Probable usual interstitial pneumonia pattern on chest CT: is it sufficient for a diagnosis of idiopathic pulmonary fibrosis?

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Except when the final diagnosis is IPF, idiopathic interstitial pneumonia (IIP) patients with a probable usual interstitial pneumonia (UIP) pattern on chest CT have a longer survival time and time to first acute exacerbation than those with a UIP pattern http://bit.ly/2FOJa2F

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ABSTRACT Recent studies have suggested that in patients with an idiopathic interstitial pneumonia (IIP), a probable usual interstitial pneumonia (UIP) pattern on chest computed tomography (CT) is sufficient to diagnose idiopathic pulmonary fibrosis (IPF) without histopathology.

We retrospectively compared the prognosis and time to first acute exacerbation (AE) in IIP patients with a UIP and a probable UIP pattern on initial chest CT.

One hundred and sixty IIP patients with a UIP pattern and 242 with a probable UIP pattern were identified. Probable UIP pattern was independently associated with longer survival time (adjusted hazard ratio 0.713, 95% CI 0.536–0.950; p=0.021) and time to first AE (adjusted hazard ratio 0.580, 95% CI 0.389–0.866; p=0.008). In subjects with a probable UIP pattern who underwent surgical lung biopsy, the probability of a histopathological UIP pattern was 83%. After multidisciplinary discussion and the inclusion of longitudinal behaviour, a diagnosis of IPF was made in 66% of cases. In IPF patients, survival time and time to first AE were not associated with CT pattern. Among subjects with a probable UIP pattern, compared to non-IPF patients, survival time and time to first AE were shorter in IPF patients.

In conclusion, IIP patients with a probable UIP pattern on initial chest CT had a better prognosis and longer time to first AE than those with a UIP pattern. However, when baseline data and longitudinal behaviour provided a final diagnosis of IPF, CT pattern was not associated with these outcomes. This suggests diagnostic heterogeneity among patients with a probable UIP pattern.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive idiopathic interstitial pneumonia (IIP) with poor prognosis that is characterised histopathologically by a usual interstitial pneumonia (UIP) pattern [1]. Due to its poor prognosis, an accurate diagnosis is important. According to the recently published Fleischner Society white paper [1] and the 2018 IPF guidelines [2], in the appropriate clinical setting a "UIP pattern" on computed tomography (CT) (subpleural basal predominance, reticular abnormality and honeycombing) is sufficient to establish a diagnosis of IPF without the need for a surgical lung biopsy (SLB). On the other hand, patients with a "probable UIP pattern" (the same criteria as for a UIP pattern but without honeycombing and with traction bronchiectasis), an "indeterminate for UIP pattern" (subpleural basal predominance, evidence of fibrosis not suggestive of a specific aetiology) or an "alternative diagnosis" on CT require SLB for a definitive diagnosis. However, a substantial number of patients will not undergo surgery for a variety of reasons, including refusal or excessive perioperative risk (*e.g.* severe physiologic impairment or comorbidities), and remain without a definitive diagnosis.

In the previous IPF guidelines, published in 2011 [3], the current probable UIP and indeterminate for UIP patterns were collectively classified as "possible UIP pattern". In the two INPULSIS trials [4], which evaluated the efficacy and safety of nintedanib in the treatment of IPF, IIP subjects who showed a fibrosing interstitial pneumonia with a combination of traction bronchiectasis and a possible UIP pattern on CT were considered to have a diagnosis of IPF, without the need for SLB. In a *post hoc* analysis, the IPF subjects enrolled with a possible UIP pattern and traction bronchiectasis showed similar disease progression and treatment responsiveness to subjects enrolled with IPF as diagnosed based strictly on the 2011 guidelines [5]. Additionally, Brownell *et al.* [6] have revealed that an increasing extent of traction bronchiectasis increases the positive predictive value (PPV) of a possible UIP pattern for an underlying histopathological UIP pattern. Others have reported that traction bronchiectasis on CT is correlated with a poor prognosis in patients with fibrotic IIP [7, 8]. These results are considered to be supportive evidence for the diagnostic value of possible UIP pattern with traction bronchiectasis (*i.e.* the current probable UIP pattern) on CT for histopathological UIP pattern.

However, the INPULSIS trials [4] recruited patients who were clinically suspected to have IPF by physicians with expertise in the diagnosis of interstitial lung disease (ILD). Therefore, it is possible that the PPV of a possible UIP pattern with traction bronchiectasis for histopathological UIP pattern and a diagnosis of IPF was higher in the INPULSIS trials than would be seen in a real-world setting (*i.e.* populations seen in routine clinical practice). Additionally, the validity of the inclusion criteria of the INPULSIS trials has never been evaluated from the perspective of survival time, a fundamental concern of both clinicians and patients.

To estimate the validity of this approach, we compared survival time in IIP patients having a UIP pattern with that in patients having a probable UIP pattern, in a real-world setting. We also compared time to first acute exacerbation (AE) between the two CT patterns.

Patients and methods

Study design and population

This study was approved by the institutional review board of Tosei General Hospital (Seto, Aichi, Japan). Informed consent was not required as the data were collected retrospectively and anonymously analysed.

A retrospective review of consecutive patients with ILD evaluated at Tosei General Hospital from January 2008 to March 2013 was performed. Patients included were those who underwent an initial workup for a suspected diagnosis of IIP and whose CT scans at initial workup were available. Patients excluded were those with an indeterminate for UIP or an alternative diagnosis pattern on CT [2], a diagnosis of connective tissue disease (CTD), chronic hypersensitivity pneumonitis (CHP) or other identifiable causes of ILD, those with concurrently associated malignant diseases, those lost to follow up within 1 year of the initial workup for reasons other than death and those who did not undergo a pulmonary function test (PFT) at the initial workup. All patients with clinically suspected IIP prior to SLB were included in the analysis, regardless of final diagnosis.

All patients with a UIP pattern or a probable UIP pattern on CT were included in the statistical analyses and we compared survival time and time to first AE between the two CT patterns. The same analyses were also performed in patients with a diagnosis of IPF and between IPF and non-IPF diagnoses in patients with a probable UIP pattern.

Data collection

Patient characteristics and test results were collected retrospectively from clinical charts. Initial workup data including PFTs, arterial blood gas analyses and CT scans conducted within 1 month were collected. Forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) were expressed as

percentages of the predicted values [9, 10]. The final follow-up date was December 31, 2016. The date of initial evaluation, date of last follow-up with survival status and date of diagnosis of the first AE were also recorded.

Definition of an AE

An AE was defined as a clinical event meeting all the following criteria [11]: 1) an acute respiratory deterioration characterised by evidence of new widespread alveolar abnormality; 2) acute worsening or development of dyspnoea within 1 month; 3) CT scan of the chest with new bilateral ground-glass opacity superimposed on a background pattern consistent with UIP; and 4) deterioration not fully explained by cardiac failure, fluid overload or infection.

Radiological and histopathological evaluation

All CT scans were independently reviewed by two experienced thoracic radiologists (TJ and HS) and an experienced thoracic physician (YK). To evaluate inter-observer variability, scans from 100 patients chosen at random from the study population were reviewed by each reviewer and Fleiss' κ-value was calculated. Published criteria were used to categorise CT scans as definite, probable or indeterminate for UIP pattern, or as findings of an alternative diagnosis [2]. Furthermore, each reviewer was blinded to the clinical and histopathological information. Given the κ-value (0.66, 95% CI 0.52–0.79), radiological interpretation of eligible cases was performed by one of the three reviewers.

A subset of patients had undergone SLB and all lung biopsy specimens were anonymised for histopathological analysis, and reviewed by two experienced pulmonary pathologists (JF and TT) who were blinded to clinical and radiological information and consulted each other about histopathological decisions. Published criteria were used to categorise histopathological findings [2].

Final diagnoses of ILDs

As the institute where the study was conducted was a local public hospital as well as a tertiary referral hospital, almost all patients were seen at least once every 3 months in the first year after initial workup, and every 3–6 months in the following years. All information regarding emergency department visits and/or hospitalisation was also captured. Under these circumstances, all available follow-up information was reviewed when making the final clinical diagnoses.

When histopathological information was available, the final diagnoses were established through multidisciplinary discussion (MDD) by clinicians, radiologists and pathologists with reference to the published criteria for IPF [2] and the classification for IIPs [12]. During the MDD, the clinical context and course, chest imaging and histopathology (if available) were reviewed in order to provide a final diagnosis. A diagnosis of "unclassifiable ILD" was made for patients with a non-IPF final diagnosis and histopathological features suggesting an alternative diagnosis (cellular inflammatory infiltration apart from areas of honeycombing, prominent lymphoid hyperplasia including secondary germinal centres, or a distinctly bronchiolocentric distribution including extensive peribronchiolar metaplasia). A diagnosis of CHP was made when histopathological features and clinical course were compatible, even if a history of exposure to specific antigens was lacking.

If histopathology was not available, the diagnosis of IPF was made when the clinical context was that of an IIP and the CT showed a UIP pattern. The patients with a probable UIP pattern on CT but no histopathology were provisionally classified as IPF when the likelihood of the diagnosis was believed to be >70% [12], while being classified as unclassifiable ILD when the clinical context was that of an IIP and clinical course did not suggest a specific diagnosis [12–14]. Findings suggestive of CTD, CHP and other identifiable causes or associations were actively sought out at the time of initial workup and during follow-up. We validated the clinical unclassifiable ILD diagnoses using a second approach (supplementary material).

Statistical analysis

Continuous variables were presented as medians with interquartile range (IQR) as they showed a non-normal distribution. Categorical variables were summarised by number of patients and percentage. To assess the differences in variables between subgroups, the Mann–Whitney U-test was used for continuous variables and the Pearson Chi-squared test was used for categorical variables. Survival time and time to first AE were measured from the date of initial workup until the date of death or the first diagnosis of AE, respectively. The Kaplan–Meier method was applied to show unadjusted survival curves, and mortality rate and AE rate were shown per 100 person-years.

Cox proportional hazards models were used to evaluate the associations between CT pattern or IPF diagnosis and survival time. The prognostic impacts were adjusted by demographic information generally associated with survival time: age, gender, baseline FVC [15], baseline D_{LCO} [16–18] and use of anti-fibrotics [4, 19]. Competing risk analyses were used to evaluate the associations between CT pattern or IPF diagnosis and time to first AE, in order to account for competing risks such as death from disease

progression without AE. The predictive values for time to first AE were adjusted by variables that have been reported to be associated with AE: baseline FVC [20–23], baseline D_{LCO} [21, 24] and use of anti-fibrotics. Multiple imputation analyses were performed to estimate survival time and time to first AE under the assumption of missing data. We carried out some imputations using all potential predictor variables in each imputation model. The overall proportion of patients with missing data was 2%, in all of whom D_{LCO} could not be assessed at baseline due to excessively low pulmonary function.

The adjusted annual rate of change in FVC was analysed with the use of a random coefficient regression model (with random slopes and intercepts) that included sex, age and height as covariates. The impact of CT pattern and IPF diagnosis were determined using estimated slopes for each study group on the basis of the time-by-treatment interaction term from the mixed model. Missing data were assumed to be missing at random and were not imputed.

All statistical tests were two sided and p-values of less than 0.05 were considered statistically significant. Statistical analyses were carried out using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) and Stata version 13.1 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

A total of 682 patients underwent an initial workup for suspected IIP that included a CT scan of the chest. After excluding 280 patients, 160 patients with a UIP pattern and 242 with a probable UIP pattern were identified (figure 1). The validity of this sample size for the analyses performed was confirmed (supplementary material). Median follow-up time was 42.9 months (range 0.8–104.4 months).

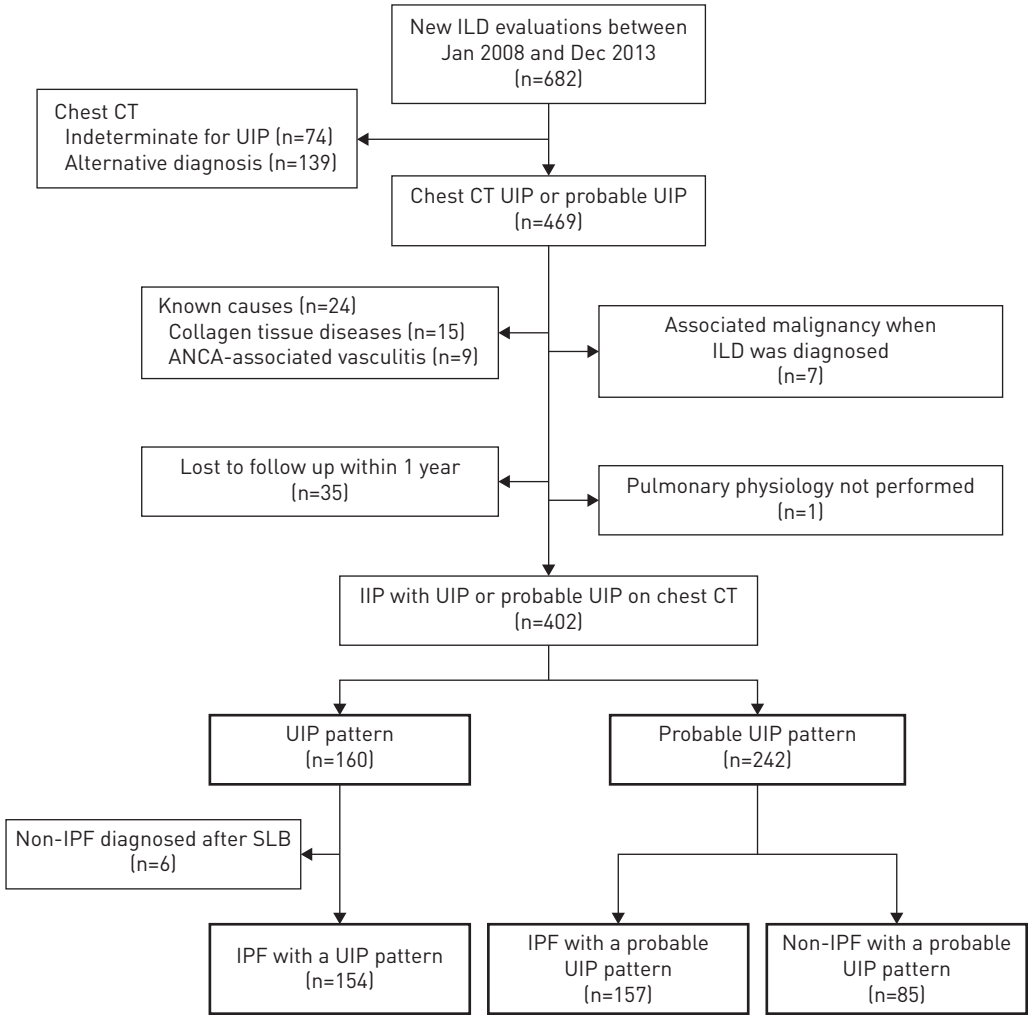

FIGURE 1 Screening and inclusion scheme for patients in the study. ILD: interstitial lung disease; CT: computed tomography; UIP: usual interstitial pneumonia; ANCA: anti-neutrophil cytoplasmic antibody; IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; SLB: surgical lung biopsy.

The clinical characteristics (table 1) showed significantly fewer males and smokers among patients with a probable UIP pattern and those with a non-IPF diagnosis when compared with other groups. Those with IPF and a UIP pattern showed a significantly lower FVC. The prevalence of a histopathological UIP pattern was 82% (27 out of 32) for a UIP pattern and 83% (90 out of 109) for a probable UIP pattern on chest CT, while the probability of an MDD diagnosis of IPF declined to 66% (72 out of 109) with a probable UIP pattern.

Prognosis: UIP pattern versus *probable UIP pattern*

The median survival time was 43.5 months for UIP pattern and 72.1 months for probable UIP pattern (figure 2a). Median time to first AE was 86.0 months for UIP pattern and 93.1 months for probable UIP pattern (figure 2b). In the imputed dataset, probable UIP pattern was independently associated with longer survival time (adjusted hazard ratio 0.722, 95% CI 0.540–0.965; p=0.028) (table 2) and longer time to first AE (adjusted hazard ratio 0.586, 95% CI 0.387–0.888; p=0.012) (table 3).

Prognosis of IPF: UIP pattern versus *probable UIP pattern*

Among subjects with a final diagnosis of IPF, survival time, time to first AE and their predictors were compared between those with a UIP pattern and those with a probable UIP pattern. Although survival time was longer in those with a probable UIP pattern, time to first AE was similar in the two groups (42.6 months *versus* 67.4 months and 86.0 months *versus* 90.9 months, respectively). CT pattern was not significantly associated with survival time (adjusted hazard ratio 0.883, 95% CI 0.640–1.218; p=0.447) (table 2) or time to first AE (adjusted hazard ratio 0.803, 95% CI 0.517–1.248; p=0.329) (table 3) in the imputed dataset.

TABLE 1 Characteristics of patients in the study

Characteristic	UIP pattern on CT (n=160)	Probable UIP pattern on CT		
		Total (n=242)	IPF (n=157)	non-IPF (n=85)
Age years	69 (65–72)	67 (61–71)[#]	66 (61–71)[#]	68 (62–71)
Male gender	131 (82)	185 (76)	126 (80)	59 (69)[#]
Smokers	129 (81) (n=159)	171 (71)[#]	116 (74)	55 (65)[#]
Smoking pack-years	39.0 (15.0–55.0) (n=159)	30.0 (0.0–50.0)[#]	30.0 (0.0–51.0)	30.0 (0.0–46.5)[#]
FVC L	2.40 (1.85–2.93)	2.73 (2.01–3.27)[#]	2.78 (2.07–3.28)[#]	2.60 (2.04–3.29)
FVC % predicted	74.0 (63.8–89.4)	88.3 (72.8–100.4)[#]	87.4 (72.8–99.9)[#]	89.2 (72.7–102.2)[#]
D_{LCO} % predicted	52.8 (41.0–66.6) (n=155)	65.6 (52.4–82.9)[#] (n=238)	63.1 (51.7–79.3)[#] (n=155)	69.6 (55.9–87.3)[#] (n=83)
P_{aO_2} mmHg	78.0 (70.8–87.7) (n=155)	82.3 (74.7–90.7)[#] (n=230)	82.0 (76.0–91.4)[#] (n=154)	82.4 (73.4–89.2) (n=76)
Treatment				
Anti-fibrotics	87 (54)	115 (48)	92 (59)	23 (27)[#,¶]
Corticosteroids	18 (11)	41 (17)	24 (15)[#]	17 (20)[#]
Histopathological pattern	n=32	n=109	n=72	n=37
Definite/probable UIP	27 (84)	90 (83)	71 (99)	19 (51)[+]
Indeterminate for UIP	2 (6)	5 (5)	1 (1)	4 (11)
Alternative diagnosis	3 (9)	14 (13)	0 (0)	14 (38)
Final diagnosis (with SLB)				
IPF	26 (81)	72 (66)	72 (100)	0 (0)
NSIP	1 (3)	8 (7)	0 (0)	8 (22)
Unclassifiable ILD	4 (13)	22 (20)	0 (0)	22 (59)
Other	1 (3)	7 (19)	0 (0)	7 (19)
Final diagnosis (with clinical diagnosis)				
IPF	154 (96)	157 (65)	157 (100)	0 (0)
NSIP	1 (1)	8 (3)	0 (0)	8 (9)
Unclassifiable ILD	4 (3)	70 (29)	0 (0)	70 (82)
Other	1 (1)	7 (3)	0 (0)	7 (8)

Data are presented as median (IQR) or n (%) unless otherwise stated. UIP: usual interstitial pneumonia; CT: computed tomography; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; SLB: surgical lung biopsy; NSIP: nonspecific interstitial pneumonia; ILD: interstitial lung disease; IQR: interquartile range. [#]: significantly different compared with a UIP pattern on CT; [¶]: significantly different compared with a probable UIP pattern and IPF diagnosis; [+]: has features that raise concerns about the likelihood of an alternative diagnosis, such as a cellular inflammatory infiltration apart from areas of honeycombing, prominent lymphoid hyperplasia including secondary germinal centres and a distinctly bronchiolocentric distribution that could include extensive peribronchiolar metaplasia.

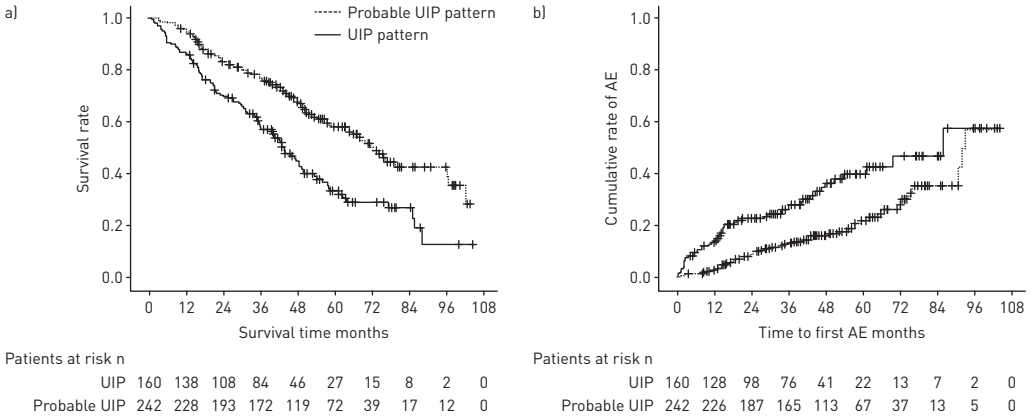

FIGURE 2 Kaplan–Meier curves of subjects with a usual interstitial pneumonia (UIP) pattern and those with a probable UIP pattern. a) Overall survival: the adjusted hazard ratio (0.722, 95% CI 0.540–0.965; p=0.028) for a probable UIP pattern (*versus* a UIP pattern) was evaluated by Cox proportional hazard analysis. b) Time to first acute exacerbation (AE): adjusted hazard ratio (0.586, 95% CI 0.387–0.888; p=0.012) for a probable UIP pattern (*versus* a UIP pattern) was evaluated by competing risk analysis.

Prognosis of probable UIP pattern: final diagnosis of IPF versus *non-IPF*

Survival time, time to first AE and factors associated with them were evaluated in IPF and non-IPF subjects with a probable UIP pattern. Both survival time (67.4 months *versus* median not reached) and time to first AE (90.9 months *versus* median not reached) were numerically shorter in IPF. In the imputed dataset, a final diagnosis of IPF was independently associated with survival time (adjusted hazard ratio 1.879, 95% CI 1.138–3.103; p=0.014) (table 2) and time to AE (adjusted hazard ratio 2.935, 95% CI 1.206–7.145; p=0.018) (table 3).

The adjusted annual rate of change in FVC did not significantly differ between UIP pattern and probable UIP pattern, nor did it differ between the two CT patterns in subjects with IPF. In subjects with a probable UIP pattern, the annual decline was significantly larger in those with a diagnosis of IPF than of non-IPF (supplementary material).

In the analyses carried out with the non-imputed dataset, survival time and time to first AE did not differ significantly between UIP pattern and probable UIP pattern, nor did they differ between the two CT patterns in subjects with IPF. In subjects with a probable UIP pattern, survival time was significantly shorter in those with a diagnosis of IPF than of non-IPF, but the difference in time to first AE was not significant.

Detail data for the adjusted annual rate of change in FVC and results from the non-imputed dataset are shown in the supplementary material.

TABLE 2 Mortality rate and Cox proportional hazard analysis for survival time

Parameters	Patients n	Deaths n	Mortality rate[#] (95% CI)	Adjusted hazard ratio (95% CI)	p-value[¶]
All patients					
UIP pattern on CT	160	99	19.8 (16.2–24.1)	Reference	0.028
Probable UIP pattern on CT	242	103	10.6 (8.8–12.9)	0.722 (0.540–0.965)	
IPF only					
UIP pattern on CT	154	96	20.5 (16.8–25.0)	Reference	0.447
Probable UIP pattern on CT	157	77	12.1 (9.7–15.2)	0.883 (0.640–1.218)	
Probable UIP pattern only					
Final diagnosis of non-IPF	85	26	7.8 (5.3–11.4)	Reference	0.014
Final diagnosis of IPF	157	77	12.1 (9.7–15.2)	1.879 (1.138–3.103)	

Hazard ratios were based on data modified by the multiple imputation method and adjusted by age, sex, baseline (% predicted) forced vital capacity (FVC), baseline (% predicted) diffusing capacity of the lung for carbon monoxide (D_{LCO}) and use of anti-fibrotics. UIP: usual interstitial pneumonia; CT: computed tomography; IPF: idiopathic pulmonary fibrosis. [#]: mortality rate per 100 person-years; [¶]: p-value for the hazard ratio.

TABLE 3 Acute exacerbation (AE) rate and competing risk analysis for time to first AE

Parameters	Patients n	AEs n	AE rate[#] (95% CI)	Adjusted hazard ratio (95% CI)	p-value[¶]
All patients					
UIP pattern on CT	160	51	11.1 (8.5–14.7)	Reference	0.012
Probable UIP pattern on CT	242	49	5.3 (4.0–7.0)	0.586 (0.387–0.888)	
IPF only					
UIP pattern on CT	154	49	11.5 (8.7–15.2)	Reference	0.329
Probable UIP pattern on CT	157	40	6.7 (4.9–9.1)	0.803 (0.517–1.248)	
Probable UIP pattern only					
Final diagnosis of non-IPF	85	9	2.7 (1.4–5.2)	Reference	0.018
Final diagnosis of IPF	157	40	6.7 (4.9–9.1)	2.935 (1.205–7.145)	

Hazard ratios were based on data modified by the multiple imputation method and adjusted by baseline (% predicted) forced vital capacity (FVC), baseline (% predicted) diffusing capacity of the lung for carbon monoxide (D_{LCO}) and use of anti-fibrotics. UIP: usual interstitial pneumonia; CT: computed tomography; IPF: idiopathic pulmonary fibrosis. [#]: AE rate per 100 person-years; [¶]: p-value for the hazard ratio.

Discussion

The INPULSIS [4] trials regarded the presence of an IIP and a probable UIP pattern as sufficient for diagnosing IPF without SLB, and showed that these subjects had a similar rate of disease progression compared to those with guideline-diagnosed IPF [5]. Based on that result and in the appropriate clinical context, patients with a probable UIP pattern can be expected to have comparable longitudinal disease behaviour to those who meet the guideline definition of IPF. However, the validity of this finding in the real-world or from the perspective of survival time has never been tested.

Our study provides new information about probable UIP pattern in a real-world setting. Among patients initially evaluated for an IIP, a probable UIP pattern is 50% more common than a UIP pattern. Prognostically, we demonstrate that patients with a probable UIP pattern on CT generally have a longer survival time and longer time to first AE than those with a UIP pattern, even after adjustment for other known prognostic factors. However, our data support the specific INPULSIS trial data (*i.e.* when patients with a final MDD diagnosis of IPF were analysed, the diagnosis predicted a poor prognosis and CT pattern was not a significant predictor of outcome), while recognising that, in our study, the diagnosis of IPF was made with the combination of baseline and longitudinal follow-up data, making it not applicable for predicting prognosis at initial presentation. Although there are some inconsistencies between the results from the imputed and non-imputed datasets, it is likely because those patients in whom D_{LCO} could not be measured due to extremely poor pulmonary function were excluded from the multivariate analyses in the non-imputed dataset. Exclusion of these subjects with the most severely impaired lung function possibly resulted in the reduction of the intergroup prognostic differences.

The probability of a histopathological UIP pattern in patients with a probable UIP pattern on CT remains controversial. Although some studies have reported PPVs of possible UIP pattern, according to the 2011 guidelines (*i.e.* ignoring the existence of traction bronchiectasis), for histopathological UIP pattern of more than 90% [25, 26], these studies have dealt with patients from randomised controlled trials for IPF (*i.e.* patients already diagnosed with IPF by expert ILD physicians). Consequently, there is unavoidable selection bias that may lead to an elevated PPV and, in real-world cohorts, the PPVs have been lower (approximately 60–70%) [6, 27, 28]. Brownell *et al.* [6] reported that the extent of traction bronchiectasis can increase the PPV of possible UIP pattern for histopathological UIP pattern and Chung *et al.* [29] found a prevalence of histopathological UIP pattern in patients with a probable UIP pattern that was similar to ours (82.4%). Thus, the inclusion of traction bronchiectasis in the definition of possible UIP pattern likely increases the PPV of histopathological UIP pattern. On the other hand, our cohort showed a final diagnosis of IPF of only 62% after MDD, suggesting that MDD is still important in making a definitive diagnosis of IPF in patients with a probable UIP pattern.

The extent of fibrosis on CT scan has been reported as a prognostic factor in both IPF [7, 17, 30] and fibrotic IIP [8, 18, 31]. However, quantification of the extent of fibrosis is difficult and alternative approaches to radiological evaluation have also been adopted to evaluate prognosis. Sumikawa *et al.* [7] showed the existence of traction bronchiectasis to be a prognostic factor, while Jeong *et al.* [32] reported that IPF with honeycombing had poorer prognosis than that without honeycombing. Although some studies demonstrated no statistical difference in survival between a UIP pattern and a possible UIP pattern in patients with fibrotic IIP based on log rank tests, the Kaplan–Meier curves shown in those articles suggest that, with greater numbers or longer follow-up, subjects with a possible UIP pattern might have

better outcomes [15, 33]. Our real-world data shows longer survival in patients with a probable UIP pattern compared with a UIP pattern, even though the definition includes the presence of traction bronchiectasis. However, in cohorts limited to subjects with a final diagnosis of IPF, we found no survival difference between UIP pattern and probable UIP pattern after adjustment for other relevant variables, as compatible with past reports [7, 34, 35].

Regarding non-radiological baseline prognostic factors, although the number of studies evaluating the prognostic impact of CT findings in multivariate analysis together with non-radiological variables is limited, the extent of fibrosis on CT and D_{LCO} or FVC have been reported as independent prognostic factors in patients with IPF [16, 17] and fibrotic IIP [15, 18]. In our study, probable UIP pattern (compared to UIP pattern) was independently associated with prognosis even when age, gender and usage of anti-fibrotics were included together with those physiological parameters.

AE has a significant impact on mortality [11], and a low FVC [20–23], low D_{LCO} [21, 24] and recent decline in FVC [20, 36, 37] are all reported to be risk factors for AE in IPF. Although AE is also reported in patients with non-IPF ILDs [38–40], it is more frequent in IPF than in IIP with a pattern other than UIP on CT scan [23]. Our results are consistent with these findings; however, as IPF patients with a probable UIP pattern showed a risk for AE similar to those with a UIP pattern in our cohort, it should be noted that an IPF diagnosis is more important than the CT pattern in predicting time to AE.

There are a number of limitations to this study. First, this was a retrospective study from a large clinical practice and the baseline disease severity varied among the groups. Patients with a UIP pattern generally had more severe disease than those in other groups. Although adjusted for well-recognised prognostic factors, caution is still necessary when interpreting our results. Moreover, treatment was not standardised and all decisions regarding starting and ending treatment rested with the individual physician, making it difficult to evaluate the effect of treatment on outcomes. As such, prospective validation will be needed to clarify these points. Secondly, the study was conducted at a single institute and all patients were Japanese, making it difficult to generalise to other cohorts.

In conclusion, in our real-world IIP cohort, patients with a probable UIP pattern had a generally better prognosis and lower risk of AE at any time point than those with a UIP pattern. Moreover, probable UIP pattern was an independent prognostic factor and associated with time to first AE. As probable UIP pattern did not predict survival in patients with a final diagnosis of IPF, diagnostic heterogeneity associated with a probable UIP pattern likely explains the difference between the two groups. As such, care is needed when extrapolating diagnostic evidence from clinical trials for IPF.

Conflict of interest: None declared.

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