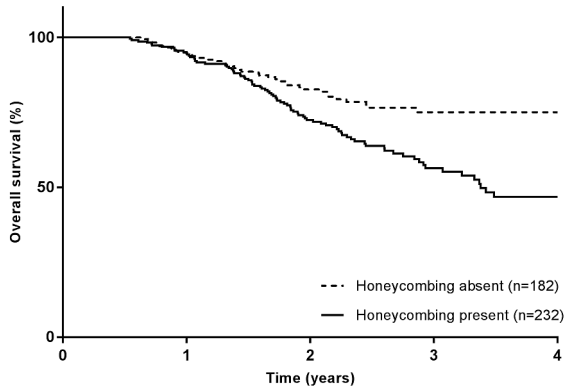


Figure 2a.tif



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