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Prognostic Value of IPF/PPF/non-PPF Classification Beyond ILD-GAP Stage in Fibrotic ILD

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Prognostic Value of IPF/PPF/non-PPF Classification Beyond ILD-GAP Stage in Fibrotic ILD

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Keywords: fibrotic interstitial lung disease; progressive pulmonary fibrosis; idiopathic pulmonary fibrosis; ILD-GAP; mortality; prognosis; risk stratification; cohort study

Abstract

Background: Progressive pulmonary fibrosis (PPF) identifies patients with fibrotic interstitial lung disease (F-ILD) who show progressive disease behaviour resembling idiopathic pulmonary fibrosis (IPF). However, it remains uncertain whether classification as IPF, PPF, or non-PPF provides prognostic information beyond established baseline mortality predictors. We compared the prognostic performance of IPF/PPF/non-PPF classification with the interstitial lung disease–gender–age–physiology (ILD-GAP) stage and assessed whether IPF/PPF/non-PPF classification provided additional prognostic information.

Methods: This is a nationwide prospective cohort study of incident F-ILD patients diagnosed at all Danish tertiary ILD centres between 1 June 2016 and 31 May 2017. Patients with fewer than two pulmonary function tests or without registry linkage were excluded. Patients were retrospectively classified as IPF, PPF, or non-PPF according to the 2022 PPF criteria. Baseline ILD-GAP stage was calculated at diagnosis. Cox proportional hazards models were used to assess all-cause mortality, and Harrell's C-index, time-dependent area under the receiver operating characteristic curve (AUC), and Akaike's Information Criterion (AIC) were used to compare discrimination and relative model fit.

Results: Among 393 incident F-ILD patients, 362 were included: 165 with IPF, 113 developed PPF, and 84 were classified as non-PPF. During follow-up, 216 patients died. In unadjusted analysis, PPF and non-PPF were associated with lower mortality hazard than IPF (HR 0.7 and 0.68; p = 0.028 and 0.035); however, these associations attenuated after adjustment for ILD-GAP stage (HR 0.93 and 0.93; p = 0.64 and 0.69). ILD-GAP stage II–III remained strongly associated with mortality in the adjusted model (HR 2.60, 95% CI 1.95–3.47; p < 0.001). Harrell's C-index was 0.54 for IPF/PPF/non-PPF classification, 0.62 for ILD-GAP stage, and 0.62 for the combined ILD-GAP and IPF/PPF/non-PPF classification model. Pairwise comparisons of Harrell's C-index showed ILD-GAP stage discriminated mortality risk significantly better than IPF/PPF/non-PPF classification, with an absolute increase in C-index of 0.085

(95% CI 0.042 to 0.127; p < 0.001). Adding IPF/PPF/non-PPF classification to ILD-GAP stage did not improve discrimination (difference 0.001)

Conclusions: After adjustment for ILD-GAP stage, the IPF/PPF/non-PPF classification did not confer prognostic value. Higher ILD-GAP was strongly associated with increased mortality, and adding IPF/PPF/non-PPF classification to ILD-GAP did not improve discrimination.

Introduction

Fibrotic interstitial lung diseases (F-ILDs) comprise a heterogeneous group of lung disorders characterised by irreversible fibrosis of the lung parenchyma, often leading to progressive physiological impairment, respiratory failure, and ultimately death [1,2]. Idiopathic pulmonary fibrosis (IPF) is the prototypical F-ILD. It is invariably progressive and generally associated with the poorest prognosis among F-ILDs. However, a substantial proportion of patients with non-IPF F-ILD show a similarly progressive disease behaviour despite treatment and removal of potential inciting factors [1,3].

The term progressive pulmonary fibrosis (PPF) was recently introduced to describe progressive fibrotic behaviour in non-IPF F-ILD. PPF is defined by at least two of three criteria occurring within the preceding year, with no alternative explanation: worsening respiratory symptoms, physiological progression, and radiological progression [3]. The INBUILD trial established the efficacy of nintedanib in non-IPF progressive fibrosing ILD, supporting the clinical importance of identifying progressive disease [4]. Accordingly, PPF has become important for identifying patients with ongoing disease progression who may benefit from antifibrotic therapy [3].

This shared progressive phenotype has led to the hypothesis that patients with PPF may have a prognosis approaching that of patients with IPF. Several studies have reported higher mortality among patients with PPF than non-PPF, approaching levels observed in IPF [5–11]. Other studies show no

significant difference in mortality [12,13], particularly after adjustment for age, sex, and/or baseline disease severity [14,15]. In our previous analysis of the non-IPF subset from the Danish ILD Database, mortality did not differ significantly between PPF and non-PPF after adjustment for ILD-GAP stage [16]. However, that study excluded IPF and did not formally assess whether disease-behaviour classification provided incremental prognostic information.

The ILD-GAP model is a mortality index that extends the original GAP model for IPF by incorporating ILD subtype, in addition to sex, age, and pulmonary physiology, to estimate mortality risk across chronic ILDs [17]. It has been validated in several ILD populations [18–21], but it predates the concept of PPF and does not explicitly account for disease progression. It remains uncertain whether the IPF/PPF/non-PPF classification provides prognostic information beyond what the ILD-GAP model captures.

We therefore investigated whether IPF/PPF/non-PPF classification provides prognostic information beyond that captured by the ILD-GAP model in a national incident F-ILD cohort. We compared the prognostic discrimination and relative model fit of IPF/PPF/non-PPF classification and ILD-GAP and examined their associations with all-cause mortality.

Methods

Study Design and Population

This prospective longitudinal cohort study included all newly diagnosed cases of F-ILD from 1 June 2016 to 31 May 2017 across all tertiary ILD centres in Denmark (Odense, Aarhus, and Herlev-Gentofte University Hospitals), serving a population of approximately 5.8 million inhabitants. Diagnoses and ILD classification were determined by multidisciplinary team (MDT) discussions, in accordance with the international guidelines applicable at the time of diagnosis [3,22]. Patients with fewer than two pulmonary function tests (PFTs) assessments were excluded from all groups to ensure comparable

eligibility and minimise immortal-time-related selection bias, as PPF classification required longitudinal assessment.

The F-ILD cohort was divided into three groups: 1) IPF, 2) other F-ILD diagnoses that met PPF criteria based on the 2022 guidelines during follow-up [16], and 3) non-PPF.

Data Sources and Variables

The Danish ILD Database (DANILDA) contains prospectively collected data from outpatient clinic files for all patients with ILD diagnosed by MDT at one of the Danish tertiary ILD centres between June 2016 and May 2017. Routine outpatient follow-up typically occurred every 6-8 months. Clinical and demographic data were entered into DANILDA at diagnosis, and subsequent records of PFTs, respiratory symptoms, 6-min walk distance, biochemistry, and treatment changes were recorded prospectively. Follow-up high-resolution computed tomography (HRCT) was performed on clinical indication; progression information derived from radiology reports and MDT conclusions was recorded.

Data on demographics, smoking history, medication, PFT, symptoms and radiology were obtained from DANILDA. All diagnoses were validated by manual review of patient files. The IPF group comprised patients with IPF. The PPF group comprised non-IPF patients who met the 2022 PPF criteria [3] during follow-up, as described in detail by Kølner-Augustson et al. [16]. In brief, PPF required at least two criteria within a 365-day window, and the PPF date was defined as the date of the second fulfilled criterion. The remaining non-IPF patients were categorised as non-PPF.

Denmark provides universal, tax-funded healthcare, with coverage tracked via national registers. Alongside DANILDA data, we retrieved data from the Danish Civil Registration System [23] (emigration and vital status) and the Danish National Patient Register (DNPR) [24] on 31 December 2023. The DNPR contains records of all hospital, outpatient, and emergency contacts, and diagnoses are

documented using the International Classification of Diseases, 10th Revision, with minor extensions [24]. Comorbidity data were obtained from the DNPR.

The baseline Charlson comorbidity index (CCI) was calculated using the updated 2011 scoring system [25]. Baseline ILD-GAP scores were determined using the validated model [17], which subtracts 2 points from the original GAP score for patients with Hypersensitivity pneumonitis (HP), idiopathic non-specific interstitial pneumonia (iNSIP), or systemic autoimmune rheumatic disease-associated ILD (SARD-ILD); negative values are set to 0. ILD-GAP stages were grouped into stage I (scores 0–3) and stage II–III (scores 4–8); stages II and III were combined due to few patients in stage III (n = 12).

Statistical analysis.

Analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) using two-sided tests at a significance level of 0.05. Baseline categorical variables are presented as n (%) and continuous variables as mean (SD). Group comparisons (IPF vs PPF or non-PPF) used χ^2 tests for categorical variables and t-tests, Wilcoxon rank-sum tests, or Kruskal–Wallis tests for continuous variables.

Overall survival was analysed as conditional survival from the first follow-up contact after MDT-confirmed diagnosis, with time recorded in months. Baseline ILD-GAP, body mass index (BMI), and CCI were measured at the MDT-confirmed incident F-ILD diagnosis. Patients alive on 31 December 2023 were administratively censored; no lung transplants or emigrations occurred during follow-up. Cox proportional hazards models were fitted, with time from the first clinical follow-up contact to death or administrative censoring as the outcome. Model 1 included IPF/PPF/non-PPF classification, with IPF as the reference. Model 2 included ILD-GAP stage. Model 3 included ILD-GAP stage and IPF/PPF/non-PPF classification. All models were fitted to the same complete-case population. Proportional hazards were assessed using a covariate-by-log(time) interaction ($p<0.05$ indicating non-proportionality); no significant violations were identified. Model fit was assessed using Akaike's Information Criterion (AIC).

Model discrimination was assessed using Harrell's C-index with 95% confidence intervals as the primary measure. Time-dependent AUC was also estimated at 3, 5, and 7 years. Pairwise differences in C-index between models were tested using z-tests based on the variance–covariance matrix of the concordance statistics, with 95% confidence intervals and p-values reported.

Because PPF develops during follow-up, it is inherently time-varying. For the primary Cox and discrimination analyses, PPF was treated as a fixed classification according to whether it was observed during follow-up. A prespecified secondary model additionally included CCI and BMI. To assess the potential influence of treating PPF as a fixed classification, this secondary model was repeated with PPF modelled as a time-varying covariate using start–stop intervals; person-time before fulfilment of PPF criteria was classified as non-PPF and subsequent person-time as PPF.

As a secondary analysis, annualised changes in FVC and DLCO were calculated as (last observed value – first observed value) / (time between measurements in days / 365). Extreme annualised changes were set to missing in accordance with predefined rules.

Results

Study population

Of 393 incident F-ILD patients, 31 were excluded: 29 had fewer than two pulmonary function tests, and two could not be linked to national registries. The final cohort comprised 362 patients (Figure 1). Compared with included patients, excluded patients had similar demographic characteristics but a higher proportion had died by the end of follow-up (83% versus 60%; $p = 0.014$). Among patients who died, time from diagnosis to death was shorter in excluded patients (median 4.5 months; $p < 0.001$; Table 1).

Diagnoses comprised mainly IPF (n = 165, 46%), unclassifiable ILD (n = 63, 17%), SARD-ILD (n = 59, 16%), HP (n = 36, 10%), and iNSIP (n = 21, 6%), but other fibrotic diagnoses were also represented

(Table 2). Progressive pulmonary fibrosis (PPF) criteria were met in 113 patients during follow-up, and 84 patients were classified as non-PPF F-ILD [16]. Baseline characteristics of the population are presented in Table 3. Patients had a mean age of 71 ± 10 years; 245 (67.7%) were male, and 259 (71.5%) had a history of smoking. Most patients were ILD-GAP stage I (63%), had a CCI of 0 (59.4%), and a well-preserved FVC (87% predicted) but reduced DLCO (53% predicted). A usual interstitial pneumonia (UIP) or probable UIP pattern on HRCT was present in 204 patients (56%), predominantly among IPF cases. In the IPF group, 104 of 165 initiated antifibrotic therapy.

The IPF group had a higher proportion of males, a slightly older age, higher baseline FVC, a lower proportion in ILD-GAP stage I, a higher proportion with CCI = 0, and less frequent prednisolone use than the other groups. (Table 3). Annualised pulmonary function trajectories were consistent with the expected disease-behaviour phenotypes: FVC declined similarly in IPF and PPF but remained relatively stable in non-PPF, while DLCO declined in both IPF and PPF but was stable on average in non-PPF (Supplementary S1).

Survival and mortality

Median follow-up across the full cohort was 80 months (6.7 years) from the first follow-up contact. During follow-up, 216 deaths occurred. Three-, five-, and seven-year survival rates were 71%, 50%, and 34% for IPF; 73%, 58%, and 48% for PPF; and 75%, 62%, and 49% for non-PPF ILD, respectively (Figure 2). By ILD-GAP stage, three-, five-, and seven-year survival rates were 82%, 68%, and 54% for stage I and 56%, 33%, and 21% for stages II–III, respectively (Figure 3).

In Model 1, both PPF (HR 0.70, 95% CI 0.51–0.96; p=0.028) and non-PPF (HR 0.68, 95% CI 0.48–0.97; p=0.035) were associated with lower mortality than IPF. After adjustment for ILD-GAP stage, these associations were attenuated (PPF: HR 0.93, 95% CI 0.67–1.28; p=0.64; non-PPF: HR 0.93, 95% CI 0.64–1.34; p=0.69). ILD-GAP stage II–III was associated with higher mortality than stage I both before

(HR 2.70, 95% CI 2.06–3.54; p<0.001) and after adjustment for disease classification (HR 2.63, 95% CI 1.97–3.51; p<0.001; Table 4).

In the prespecified secondary model additionally adjusted for CCI and BMI, estimates obtained with PPF modelled as a time-varying covariate were similar to those from the corresponding fixed-classification model: HR 0.79 (95% CI 0.56–1.13) for PPF, 0.81 (95% CI 0.55–1.20) for non-PPF, and 2.59 (95% CI 1.94–3.45) for ILD-GAP stage II–III (Supplementary S2).

Model discrimination

Harrell's C-index was 0.538 for IPF/PPF/non-PPF classification, 0.623 for ILD-GAP stage, and 0.622 for the combined model (Table 4). ILD-GAP stage discriminated mortality better than IPF/PPF/non-PPF classification (difference in C-index 0.085, 95% CI 0.042–0.127; p<0.001), whereas adding classification to ILD-GAP stage did not improve discrimination (difference 0.001, 95% CI −0.019 to 0.021; p=0.934; Table 5). Relative model fit showed the same pattern: AIC was 2312 for classification alone, 2268 for ILD-GAP stage, and 2272 for the combined model. Time-dependent AUCs showed no consistent improvement after adding IPF/PPF/non-PPF classification to ILD-GAP stage across the 3-, 5-, and 7-year prediction horizons (Table 4).

Discussion

In this nationwide prospective cohort of patients with incident F-ILD, IPF/PPF/non-PPF classification did not provide prognostic information beyond that captured by ILD-GAP stage. ILD-GAP stage was strongly associated with mortality and showed better prognostic discrimination than disease classification, whereas adding IPF/PPF/non-PPF classification to ILD-GAP stage did not improve discrimination or relative model fit. These findings suggest that longitudinal disease-behaviour classification and baseline mortality risk stratification capture different aspects of F-ILD.

Importantly, the limited prognostic contribution of PPF classification should not be taken to indicate an absence of clinically relevant disease progression. Longitudinal changes in pulmonary function were consistent with the expected distinction between progressive and non-progressive phenotypes, with greater functional decline in the IPF and PPF groups than in the non-PPF group (Supplementary S1). Rather, our findings suggest that the presence of progressive disease behaviour does not, in itself, provide substantial additional information about long-term mortality once established baseline prognostic factors incorporated in ILD-GAP are taken into account.

Previous studies comparing IPF, PPF, and non-PPF have reported inconsistent survival patterns. Some cohorts have found PPF associated with higher mortality than non-PPF [5–11], whereas others have not [12–15]. However, these studies vary in design and which covariates they adjust for. In the present cohort, apparent mortality differences were attenuated after accounting for ILD-GAP stage. Extending these observations, our model-comparison analyses showed that ILD-GAP discriminated mortality better than IPF/PPF/non-PPF classification, and that adding disease classification to ILD-GAP provided essentially no additional discriminatory information.

Included versus excluded patients

Patients excluded for insufficient follow-up had shorter survival, with a median time to death of 4.5 months after diagnosis, which was shorter than the usual follow-up interval (approximately 6 months). This explains most exclusions, as several patients must have died before PFT could be repeated. Although excluding these patients might have led to an underestimation of survival, PPF status could not be assessed without a follow-up PFT or HRCT, highlighting some of the limitations of the PPF definition. Including them would therefore have introduced differential misclassification and amplified immortal-time-related bias.

Strengths and limitations

The main strengths of this study are its nationwide, multicentre, real-world design and the inclusion of all newly diagnosed F-ILD patients from the referral network of tertiary Danish ILD centres. This reduces referral bias, supports the broad capture of clinically relevant cases, and strengthens external validity across similar healthcare systems. Diagnoses were MDT-based and manually validated, and linkage between DANILDA and national registries ensured near-complete ascertainment of vital status and minimal loss to follow-up. The direct comparison of ILD-GAP stage and IPF/PPF/non-PPF classification further enabled assessment of which framework better explained survival differences across fibrotic ILD.

The study has several limitations. First, classifying PPF requires at least two PFT assessments. Applying this requirement across all groups improved comparability but excluded patients with early mortality; accordingly, survival estimates should be interpreted as conditional on reaching the first follow-up contact after MDT-confirmed diagnosis. Second, PPF status was derived from routinely collected follow-up data, with HRCT and symptom assessment performed according to clinical practice rather than a fixed protocol, which may introduce surveillance bias. For the primary analyses, PPF was treated as an ever-observed fixed classification, incorporating information unavailable at baseline. However, in a prespecified secondary model additionally adjusted for CCI and BMI, modelling PPF as a time-varying covariate yielded nearly identical estimates, suggesting limited influence of this modelling choice on the observed associations. Finally, residual confounding from unmeasured disease characteristics and time-varying treatment cannot be excluded.

Clinical implications

The present findings suggest that we should not expect high mortality in patients simply because their fibrotic ILD shows progressive behaviour. Baseline ILD-GAP stage provides an informative framework for predicting long-term mortality, independent of progression status. However, progression remains important for identifying active disease, thereby guiding monitoring and decisions on initiating

immunomodulatory or antifibrotic treatment. PPF remains an important marker of active fibrotic disease behaviour.

Conclusion

In this nationwide incident F-ILD cohort, IPF/PPF/non-PPF classification did not provide prognostic information beyond ILD-GAP stage. ILD-GAP stage showed better discrimination for mortality than IPF/PPF/non-PPF classification, and adding IPF/PPF/non-PPF classification to ILD-GAP did not improve discrimination or model fit. These findings suggest that PPF and ILD-GAP capture different aspects of disease: PPF reflects active fibrotic disease behaviour, whereas ILD-GAP provides more informative baseline mortality risk stratification.

List of abbreviations

AIC: Akaike's information criterion

AUC: area under the receiver operating characteristic curve

BMI: body mass index

CCI: Charlson comorbidity index

DANILDA: Danish Interstitial Lung Disease Database

DLCO: diffusing capacity of the lung for carbon monoxide

DNPR: Danish National Patient Register

F-ILD: fibrotic interstitial lung disease

FVC: forced vital capacity

HR: hazard ratio

HRCT: high-resolution computed tomography

ILD: interstitial lung disease

ILD-GAP: interstitial lung disease–gender–age–physiology

IPF: idiopathic pulmonary fibrosis

MDT: multidisciplinary team

PFT: pulmonary function test

PPF: progressive pulmonary fibrosis

SARD-ILD: systemic autoimmune rheumatic disease-associated interstitial lung disease

UIP: usual interstitial pneumonia

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, Danish data-protection legislation, and applicable ethical standards. Approval was obtained from the Danish Patient Safety Authority (journal no. 3-3013-2504/1). Individual informed consent was waived because the study relied on registry-based and routinely collected clinical data, in accordance with Danish law. Data were pseudonymised before analysis and processed on secure servers in compliance with the General Data Protection Regulation.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Availability of data and materials

The data supporting this study's findings contain individual-level clinical and registry information and cannot be made publicly available under Danish data-protection legislation. Access may be obtained through application to the relevant Danish authorities and data custodians, subject to approval.

Competing interests

All reported relationships are outside the submitted work. L.K. reports honoraria for a presentation from Boehringer Ingelheim. N.M. reports honoraria for invited speaking and support for attending meetings from Boehringer Ingelheim and Chiesi. T.P. reports lecture fees from Boehringer Ingelheim and AstraZeneca, support for attending meetings from Boehringer Ingelheim, and participation in advisory boards for Boehringer Ingelheim. J.R.D. reports research grants from Boehringer Ingelheim, honoraria for lectures from Boehringer Ingelheim and AstraZeneca, support for attending meetings from Boehringer Ingelheim, and participation in advisory boards for Boehringer Ingelheim and AstraZeneca. S.S. reports honoraria for lectures from Boehringer Ingelheim, Novartis and AstraZeneca, support for attending meetings from Boehringer Ingelheim, and advisory board membership for Boehringer Ingelheim. E. B. reports honoraria for lectures from Boehringer Ingelheim, AstraZeneca, Daiichi Sankyo and Bristol Myers Squibb, support for attending meetings from Boehringer Ingelheim, and participation in advisory boards for Boehringer Ingelheim, Simbec Orion and Oxcia. A.L. reports lecture fees from GSK, Novo Nordisk, Chiesi, Sanofi Genzyme and AstraZeneca, support for attending meetings from AstraZeneca, GSK, Chiesi, and Sanofi Genzyme, and grants from AstraZeneca, Chiesi, and Sanofi Genzyme. O.H. reports grants from the Novo Nordisk Foundation and Boehringer Ingelheim, honoraria for lectures from Boehringer Ingelheim, AstraZeneca, GSK and Chiesi, support for attending meetings from AstraZeneca, GSK and Boehringer Ingelheim, and participation in advisory boards for Boehringer Ingelheim, Simbec Orion and Oxcia.

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Authors' contributions

L.K. and O.H. were responsible for the study's conception and design. J.D., E.B., and S.S. contributed to data acquisition, while M.K. managed data curation and validation. L.K., A.L., and O.H. designed the statistical analyses. The data analysis and interpretation were carried out by L.K., T.P., and J.D. L.K. drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work, ensuring the integrity and accuracy of the data and analyses.

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Table 1: Comparison of included and excluded patients.

	Included (n = 362)	Excluded (n = 29)	p-value
IPF n (%)	165 (46)	9 (31)	0.17
Men n (%)	245 (68)	19 (66)	0.81
Age mean (SD)	71.5 (10)	72.6 (10)	0.56
Current/ previous Smoker n (%)	259 (71)	20 (69)	0.86
BMI >25 n (%)	249 (69)	19 (66)	0.70
Dead n (%)	216 (60)	24 (83)	0.014
Time to death in months* median (IQR)	40 (38)	4.5 (7.5)	<0.001

* Time to death was calculated in months from the MDT-confirmed diagnosis date to the date of death. Patients without linkage to national registries (n = 2) were excluded because mortality data were unavailable.
Abbreviations: BMI, body mass index; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range.

Table 2:
The distribution of fibrotic diagnoses in the cohort.

Diagnosis	n	%
Idiopathic pulmonary fibrosis	165	45.6
Unclassifiable interstitial lung disease	63	17.4
Systemic Autoimmune Rheumatic Disease-associated interstitial lung disease	59	16.3
Hypersensitivity pneumonitis	36	9.9
Idiopathic non-specific interstitial pneumonia	21	5.8
Asbestosis	8	2.2
Desquamative interstitial pneumonia	4	1.1
Interstitial pneumonia with autoimmune features	3	0.8
Idiopathic pleuroparenchymal fibroelastosis	2	0.6
Combined Pulmonary Fibrosis and Emphysema	1	0.3

The incident ILD diagnosis was determined at the multidisciplinary team assessment and was manually validated. Percentages are calculated using the total included cohort as the denominator. Diagnostic categories are mutually exclusive.

Table 3 – Baseline characteristics of 362 patients with fibrotic interstitial lung disease.

Characteristic	Entire cohort n = 362	IPF n = 165	PPF n= 113	Non-PPF n = 84
Men, n (%)	245 (67.7)	127 (77.0)	60 (53.1)	58 (69.0)
Age, Mean (SD)	71 (10)	73 (7.2)	69 (11.5)	71 (12.6)
FVC L, Mean (SD)	2.9 (0.8)	3.0 (0.8)	2.7 (0.8)	3.0 (0.9)
FVC % predicted, Mean (SD)	87 (21)	90 (20)	83 (20)	86 (22)
DLCO % predicted, Mean (SD)	53 (15)	53 (15)	51 (16)	54 (15)
Smoking status, n (%)				
- Current	40 (11.0)	18 (10.9)	8 (7.1)	14 (16.7)
- Previous	219 (60.5)	110 (66.7)	66 (58.4)	43 (51.2)
- Never	96 (26.5)	35 (21.2)	37 (32.7)	24 (28.6)
- Missing	7 (1.9)	2 (1.2)	2 (1.8)	3 (3.5)
BMI, n (%)				
- < 25	112 (30.9)	44 (26.7)	38 (33.6)	30 (35.7)
- ≥ 25	249 (68.8)	120 (72.7)	75 (66.4)	54 (64.3)
- Missing	1 (0.3)	1 (0.6)	0 (0)	0 (0)
Education, n (%)				
- Lower education (ISCED = 0-2)	135 (37.3)	58 (35.2)	48 (42.5)	29 (34.5)
- Medium education (ISCED = 3-4)	138 (38.1)	68 (41.2)	44 (38.9)	26 (31.0)
- High education (ISCED = 5-8)	78 (21.5)	32 (19.4)	21 (18.6)	25 (29.8)
- Missing	11 (3.1)	7 (4.2)	0.(0.0)	4 (4.7)
6MWD, m,	n = 302,	n = 152,	n = 85,	n = 65,
- Mean (SD)	422 (122)	426 (112)	410 (124)	426 (139)
UIP pattern on HRCT*, n (%)	204 (56.4)	142 (86.1)	31 (27.4)	31 (36.9)
ILD-GAP, n (%)				
- Stage I	228 (63.0)	77 (46.7)	87 (77.0)	64 (76.2)
- Stage II-III	129 (35.6)	86 (52.1)	25 (22.2)	18 (21.4)
- Missing	5 (1.4)	2 (1.2)	1 (0.8)	2 (2.4)
Comorbidities, n (%)				
- Diabetes	62 (17.1)	28 (17.0)	24 (21.2)	10 (11.9)
- Hypertension	112 (30.9)	49 (29.7)	38 (33.6)	25 (29.8)
- Ischaemic heart disease	64 (17.7)	27 (16.4)	25 (22.1)	12 (14.3)
- Osteoporosis	47 (13.0)	20 (12.1)	18 (15.9)	9 (10.7)
- Atrial fibrillation	38 (10.5)	17 (10.3)	14 (12.4)	7 (8.3)
- Other cardiovascular disease	36 (9.9)	15 (9.1)	14 (12.4)	7 (8.3)
- Stroke	18 (5.0)	14 (8.5)	4 (3.5)	0 (0)
Charlson Comorbidity Index, n (%)				
- CCI = 0	215 (59.4)	128 (77.6)	46 (40.7)	41 (48.8)
- CCI = 1	86 (23.7)	17 (10.3)	41 (36.3)	28 (33.3)
- CCI = 2	61 (16.9)	20 (12.1)	26 (23.0)	15 (17.9)
Treatment, n (%)				
- Antifibrotics	106 (29.3)	104 (63.0)	2 (1.8)	0 (0.0)
- Prednisolone	49 (13.5)	7 (4.2)	28 (24.8)	14 (16.7)

* Definite or probable usual interstitial pneumonia pattern on high-resolution computed tomography. Data are n (%) with percentages calculated using the number included in the group as the denominator; missing data are shown where applicable. Categorical variables are compared using χ^2 tests. Comorbidities and treatments are not mutually exclusive; patients may contribute to multiple categories. p-values compare IPF versus PPF. Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; ISCED, International Standard Classification of Education; ILD-GAP, Interstitial Lung Disease–Gender-Age-Physiology score; IPF, Idiopathic Pulmonary Fibrosis; PPF, progressive pulmonary fibrosis; FVC, forced vital capacity; 6MWD, 6-minute walk distance.

Table 4. Associations with all-cause mortality, discriminatory performance, and relative model fit of Cox proportional hazards models.

	Model 1: IPF/PPF/non-PPF classification	Model 2: ILD-GAP	Model 3: IPF/PPF/non-PPF classification and ILD-GAP.
Cox regression estimates, HR (95%CI); p-value			
PPF vs IPF	0.70 (0.51–0.96); **0.028**		0.93 (0.67–1.28); 0.642
Non-PPF vs IPF	0.68 (0.48–0.97); **0.035**		0.93 (0.64–1.34); 0.692
ILD-GAP stage II–III vs I		2.70 (2.06–3.54); **<0.001**	2.63 (1.97–3.51); **<0.001**
Model performance			
Harrell's C-index (95% CI)	0.538 (0.500–0.576)	0.623 (0.591–0.654)	0.622 (0.583–0.660)
3-year AUC (95% CI)	0.528 (0.466–0.591)	0.666 (0.609–0.722)	0.640 (0.572–0.708)
5-year AUC (95% CI)	0.557 (0.501–0.612)	0.658 (0.610–0.706)	0.660 (0.603–0.716)
7-year AUC (95% CI)	0.612 (0.540–0.684)	0.649 (0.591–0.707)	0.681 (0.611–0.751)
AIC	2312	2268	2272

Cox proportional hazards models were used to estimate hazard ratios for all-cause mortality from the first clinical follow-up contact to death or administrative censoring. PPF status was treated as a fixed classification based on whether PPF was observed during follow-up. Model 1 included IPF/PPF/non-PPF classification; Model 2 included ILD-GAP stage; and Model 3 included ILD-GAP stage and IPF/PPF/non-PPF classification. All models were fitted to the same complete-case population (n=356; 216 deaths). Harrell's C-index was the primary measure of discrimination. Time-dependent AUCs were estimated at 3, 5, and 7 years. Higher C-index and AUC values indicate better discrimination, whereas lower AIC values indicate better relative model fit. Abbreviations: AIC, Akaike information criterion; AUC, area under the time-dependent receiver operating characteristic curve; CI, confidence interval; HR, hazard ratio; ILD-GAP, interstitial lung disease–gender–age–physiology; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.

Table 5. Pairwise comparisons of Harrell's C-index.

Comparison	Difference in C-index (95% CI)	p-value
Model 1 vs Model 2	−0.085 (−0.127 to −0.042)	**<0.001**
Model 1 vs Model 3	−0.084 (−0.121 to −0.046)	**<0.001**
Model 2 vs Model 3	0.001 (−0.019 to 0.021)	0.934

Pairwise differences of Harrell's C-index were tested using a z-test based on the variance–covariance matrix of the concordance statistics. PPF was treated as a fixed classification for these analyses. Model 1: IPF/PPF/non-PPF classification. Model 2: ILD-GAP. Model 3: IPF/PPF/non-PPF classification and ILD-GAP. Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; ILD-GAP, interstitial lung disease–gender-age-physiology; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.

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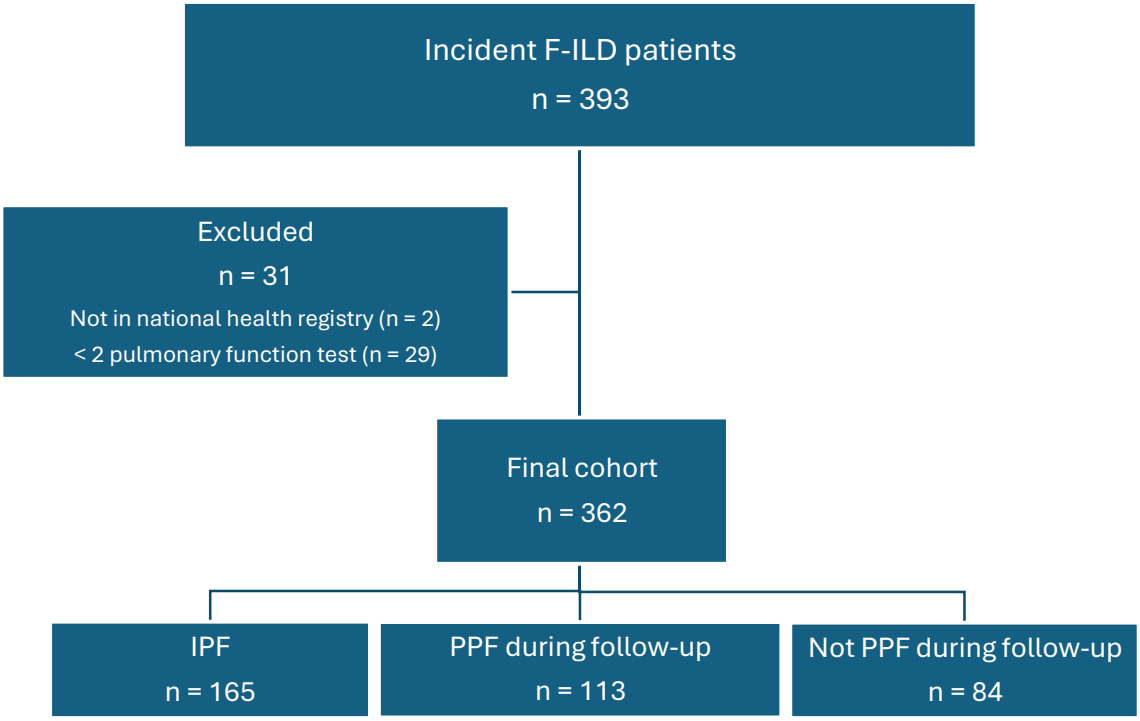
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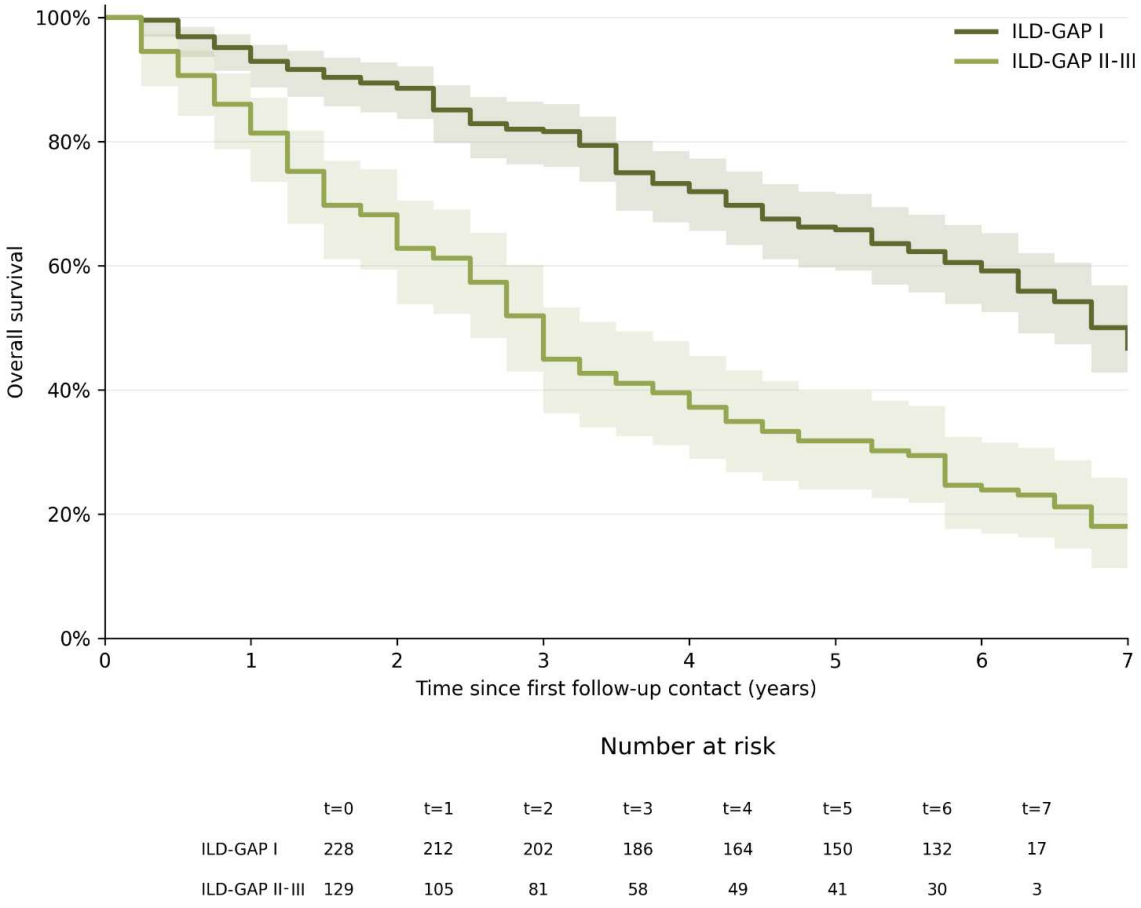
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Figure 1. Study flow diagram.



During the inclusion period (1 June 2016 to 31 May 2017), 393 patients were diagnosed with fibrotic interstitial lung disease (F-ILD) in Denmark. We excluded 29 patients with fewer than two pulmonary function tests and two patients not registered in the national registries. The final study cohort comprised 362 patients and was divided into the following groups for comparison: patients with idiopathic pulmonary fibrosis (IPF) (n=165), non-IPF patients who developed progressive pulmonary fibrosis (PPF) during follow-up (n=113), and non-IPF patients who did not develop PPF (non-PPF) (n=84).

Figure 3. Unadjusted Kaplan–Meier estimates of overall survival in F-ILD, divided by ILD-GAP stage

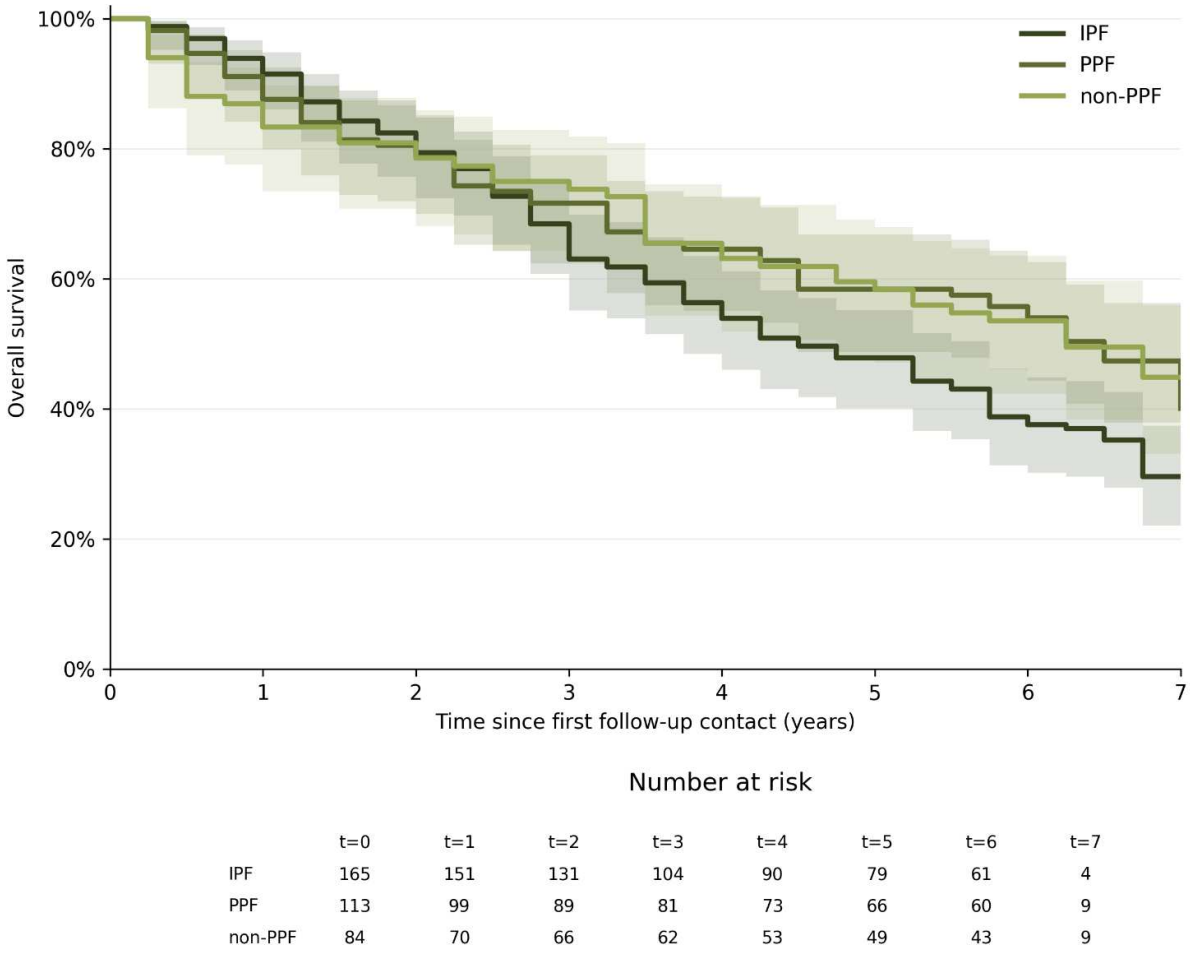


Number at risk

	t=0	t=1	t=2	t=3	t=4	t=5	t=6	t=7
ILD-GAP I	228	212	202	186	164	150	132	17
ILD-GAP II-III	129	105	81	58	49	41	30	3

Time zero was the first follow-up contact after diagnosis (i.e., the earliest recorded clinical assessment or pulmonary function test). Participants were followed until death or administrative censoring on 31 December 2023; no lung transplantations or emigrations occurred during follow-up. Abbreviations: F-ILD, fibrotic interstitial lung disease; ILD-GAP = mortality index based on gender, age, physiology and interstitial lung disease.

Figure 2. Unadjusted Kaplan–Meier estimates of overall survival in fibrotic ILD, divided by IPF/PPF/non-PPF classification.



Number at risk

	t=0	t=1	t=2	t=3	t=4	t=5	t=6	t=7
IPF	165	151	131	104	90	79	61	4
PPF	113	99	89	81	73	66	60	9
non-PPF	84	70	66	62	53	49	43	9

Time zero was the first follow-up contact after diagnosis (i.e., the earliest recorded clinical assessment or pulmonary function test). Participants were followed until death or administrative censoring on 31 December 2023; no lung transplantations or emigrations occurred during follow-up. Abbreviations: F-ILD, fibrotic interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; non-PPF, not IPF or PPF.

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