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Please cite this article as: Gudmundsson E, Zhao A, Mogulkoc N, *et al*. Delineating associations of progressive pleuroparenchymal fibroelastosis in patients with pulmonary fibrosis. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00637-2022).

# Delineating associations of progressive pleuroparenchymal fibroelastosis in patients with pulmonary fibrosis

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# ABSTRACT

*Background:* Computer quantification of baseline computed tomography (CT) radiologic pleuroparenchymal fibroelastosis (PPFE) associates with mortality in idiopathic pulmonary fibrosis (IPF). We examined mortality associations of longitudinal change in computer quantified PPFE-like lesions in IPF and fibrotic hypersensitivity pneumonitis (FHP).

*Methods:* Two CT scans 6-36 months apart were retrospectively examined in one IPF (n=414) and one FHP population (n=98). Annualised change in computerised upper-zone pleural surface area comprising radiologic PPFE-like lesions (Δ-PPFE) was calculated. Δ-PPFE >1.25% defined progressive PPFE above scan noise. Mixed-effects models evaluated Δ-PPFE against change in visual CT interstitial lung disease (ILD) extent and annualised forced vital capacity (FVC) decline. Multivariable models were adjusted for age, gender, smoking history, baseline emphysema presence, antifibrotic use and diffusion capacity for carbon monoxide. Mortality analyses further adjusted for baseline presence of clinically important PPFE-like lesions and ILD change.

*Findings:* Δ-PPFE associated weakly with ILD and FVC change. 22–26% of IPF and FHP cohorts demonstrated progressive PPFE-like lesions which independently associated with mortality in the IPF cohort (HR=1.25, 95% CI 1.16–1.34, p<0.0001) and the FHP cohort (HR=1.16, 95% CI 1.00–1.35, p=0.045).

*Interpretation:* Progression of PPFE-like lesions independently associates with mortality in IPF and FHP but does not associate strongly with measures of fibrosis progression.

*Funding:* Wellcome Trust [209553/Z/17/Z]; NIHR UCLH Biomedical Research Centre, UK.

**KEYWORDS:** Pleuroparenchymal fibroelastosis, PPFE, idiopathic pulmonary fibrosis, IPF, computed tomography, quantitative analysis, fibrotic hypersensitivity pneumonitis, chronic hypersensitivity pneumonitis

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease characterised by lower zone predominant honeycomb cysts and traction bronchiectasis[1] on computed tomography (CT) imaging.[2] IPF can show a variable disease course.[3] Quantifying disease progression on imaging is important and has primarily involved visual semi-quantification of changes in CT extents of honeycomb cysts, reticulation, ground glass opacities and traction bronchiectasis,[4] patterns reflecting pulmonary sequelae of fibrotic damage. Yet estimation of serial CT change in these patterns have shown limited correlations with measures of disease progression[5–7] (change in forced vital capacity [FVC]) and variable correlation with mortality in IPF patients.[7]

Computational analysis of CT imaging can identify alternative CT patterns such as vessel-related structures[8–10] which associate with mortality in patients with IPF. Exploration of novel imaging features has also delineated patterns such as pleuroparenchymal fibroelastosis (PPFE) which do not directly result from the fibrotic process, but which may influence patient survival.[11] PPFE is characterised by dense triangular pleurally-based opacities occurring in the upper lobes on CT.[12] PPFE scored visually on a single baseline CT has been shown to associate with reduced survival time in IPF patients[11,13] and other fibrosing lung diseases.[14,15] Computer quantitation of baseline upper lobe PPFE-like lesions (incidence 25–36%) was shown to associate with mortality in IPF independent of baseline disease severity (measured by either FVC, ILD extent or diffusion capacity for carbon monoxide [DLco]) and identified more patients with a poor outcome than equivalent semi-quantitative visual CT analysis.[11] PPFE-like lesions scored by computer did not associate with baseline measures of IPF-related fibrosis on univariable or multivariable analyses,

suggesting that PPFE-related damage might represent injury occurring independent to IPF-related lung fibrosis.[11]

Careful delineation of patients with clinically meaningful progressive PPFE-like lesions using computational analysis of time-series CTs may highlight a lung fibrosis endotype benefiting from alternative management strategies.[16] Sensitive quantification of progressive PPFE could also evaluate treatment response in future trials of therapies targeting PPFE and/or progressive fibrotic phenotypes[17] where PPFE change might influence outcome measures. Our current study therefore aimed to delineate in IPF and fibrotic hypersensitivity pneumonitis (FHP) populations the prevalence and prognostic impact of progressive PPFE-like lesions. We also examined whether PPFE change associated with other measures of disease progression in IPF.

## Material and Methods

### Study subjects and clinical information

Patients with a multidisciplinary team diagnosis of IPF or FHP with two volumetric CT examinations separated by 6–36 months were identified from five medical centres (Ege University Hospital, Izmir, Turkey; St Antonius Hospital, Nieuwegein, Netherlands; University Hospital Southampton NHS Foundation Trust, UK; University College London Hospitals NHS Foundation Trust, UK; University Hospitals Leuven, Belgium) [Supplementary Table 1]. CONSORT diagrams for the two study populations are shown in Figure 1 and Supplementary Figure 1; patient demographics for patients included in the study are shown in Table 1. Approval for this retrospective study of clinically indicated pulmonary function and CT data was obtained from the local research ethics committees and Leeds East Research Ethics Committee: 20/YH/0120.

### Visual CT Evaluation

A subspecialist radiologist (JJ) with 14-years thoracic imaging experience determined lobar percentages of ILD (sum of ground glass density, reticulation, traction bronchiectasis volume and honeycomb cysts, averaged across six lobes[11]) on two timepoint CTs, and emphysema presence (absent/present) on baseline CTs of all IPF and FHP patients. Change in CT ILD extent was annualised ("Δ-ILD"). The radiologist was blinded to outcome data when visually evaluating the CTs of the study.

### Computer-Based CT Evaluation

Computerised quantification of the percentage of visceral pleural surface (most peripheral 3 lung surface pixels) affected by radiologic PPFE-like lesions, was obtained on CT pairs of IPF and FHP patients as previously described.[11] PPFE-like lesions were only quantified in the upper zones (region extending from carina to 5 mm below lung apices – thereby avoiding capturing an apical cap) which approximated the upper lobes, where radiologic PPFE is most typically found. A 2.5% threshold of PPFE extent on baseline imaging, derived in a previous IPF study,[11] delineated clinically important PPFE at baseline for IPF and FHP cohorts.

The annualised change in computerised upper-zone extent of PPFE-like lesions between scans ("Δ-PPFE") was calculated as the difference in computerised PPFE between the baseline and follow-up CTs, divided by the scan interval in years. It is important to account for the contribution of noise to the estimation of PPFE change between CT scans. Noise can occur between CT timepoints due to differences in e.g., CT acquisition parameters including scanner model and reconstruction algorithm variability, differences in the level of patient inspiration, and patient positioning. Δ-PPFE of 1.25% or more of the pleural surface area was used to identify patients with morphologically definitive "progressive" radiologic PPFE-like lesions. The estimation of noise contained within the longitudinal CT imaging was determined by calculating one half of the standard deviation of baseline PPFE in the derivation IPF cohort,[11] which corresponds to a moderate effect size. This method has previously been suggested to determine the minimal clinically important difference in biomarker studies in IPF.[18–20] A continuous variable ("Δ-PPFE-adj") reflecting definitive change in extent of PPFE-like lesions above scan noise was created by subtracting 1.25% from Δ-PPFE values of progressive radiologic PPFE patients and setting Δ-PPFE-adj values to 0% for non-progressive patients.

**Modelling Strategy**

Linear mixed-effects (LME) regression analyses, with a single fixed effect and a random intercept for each centre, investigated the association between longitudinal change of ILD extent and PPFE extent, and baseline ILD, PPFE, DLco% predicted, and FVC% predicted in both cohorts. LME models with multiple fixed effects were also used to investigate the association between change in FVC and Δ-PPFE. The temporal trajectories of FVC measurements were modelled between baseline and follow-up CTs separately for each cohort, with a random intercept for each centre and each subject, and with a random slope for each subject. These models included fixed effects of age at baseline, patient gender, smoking status (never/ever), baseline emphysema presence, baseline FVC% predicted, study time, and Δ-PPFE. In the IPF cohort, these models also included fixed effects of antifibrotic use across follow-up (never/ever).

Across all LME models for FVC, patients who did not have at least two absolute FVC measurements (one within 6 months of baseline CT and another within 6 months of follow-up CT) were excluded (IPF: n=81/414 excluded; FHP: n=20/98 excluded). Modelled FVC measurements were restricted to 6 months prior to the baseline CT of each patient and 6 months after the follow-up CT of each patient, to ensure that FVC trajectories were representative of the development of disease between the scans.

Univariable and multivariable Cox regression analyses explored determinants of mortality, with a single frailty variable for centre to adjust for average differences between patient centres within each cohort. Entry time for survival analysis was taken as the date of second CT. All

multivariable mortality models were adjusted for patient age at baseline, patient gender, smoking status (never/ever), baseline emphysema presence (absent/present), Δ-ILD, clinically important PPFE at baseline (no/yes), and DLco% predicted. Antifibrotic use (never/ever) adjustments were used in the IPF cohort only.

Baseline DLco% predicted and baseline FVC% predicted were considered if available within 3 months of baseline CT. Missing baseline DLco% predicted and baseline FVC% predicted were imputed and considered missing at random (details in online supplement).

**Statistical analysis**

Data are presented as patient proportions (percentages) or means (with standard deviations) or medians (with range of values), as appropriate. Differences in categorical variables were assessed using the $\chi^2$ test. Differences in medians of continuous variables were assessed using the two-sided Mann–Whitney U test. Differences in means of continuous variables were assessed using the two-sided Student's t-test. In three-group comparisons, a Kruskal-Wallis rank sum test evaluated differences in medians and a one-way ANOVA evaluated differences in means. A p-value $<0.05$ was considered significant across all analyses. Multivariable linear models were tested for heteroscedasticity using the studentised Breusch-Pagan test.[21] The Concordance index (C-index) compared the goodness of fit of Cox regression models.[22] $R^2$ values reported for LME models are the "marginal" $R^2$, which describes the proportion of variance explained by fixed factor(s) alone.[23] Bootstrapping with 500 iterations was used to estimate sampling distributions of the C-index. Kaplan-Meier curves were truncated at 5 years. LME model analyses, Cox regression and Kaplan-Meier analyses, and multiple imputations were performed with the lme4,

survival, and mice packages in R, respectively (version 4.1.1 with Rstudio version 1.4.1717, Rstudio, Massachusetts, US).

## Results

### Baseline data

Demographic data, baseline pulmonary function tests, and mean visual ILD extent and computerised PPFE scores for the IPF cohort (n=414) and the FHP cohort (n=98) are shown in Table 1. Baseline characteristics of IPF patients and HP patients excluded from the study are shown in Supplementary Table 2 and 3, respectively.

### Computerised PPFE extent associations

The prevalence of clinically important PPFE (i.e., PPFE extent > 2.5%) on baseline imaging was 29.5% in the IPF cohort and 26.5% in the FHP cohort (Table 1). Baseline computerised PPFE extent weakly associated with Δ-PPFE in the IPF cohort but slightly more strongly in the FHP cohort (Figure 2, Supplementary Table 4). Baseline PPFE weakly associated with Δ-ILD in univariable models in the IPF cohort only (Supplementary Figure 2, Supplementary Table 4).

Δ-PPFE weakly associated with Δ-ILD in the IPF cohort but not the FHP cohort (Supplementary Figure 3, Supplementary Table 4). Δ-PPFE weakly associated with baseline DLco% and baseline FVC% in multivariable models in both cohorts (Supplementary Table 4 and 5, Supplementary Figure 4 and 5). Comparisons between baseline ILD and Δ-ILD and Δ-PPFE are shown in Supplementary Figures 6-7.

### PPFE change and FVC decline

Demographic data, baseline pulmonary function tests, and mean visual ILD extent and computerised PPFE scores for patients included and excluded from FVC modelling in the IPF

cohort and the FHP cohort are shown in Supplementary Table 6 and 7, respectively. Δ-PPFE weakly associated with FVC change in univariable models in the IPF cohort only (-0.13 l/year, 95% CI -0.18– -0.08 l/year, p<0.0001, $R^2$=0.07) and in multivariable models in the IPF cohort only (effect: -0.09 l/year, 95% CI -0.13– -0.05 l/year, p<0.0001, $R^2$=0.34) [Supplementary Table 8–9]. Results were maintained in non-imputed models in both cohorts (Supplementary Table 10).

**PPFE change associations with mortality**

In univariable Cox regression models in the IPF cohort, covariates significantly associated with mortality included: baseline DLco% predicted, baseline FVC% predicted, baseline ILD extent, baseline PPFE extent, presence of clinically important PPFE at baseline, Δ-PPFE, and Δ-PPFE-adj (Supplementary Table 11). In the FHP cohort, covariates significantly associated with mortality in univariable Cox regression models included: patient age at baseline, baseline DLco% predicted, baseline ILD extent, baseline PPFE extent, Δ-PPFE, and Δ-PPFE-adj (Supplementary Table 11).

In multivariable Cox regression models, Δ-PPFE was significantly associated with mortality in the IPF cohort (hazard ratio [HR]=1.20, 95% CI 1.13–1.28, p<0.0001) and the FHP cohort (HR=1.18, 95% CI 1.05–1.34, p=0.008) [Supplementary Table 12]. Results were maintained in non-imputed models in both cohorts (Supplementary Table 13). Multivariable Cox regression models without adjustment for Δ-PPFE are shown in Supplementary Table 14.

**PPFE progression above scan noise**

89/414 (21%) patients in the IPF cohort and 25/98 (26%) patients in the FHP cohort had progressive radiologic PPFE as determined by Δ-PPFE > 1.25%/year (Figure 3). Demographic data, baseline pulmonary function tests, and mean visual ILD extent and computerised PPFE scores for non-progressive PPFE patients without clinically important PPFE at baseline, non-progressive PPFE patients with clinically important PPFE at baseline, and progressive PPFE patients are shown in Supplementary Table 15–16.

Definitive PPFE change above scan noise (Δ-PPFE-adj) was independently associated with mortality in multivariable Cox regression models in the IPF cohort (HR=1.25, 95% CI 1.16–1.34, p<0.0001) and the FHP cohort (HR=1.16, 95% CI 1.00–1.35, p=0.045) [Table 2] regardless of the degree of ILD progression or the presence of clinically important PPFE at baseline. Results were maintained in non-imputed models and in models not adjusted for baseline presence of clinically important PPFE (Supplementary Table 17–18). Sensitivity analyses investigating noise threshold values in the range 0.5%/year – 1.5%/year showed maintained results (Supplementary Table 19). Kaplan-Meier analyses reflected the poor survival in patients with progressive PPFE (Figure 4).

## Discussion

In our study of computerised quantitation of radiologic PPFE change we demonstrate that in patients with IPF and FHP, worsening computerised PPFE independently associates with increased patient mortality with similar effect sizes seen in two separate patient populations. Limited associations were seen between PPFE worsening and measures used to estimate disease progression in IPF and FHP (radiologic ILD progression and FVC decline) suggesting that PPFE progression occurs independent of established fibrotic pathways. When evaluating morphologically important PPFE change, over 20% of patients in the IPF and FHP cohorts demonstrated progressive PPFE.

Radiologic PPFE on CT has been well characterised over the last 10 years following detailed histopathological-radiological correlative studies.[24–26] PPFE quantification has primarily been attempted using crude categorical visual scales of CT disease extent,[11,14] but computer quantitation can improve identification of PPFE patients with a poor prognosis.[11] In the current study the high prevalence of PPFE noted in FHP[15] and similar survival between FHP and IPF patients[27,28] underpinned the rationale for extending our analysis to a multicentered FHP cohort. We show that across two cohorts of patients with fibrosing lung disease similar proportions of patients demonstrated a progressive PPFE phenotype. The disassociation between PPFE progression and ILD progression in the current study (as delineated by CT change in visual ILD scores or FVC decline) matched disassociation between baseline PPFE extent and measures of IPF severity in our previous study.[11]

While PPFE has been increasingly reported in patients with underlying lung fibrosis,[11,14] PPFE has also been identified in the setting of bone marrow[25,29] and lung transplantation[30–32] recipients, patients exposed to dusts[33] and as a long-term sequelae of patients receiving chemotherapeutic agents.[34] Hypotheses for potential causes of PPFE might include occult infectious agents, excessive reaction to recurrent pulmonary infections in patients with pre-existing immune dysregulation, or a manifestation of a pulmonary malignancy. Associations seen in patients with PPFE include genetic predispositions (telomere-related gene mutations[35,36]), recurrent pulmonary infections[24] and ischaemia in apical lung vessels.[30,37,38] Despite the high prevalence of PPFE reported in patients with interstitial fibrosis, the location of PPFE in the lung apices, its occurrence in patients without fibrosis and specifically the lack of major association between PPFE progression and measures of fibrosis progression support our contention[11] that PPFE occurring in fibrosing lung diseases represents a distinct disease endotype.

The increased mortality seen in patients with progressive PPFE may reflect the replacement of upper zone lung tissue in patients with IPF/FHP with an elastotic process. The lung in the upper zones is often spared in IPF and its loss may disproportionately impact gas exchange in patients where the middle/lower zones demonstrate airspace and vascular destruction. It has also been observed in studies using corrosion casting of the lung microvasculature that extensive intussusceptive angiogenesis occurs in areas of PPFE.[39] It is therefore possible that as PPFE proliferates, there may be accentuation in ventilation-perfusion mismatches which in turn further exacerbate hypoxia in patients with concomitant fibrosing lung disease.

There remains an urgent need to invest more resources to examine specific treatments that can target PPFE in the subgroups of patients with IPF and FHP. Application of computer tools to baseline CT data[11] can aid in cohort enrichment when recruiting patients to therapeutic trials for PPFE, which can in turn improve the power of clinical trials. Therapeutic trials in IPF have been constrained by a lack of reliable endpoints, which necessitate larger sample sizes and therefore more expensive trials. Our current study emphasizes the potential for computer-based delineation of PPFE progression to act as a drug trial endpoint when determining treatment response.

There were several limitations to the current study. Reasons for performing longitudinal imaging in IPF and FHP patients can be varied. Disproportionately, imaging is repeated following clinical deterioration. Consequently, patients with acute exacerbations, infections, pneumothoraces[25,40] and pneumomediastinums, which occur with increased frequency in PPFE, were not infrequent in our study cohorts (Figure 1, Supplementary Figure 1). These patients, and those with co-existing lung malignancies were excluded from the current analysis to avoid non-PPFE pathology being mistakenly characterised as PPFE by the computer. We may therefore have underestimated the prevalence of progressive PPFE occurring in IPF and FHP. In addition, we did not have detailed information in the study population on the use of immunomodulatory therapies, which could have influenced the progression of PPFE.

Though a retrospective analysis of non-protocolised scans, our study demonstrated a strong mortality signal in real world multicentered noisy data. While we adjusted our analyses to account for biases between study centres through mixed-effects models and frailty Cox models, we also tried to delineate measurement noise associated with quantitative analysis of longitudinal

CT imaging. As it is only necessary to detect a digital signature equivalent to PPFE on one single voxel out of the many millions of lung voxels present on a single CT, some measure of PPFE will invariably be detected by computational CT analysis. However not all PPFE or PPFE change detected by a computer is real, e.g., PPFE change could be artificially inflated by a poor inspiratory effort on a second timepoint CT. We estimated the degree of noise from longitudinal CT analysis of PPFE change as 50% of the standard deviation of PPFE seen at baseline, in accordance with similar prior work in IPF. The similar effect size of our adjusted PPFE quantitation on mortality analysis across the two study cohorts reinforces our belief that our estimation of noise is appropriate and has clinical utility.

In conclusion, our study highlights the independent deleterious prognostic effect of worsening computerised PPFE-like lesions in patients with IPF and FHP. PPFE progression only associated weakly with measures of ILD progression in IPF suggesting that the distinct disease trajectories for ILD and PPFE may represent separate pathophysiological pathways. Over 20% of patients in the two study cohorts were identified with a progressive PPFE phenotype which independently associated with mortality. Given the need for new targeted therapies for PPFE, our computer-based quantitation of PPFE could act as a new endpoint in randomised clinical trials.

## Acknowledgments

This research was funded in whole or in part by the Wellcome Trust [209553/Z/17/Z]. For the purpose of open access, the author has applied a CC-BY public copyright licence to any author accepted manuscript version arising from this submission. This project, JJ, EG, ED, JCP and SMJ were also supported by the NIHR UCLH Biomedical Research Centre, UK. MGJ, TW and CB acknowledge the support of the NIHR Southampton Biomedical Research Centre.

## Disclosure of Conflicts of Interest

JJ reports fees from Boehringer Ingelheim, Roche, NHSX, Takeda and GlaxoSmithKline unrelated to the submitted work. JJ was supported by Wellcome Trust Clinical Research Career Development Fellowship 209553/Z/17/Z and the NIHR Biomedical Research Centre at University College London. SMJ reports fees from Astra-Zeneca, Bard1 Bioscience, Achilles Therapeutics, and Jansen unrelated to the submitted work. SMJ received assistance for travel to meetings from Astra Zeneca to American Thoracic Conference 2018 and from Takeda to World Conference Lung Cancer 2019 and is the Investigator Lead on grants from GRAIL Inc, GlaxoSmithKline plc and Owlstone. AUW personal fees and non-financial support from Boehringer Ingelheim, Bayer and Roche Pharmaceuticals; and personal fees from Blade, outside of the submitted work. EG, AZ, NM, IS, MGJ, CvM, RS, CJB, HWvE, OU, KP, FvB, TW, MV, BG, AN, DA, TG, RC, HG, MH, AA, AP, LDS, ED, MD, MT, SV, JP and WW report no relevant conflicts of interest.

## Author Contributions

EG, AZ, IS, AUW, SMJ, DCA, and JJ contributed to study design and data interpretation. EG, AZ, NM, MGJ, CHMvM, WW, JP, SV, RS, CJB, HWvE, TG, MH, OU, KP, FvB, MV, TW, BG, LDS, ED, AN, RC, MV, AA, MT, MD, AP, HG, and JJ were responsible for data acquisition. EG, AZ, IS, and JJ contributed to the statistical analysis. EG and JJ prepared the first draft of the manuscript. EG and JJ were responsible for study data integrity. All authors reviewed the manuscript and approved the final submitted version.

**Table 1**: **Patient demographics, pulmonary function indices and visual and computer-based scores of ILD and PPFE severity for IPF and FHP patients in the study.** Pulmonary function indices, ILD extent, and PPFE scores are described as means and standard deviations. Clinically important PPFE at baseline was defined as baseline PPFE extent >2.5%. Progressive PPFE was defined as Δ-PPFE >1.25%/year. IPF=idiopathic pulmonary fibrosis, FHP=fibrotic hypersensitivity pneumonitis, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, ILD=interstitial lung disease, Δ-ILD=annualised change in ILD extent between CT scans, PPFE=pleuroparenchymal fibroelastosis, Δ-PPFE=annualised change in computerised upper-zone PPFE between scans, Δ-PPFE-adj=Δ-PPFE above scan noise.

| Variable | IPF cohort (n = 414) | FHP cohort (n = 98) | p-value |
|---|---|---|---|
| Median baseline age in years (range) | 69 (32 – 95) | 64 (28 – 85) | 0.0001 |
| Male/female | 24.2% / 75.8% | 62.2% / 37.8% | <0.0001 |
| Survival (alive/dead) | 44.4% / 55.6% | 54.1% / 45.9% | 0.11 |
| Median years of follow-up (range) | 2.2 (0.0 - 9.0) | 2.7 (0.0 - 12.0) | 0.013 |
| Median years between CT scans (range) | 1.1 (0.5 - 3.0) | 1.1 (0.5 - 2.9) | 0.81 |
| Never/ever smokers | 30.7% / 69.3% | 50.0% / 50.0% | 0.0005 |
| Antifibrotic (never/ever) | 30.7% / 69.3% | - | - |
| Baseline FVC% predicted | 81.3 +/- 19.7 | 64.2 +/- 19.6 | <0.0001 |
| Baseline DLco% predicted | 48.8 +/- 15.9 | 50.5 +/- 16.8 | 0.44 |
| Baseline emphysema (absent/present) | 32.4% / 67.6% | 69.4% / 30.6% | <0.0001 |
| Baseline ILD extent (%) | 39.0 +/- 12.3 | 33.3 +/- 14.0 | 0.0003 |
| Δ-ILD (%/year) | 7.7 +/- 8.7 | 4.0 +/- 5.6 | <0.0001 |
| Baseline PPFE extent (%) | 2.0 +/- 2.4 | 1.9 +/- 2.3 | 0.74 |
| Δ-PPFE (%/year) | 0.8 +/- 2.0 | 0.8 +/- 2.4 | 0.93 |
| Clinically important baseline PPFE prevalence | 29.5% | 26.5% | 0.65 |
| Progressive PPFE prevalence | 21.5% | 25.5% | 0.47 |
| Δ-PPFE-adj in progressive PPFE patients (%/year) | 2.3 +/- 2.7 | 2.4 +/- 3.3 | 0.86 |

**Table 2: Association of Δ-PPFE-adj with mortality in multivariable Cox regression models in the IPF cohort and in the FHP cohort**. Models in all cohorts were adjusted for patient age, gender, smoking history (never/ever), emphysema presence at baseline, clinically important PPFE at baseline (baseline PPFE >2.5% upper-zone pleural surface area), baseline DLco% predicted, annualised change in interstitial lung disease extent (Δ-ILD), and Δ-PPFE-adj. Models in the IPF cohort were also adjusted for antifibrotic treatment (never/ever). DLco=diffusing capacity for carbon monoxide, PPFE=pleuroparenchymal fibroelastosis, AF=antifibrotic, ILD=interstitial lung disease, Δ-PPFE-adj=annualised change in computerised upper-zone PPFE between scans above scan noise.

| Cohort | Variable | Hazard ratio | 95% Confidence Interval | p-value | Model C-index |
|---|---|---|---|---|---|
| IPF | Baseline age (years) | 1.00 | 0.99, 1.02 | 0.73 | 0.75 |
| | Male gender | 1.46 | 1.00, 2.14 | 0.047 | |
| | Ever smoker | 1.22 | 0.87, 1.71 | 0.25 | |
| | Baseline emphysema (absent/present) | 0.93 | 0.67, 1.31 | 0.69 | |
| | AF treatment (never/ever) | 0.72 | 0.54, 0.97 | 0.033 | |
| | Δ-ILD (%/year) | 1.01 | 0.98, 1.03 | 0.62 | |
| | Baseline PPFE extent >2.5% | 1.72 | 1.27, 2.33 | 0.0006 | |
| | Baseline DLco% predicted | 0.96 | 0.94, 0.97 | <0.0001 | |
| | Δ-PPFE-adj (%/year) | 1.25 | 1.16, 1.34 | <0.0001 | |
| FHP | Baseline age (years) | 1.08 | 1.03, 1.13 | 0.004 | 0.79 |
| | Male gender | 1.02 | 0.41, 2.52 | 0.97 | |
| | Ever smoker | 1.75 | 0.63, 4.86 | 0.27 | |
| | Baseline emphysema (absent/present) | 0.71 | 0.29, 1.74 | 0.44 | |
| | Δ-ILD (%/year) | 1.13 | 1.04, 1.23 | 0.004 | |
| | Baseline PPFE extent >2.5% | 2.11 | 0.89, 5.00 | 0.086 | |
| | Baseline DLco% predicted | 0.96 | 0.93, 0.99 | 0.014 | |
| | Δ-PPFE-adj (%/year) | 1.16 | 1.00, 1.35 | 0.045 | |

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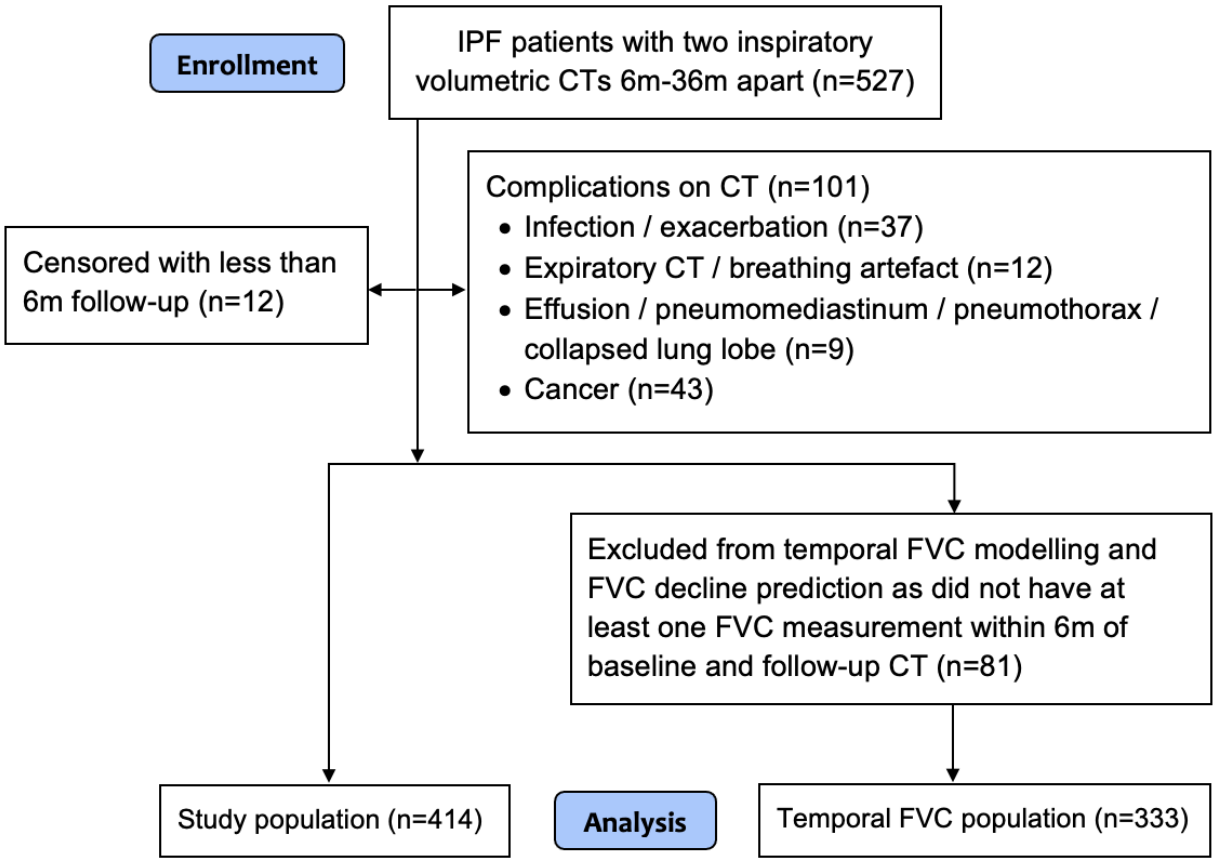



Figure 1: CONSORT diagram showing patient exclusions for IPF patients in the study. CONSORT flow diagrams for IPF patients in the study. IPF = idiopathic pulmonary fibrosis, CT = computed tomography, FVC = forced vital capacity.

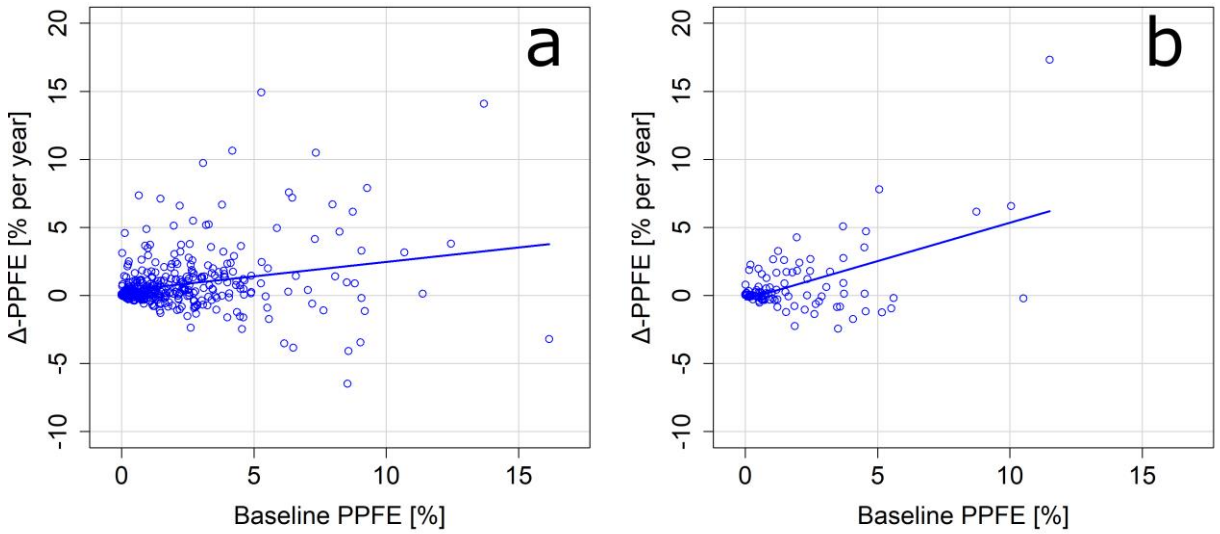



Figure 2. Association between Δ-PPFE and baseline PPFE extent in patients in the IPF cohort (a) and the FHP cohort (b). Association between Δ-PPFE and baseline PPFE extent in a) the IPF cohort (effect=0.21%/year, 95% CI=0.13–0.29%/year, p<0.0001, R2=0.06), and b) the FHP cohort (effect=0.56%/year, 95% CI=0.38–0.75%/year, p<0.0001, R2=0.28). PPFE=pleuroparenchymal fibroelastosis, Δ-PPFE=annualised change in computerised upper-zone PPFE between scans, IPF=idiopathic pulmonary fibrosis, FHP=fibrotic hypersensitivity pneumonitis.

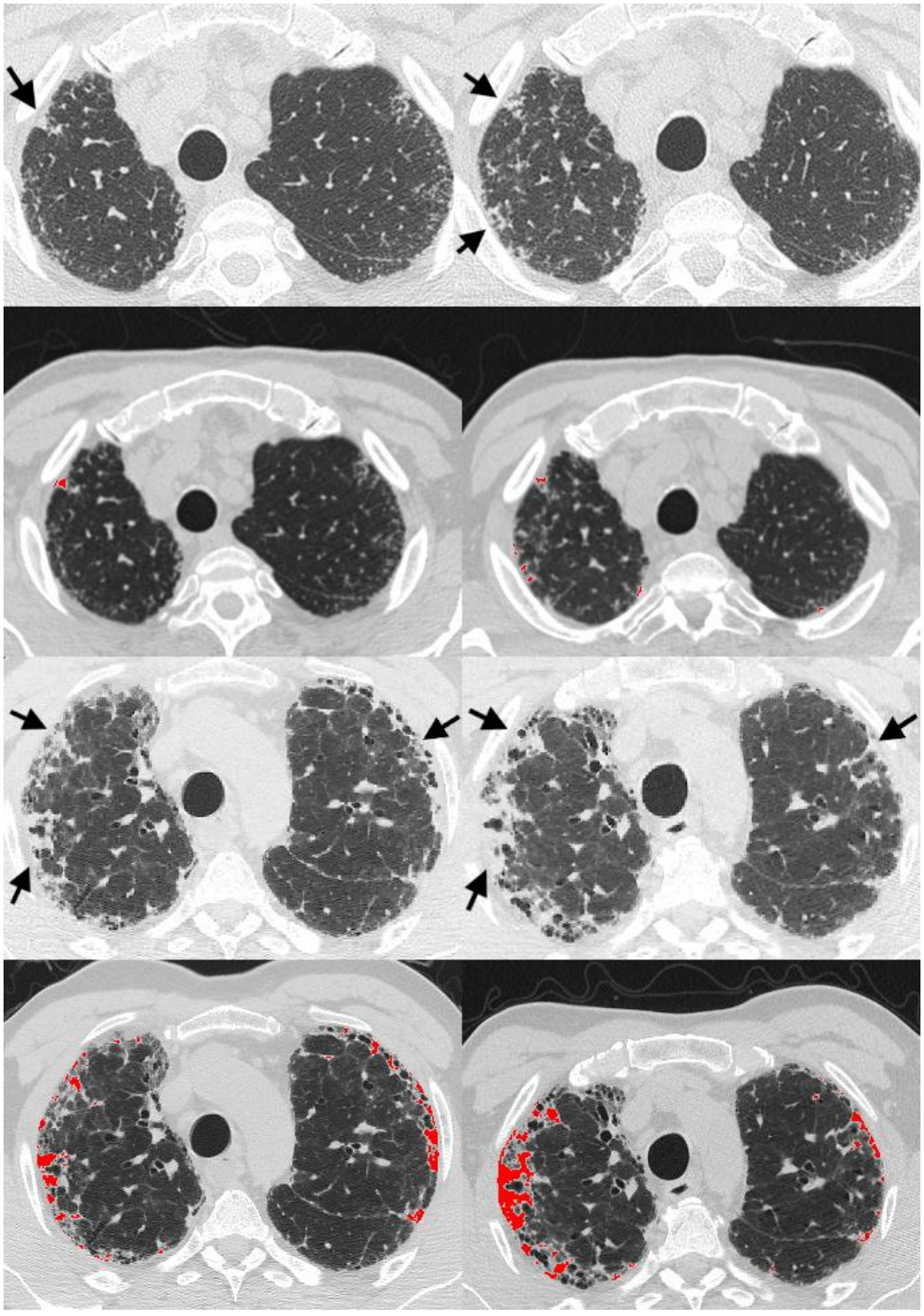


Figure 3: Visual characteristics of progressive PPFE. Baseline (left column) and follow up (right column) CT scans in patients diagnosed with idiopathic pulmonary fibrosis by multidisciplinary team. The top two rows show axial CT images of the upper zones taken 13 months apart in a 73-year-old male with normal baseline FVC (83%) and DLco (74%). Arrows (top row) show areas of PPFE increasing in extent on the second CT, also highlighted by image overlays of PPFE regions (second row). The bottom two rows show axial CT images taken 9 months apart in a 54-year-old male with abnormal baseline FVC (46%) and DLco (35%). Arrows (third row) show more extensive PPFE proliferating dramatically on the second CT, again highlighted on image overlays of PPFE regions (bottom row).

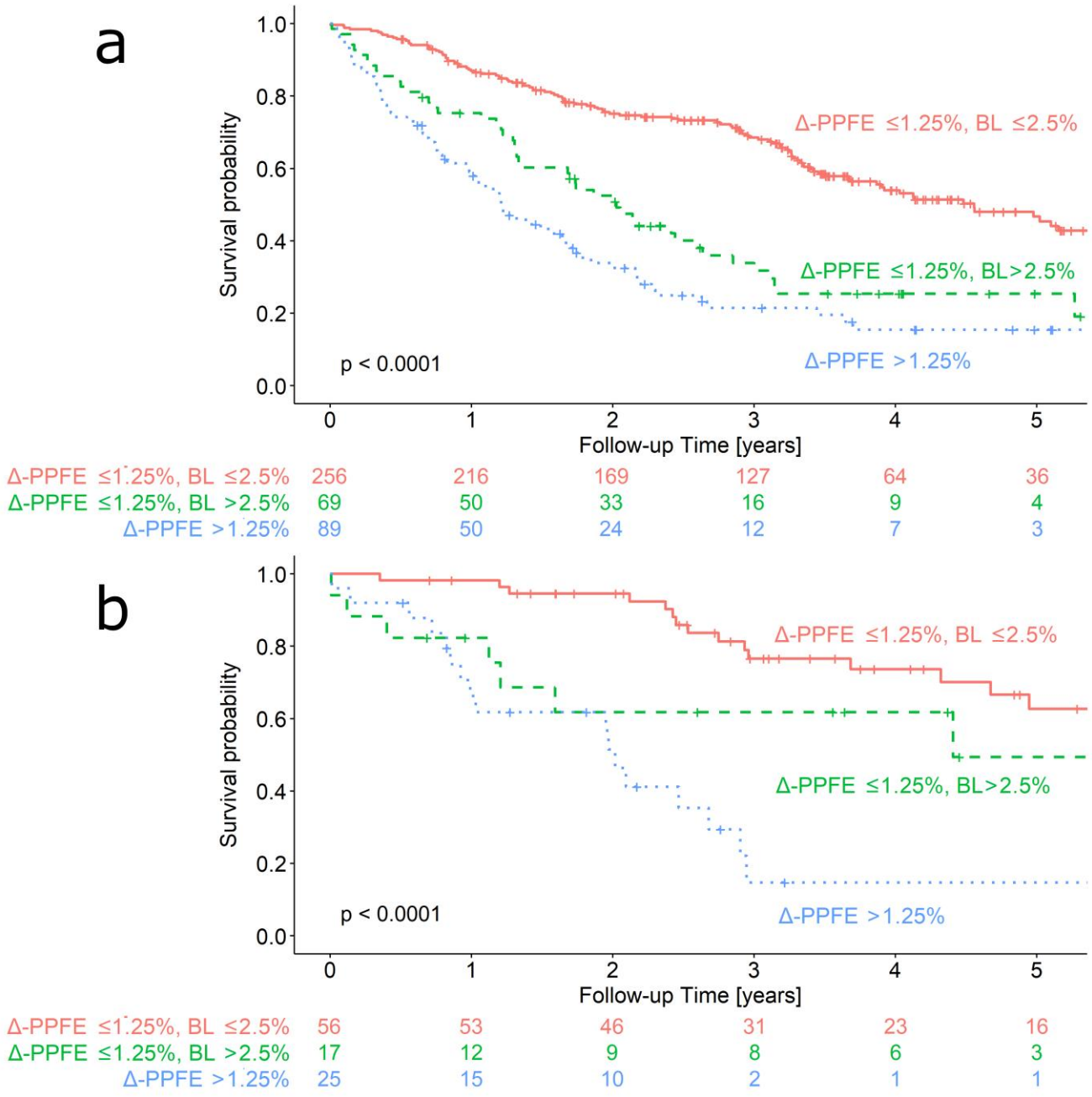



Figure 4: The impact of progressive PPFE and clinically important PPFE at baseline on survival in IPF and FHP patients. Kaplan-Meier survival curves for i) patients without clinically important PPFE at baseline and without progressive PPFE ("Δ-PPFE ≤1.25%, BL ≤2.5%"), ii) patients with clinically important PPFE at baseline and without progressive PPFE ("Δ-PPFE ≤1.25%, BL >2.5%"), and iii) patients with progressive PPFE ("Δ-PPFE >1.25%") in the IPF cohort (a) and the FHP cohort (b). Progressive PPFE was defined as patients with Δ-PPFE greater than 1.25%/year change in pleural surface area. Clinically important PPFE at baseline was defined as PPFE baseline extent greater than 2.5%. Survival curves were truncated at 5 years. Tables below each plot show number of patients at risk at 1-year intervals. p-values are based on a log-rank test of differences in the survival curves of each plot. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans.

# Supplementary Appendix

## Supplementary Methods

### Imputation of missing DLco and FVC values at baseline

Missing values of DLco% predicted and FVC% predicted within 3 months of baseline CT were considered missing at random. These values were imputed in LME models for FVC change and Cox regression models for mortality using the predictive mean matching method of multiple imputation. Multiple imputations were performed with the mice package in R (version 4.1.1 with Rstudio version 1.4.1717, Rstudio, Massachusetts, US). Patient centre, patient age at baseline CT, and patient gender were used as predictor variables in all imputed models, with the first available FVC (l) measurement of each patient also included in all imputed LME models for FVC change. Other predictor variables were determined using the default settings of the built-in quickpred function of the mice package. An indicator whether patient passed away during follow-up and follow-up time (in years) were included as the set of potential predictor variables in imputed Cox regression models for mortality. $R^2$ and C-index values for imputed models are the median values across all imputed models. 100 imputed models were generated for each analysis.[1] Parameter values were pooled according to Rubin's rules using the pool function of the mice package.

**Supplementary Table 1**. **Patient cohorts and medical centres.** The IPF cohort comprised patients presenting to Ege University Hospital, Izmir, Turkey between 2008-2015, St Antonius Hospital, Nieuwegein, Netherlands between 2004-2019, University Hospital Southampton NHS Foundation Trust, Southampton, UK between 2013-2015, University College London Hospitals NHS Foundation Trust, London, UK between 2012-2019, and University Hospitals Leuven, Leuven, Belgium between 2012-2017. The FHP cohort consisted of patients presenting to Ege University Hospital, Izmir, Turkey between 2008-2015, University Hospital Southampton NHS Foundation Trust, Southampton, UK between 2013-2015, University College London Hospitals NHS Foundation Trust, London, UK between 2012-2019, and St Antonius Hospital, Nieuwegein, Netherlands between 2007-2019. IPF = idiopathic pulmonary fibrosis, PPFE = pleuroparenchymal fibroelastosis, FHP = fibrotic hypersensitivity pneumonitis.

| Cohort | Medical centre | No. patients |
|---|---|---|
| IPF cohort (n = 414) | Ege University Hospital, Izmir, Turkey | 94 |
| | St Antonius Hospital, Nieuwegein, Netherlands | 166 |
| | University Hospital Southampton NHS Foundation Trust, Southampton, UK | 24 |
| | University College London Hospitals NHS Foundation Trust, London, UK | 80 |
| | University Hospitals Leuven, Leuven, Belgium | 50 |
| FHP cohort (n = 98) | Ege University Hospital, Izmir, Turkey | 18 |
| | University Hospital Southampton NHS Foundation Trust, Southampton, UK | 23 |
| | University College London Hospitals NHS Foundation Trust, London, UK | 16 |
| | St Antonius Hospital, Nieuwegein, Netherlands | 41 |

**Supplementary Table 2. Demographic data for IPF patients excluded from the study.** Baseline demographic data and pulmonary function indices in patients who were excluded from the IPF cohort. Statistical comparisons were made against the patients of the IPF cohort included in the study (Table 1). IPF = idiopathic pulmonary fibrosis, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide.

| Variable | Excluded IPF (n = 113) | p-value |
|---|---|---|
| Median baseline age in years (range) | 67 (28 – 97) | 0.57 |
| Male / female | 83.2% / 16.8% | 0.13 |
| Survival (alive / dead) | 28.3% / 71.7% | 0.003 |
| Median years of follow-up (range) | 0.8 (0.0 – 7.6) | <0.0001 |
| Never / ever smokers | 12.4% / 87.6% | 0.0002 |
| Antifibrotic (never / ever) | 44.2% / 55.8% | 0.009 |
| FVC% predicted | 60.6 +/- 22.6 | <0.0001 |
| DLco% predicted | 57.9 +/- 25.7 | 0.004 |
| Median years between CT scans (range) | 1.1 (0.0 – 9.4) | 0.60 |

**Supplementary Table 3. Demographic data for FHP patients excluded from the study.** Baseline demographic data and pulmonary function indices in patients who were excluded from the FHP cohort. Statistical comparisons were made against the patients of the FHP cohort included in the study (Table 1). FHP = fibrotic hypersensitivity pneumonitis, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide.

| Variable | Excluded FHP (n = 19) | p-value |
|---|---|---|
| Median baseline age in years (range) | 67 (54 – 80) | 0.08 |
| Male / female | 42.1% / 57.9% | 0.92 |
| Survival (alive / dead) | 63.2% / 36.8% | 0.63 |
| Median years of follow-up (range) | 0.5 (0.0 – 6.2) | 0.003 |
| Median years between CT scans (range) | 1.0 (0.5 – 2.7) | 0.60 |
| Never / ever smokers | 78.9% / 21.1% | 0.04 |
| FVC% predicted | 68.6 +/- 15.7 | 0.33 |
| DLco% predicted | 47.0 +/- 18.5 | 0.51 |

**Supplementary Table 4. Univariable linear mixed-effects regression analyses between Δ-ILD and baseline PPFE, Δ-PPFE, and baseline ILD extent, and between Δ-PPFE and baseline PPFE, baseline ILD extent, baseline DLco and baseline FVC in IPF patients and FHP patients in the study.** Univariable linear mixed-effects regression analyses, adjusted for patient centre as a random intercept, demonstrating relationships between Δ-ILD and i) baseline PPFE, ii) Δ-PPFE, and iii) baseline ILD extent, and between Δ-PPFE and i) baseline PPFE extent, ii) baseline ILD extent, iii) baseline DLco% predicted, and iv) baseline FVC% predicted in the IPF cohorts and the FHP cohort. The marginal $R^2$ values shown describe only the proportion of variance explained by the fixed effect of each model. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, FVC = forced vital capacity, ILD = interstitial lung disease, Δ-ILD = annualised change in ILD extent between scans, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans.

| Cohort | Dependent variable | Independent variable | Effect [%/year] | 95% Confidence Interval [%/year] | p-value | Model $R^2$ value |
|---|---|---|---|---|---|---|
| IPF | Δ-ILD | Baseline PPFE | 0.36 | 0.01, 0.70 | 0.043 | 0.01 |
| | | Δ-PPFE | 1.05 | 0.66, 1.44 | <0.0001 | 0.06 |
| | | Baseline ILD | -0.15 | -0.22, -0.09 | <0.0001 | 0.05 |
| | Δ-PPFE | Baseline PPFE | 0.21 | 0.13, 0.29 | <0.0001 | 0.06 |
| | | Baseline ILD | 0.02 | -0.001, 0.03 | 0.064 | 0.01 |
| | | Baseline DLco | -0.01 | -0.03, 0.0001 | 0.051 | 0.01 |
| | | Baseline FVC | -0.02 | -0.03, -0.01 | 0.0003 | 0.04 |
| FHP | Δ-ILD | Baseline PPFE | 0.32 | -0.17, 0.80 | 0.20 | 0.02 |
| | | Δ-PPFE | 0.37 | -0.08, 0.82 | 0.11 | 0.03 |
| | | Baseline ILD | -0.02 | -0.10, 0.06 | 0.59 | 0.003 |
| | Δ-PPFE | Baseline PPFE | 0.56 | 0.38, 0.75 | <0.0001 | 0.28 |
| | | Baseline ILD | 0.03 | -0.002, 0.07 | 0.063 | 0.04 |
| | | Baseline DLco | -0.03 | -0.07, 0.003 | 0.076 | 0.05 |
| | | Baseline FVC | -0.03 | -0.06, -0.005 | 0.023 | 0.07 |

**Supplementary Table 5. Multivariable linear mixed-effects regression analyses between Δ-PPFE and baseline DLco and baseline FVC, adjusted for patient centre as a random intercept, in IPF patients and FHP patients in the study.** Multivariable linear mixed-effects regression analyses, adjusted for patient centre as a random intercept, demonstrating relationships between Δ-PPFE and a) baseline DLco% predicted, b) baseline FVC% predicted in the IPF cohort and the FHP cohort. The marginal $R^2$ values shown describe only the proportion of variance explained by the fixed effect in each model. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, FVC = forced vital capacity, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans. *: model Breusch-Pagan p value < 0.05.

| Cohort | Dependent variable | Independent variable | Effect [%/year] | 95% Confidence Interval [%/year] | p-value | Model $R^2$ value |
|---|---|---|---|---|---|---|
| IPF | Δ-PPFE | Baseline DLco | -0.02* | -0.03, -0.004 | 0.01 | 0.04 |
| | | Baseline FVC | -0.02* | -0.03, -0.01 | 0.0002 | 0.07 |
| FHP | Δ-PPFE | Baseline DLco | -0.09 | -0.16, -0.02 | 0.01 | 0.18 |
| | | Baseline FVC | -0.04 | -0.08, -0.007 | 0.021 | 0.15 |

**Supplementary Table 6. Demographic data for IPF patients included and excluded from FVC modelling.** Baseline demographic data, baseline pulmonary function indices, mean visual ILD extent, and computerised PPFE scores in IPF patients who were included in FVC modelling and IPF patients who were excluded from FVC modelling. Clinically important PPFE at baseline was defined as baseline PPFE extent >2.5%. Progressive PPFE was defined as Δ-PPFE >1.25%/year. IPF = idiopathic pulmonary fibrosis, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, Δ-PPFE-adj = annualised change in computerised upper-zone PPFE between scans above scan noise.

| **Variable** | **IPF patients included in FVC modelling (n = 333)** | **IPF patients excluded from FVC modelling (n = 81)** | **p-value** |
|---|---|---|---|
| Median baseline age in years (range) | 69 (32 – 88) | 70 (50 – 95) | 0.25 |
| Male / female | 73.9% / 26.1% | 84.0% / 16.0% | 0.079 |
| Survival (alive / dead) | 46.2% / 53.8% | 37.0% / 63.0% | 0.17 |
| Median years of follow-up (range) | 2.4 (0.1 - 8.2) | 1.4 (0.0 - 9.0) | 0.0003 |
| Never / ever smokers | 32.1% / 67.9% | 24.7% / 75.3% | 0.24 |
| Antifibrotic (never / ever) | 26.7% / 73.3% | 46.9% / 53.1% | 0.0007 |
| FVC% predicted | 81.5 +/- 20.0 | 79.0 +/- 16.5 | 0.43 |
| DLco% predicted | 48.8 +/- 16.1 | 49.3 +/- 14.0 | 0.86 |
| Median years between CT scans (range) | 1.1 (0.5 - 3.0) | 1.2 (0.5 - 3.0) | 0.18 |
| Baseline emphysema (absent/present) | 33.6% / 66.4% | 27.2% / 72.8% | 0.32 |
| Baseline ILD extent (%) | 38.7 +/- 12.5 | 40.5 +/- 11.5 | 0.21 |
| Δ-ILD (%/year) | 7.8 +/- 8.8 | 7.0 +/- 8.3 | 0.42 |
| Baseline PPFE extent (%) | 2.0 +/- 2.3 | 2.1 +/- 2.5 | 0.83 |
| Δ-PPFE (%/year) | 0.6 +/- 1.8 | 1.3 +/- 2.9 | 0.044 |
| Clinically important baseline PPFE prevalence | 30.0% | 27.2% | 0.71 |
| Progressive PPFE prevalence | 19.8% | 28.4% | 0.13 |
| Δ-PPFE-adj in progressive PPFE patients (%/year) | 2.0 +/- 2.3 | 3.0 +/- 3.8 | 0.22 |

**Supplementary Table 7. Demographic data for FHP patients included and excluded from FVC modelling.** Baseline demographic data, baseline pulmonary function indices, mean visual ILD extent, and computerised PPFE scores in FHP patients who were included in FVC modelling and patients who were excluded from FVC modelling. Clinically important PPFE at baseline was defined as baseline PPFE extent >2.5%. Progressive PPFE was defined as Δ-PPFE >1.25%/year. FHP = fibrotic hypersensitivity pneumonitis, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, Δ-PPFE-adj = annualised change in computerised upper-zone PPFE between scans above scan noise.

| Variable | FHP patients included in FVC modelling (n = 78) | FHP patients excluded from FVC modelling (n = 20) | p-value |
|---|---|---|---|
| Median baseline age in years (range) | 64 (28 – 85) | 63 (40 – 85) | 0.97 |
| Male / female | 38.5% / 61.5% | 35.0% / 65.0% | 0.98 |
| Survival (alive / dead) | 50.0% / 50.0% | 70.0% / 30.0% | 0.18 |
| Median years of follow-up (range) | 2.7 (0.0 - 10.4) | 2.9 (0.0 - 12.0) | 0.66 |
| Never / ever smokers | 52.6% / 47.4% | 40.0% / 60.0% | 0.45 |
| FVC% predicted | 65.9 +/- 18.9 | 52.9 +/- 21.0 | 0.090 |
| DLco% predicted | 50.3 +/- 16.6 | 52.9 +/- 19.3 | 0.74 |
| Median years between CT scans (range) | 1.1 (0.5 - 2.9) | 1.3 (0.5 - 2.8) | 0.14 |
| Baseline emphysema (absent/present) | 73.1% / 26.9% | 55.0% / 45.0% | 0.20 |
| Baseline ILD extent (%) | 33.2 +/- 13.7 | 33.8 +/- 15.3 | 0.87 |
| Δ-ILD (%/year) | 3.6 +/- 5.6 | 5.6 +/- 5.2 | 0.13 |
| Baseline PPFE extent (%) | 1.8 +/- 1.9 | 2.5 +/- 3.3 | 0.34 |
| Δ-PPFE (%/year) | 0.6 +/- 1.7 | 1.6 +/- 4.2 | 0.29 |
| Clinically important baseline PPFE prevalence | 23.1% | 40.0% | 0.21 |
| Progressive PPFE prevalence | 25.6% | 25.0% | 1.00 |
| Δ-PPFE-adj in progressive PPFE patients (%/year) | 1.6 +/- 1.7 | 5.5 +/- 6.1 | 0.23 |

**Supplementary Table 8**. **Univariable linear mixed-effects regression analyses between temporal FVC (l) measurements and Δ-PPFE.** Univariable linear mixed-effects regression analyses, adjusted for patient centre as a random intercept and for subject as a random slope and a random intercept, demonstrating relationships between FVC (l) change within a 6-month window of the baseline and follow-up CT scans of each patient and Δ-PPFE in the IPF cohort and the FHP cohort. $R^2$ values shown are the marginal $R^2$ describing only the proportion of variance explained by the fixed effect of Δ-PPFE. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, FVC = forced vital capacity, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE extent between scans.

| Cohort | Dependent variable | Independent variable | Effect [l/year] | 95% Confidence Interval [l/year] | p-value | Model $R^2$ value |
|---|---|---|---|---|---|---|
| IPF (n = 333) | FVC (l) | Δ-PPFE | -0.13 | -0.18, -0.08 | <0.0001 | 0.07 |
| FHP (n = 78) | FVC (l) | Δ-PPFE | -0.08 | -0.19, 0.02 | 0.10 | 0.03 |

**Supplementary Table 9 Multivariable linear mixed-effects regression analyses between temporal FVC (l) measurements and Δ-PPFE.** Multivariable linear mixed-effects regression analyses, adjusted for patient centre as a random intercept and for subject as a random slope and a random intercept, demonstrating relationships between FVC (l) change within a 6-month window of the baseline and follow-up CT scans of each patient and Δ-PPFE in the IPF cohort and in the FHP cohort. All models were adjusted for patient age at baseline, patient gender, smoking history (never/ever), baseline emphysema (absent/present), baseline FVC% predicted and Δ-PPFE. Models in the IPF cohort were also adjusted for antifibrotic treatment (never/ever). $R^2$ values shown are the marginal $R^2$ describing only the proportion of variance explained by fixed effects. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, FVC = forced vital capacity, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans.

| Cohort | Dependent variable | Independent variable | Effect [l/year] | 95% Confidence Interval [l/year] | p-value | Model $R^2$ value |
|---|---|---|---|---|---|---|
| IPF (n = 333) | FVC (l) | Δ-PPFE | -0.09 | -0.13, -0.05 | <0.0001 | 0.34 |
| FHP (n = 78) | FVC (l) | Δ-PPFE | -0.04 | -0.08, 0.004 | 0.08 | 0.61 |

**Supplementary Table 10**. **Non-imputed multivariable linear mixed-effects regression analyses between temporal FVC (l) measurements and Δ-PPFE.** Multivariable linear mixed-effects regression analyses, adjusted for patient centre as a random intercept and for subject as a random slope and a random intercept, demonstrating relationships between FVC (l) change within a 6-month window of the baseline and follow-up CT scans of each patient and Δ-PPFE in the IPF cohort and in the FHP cohort. All models were adjusted for patient age at baseline, patient gender, smoking history (never/ever), baseline emphysema presence (absent/present), baseline FVC% predicted and Δ-PPFE. Models in the IPF cohort were also adjusted for antifibrotic treatment (never/ever). In non-imputed models, patients with missing FVC% predicted within 3 months of baseline CT were excluded. $R^2$ values shown are the marginal $R^2$ describing only the proportion of variance explained by fixed effects. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, FVC = forced vital capacity, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans.

| Cohort | Dependent variable | Independent variable | Effect [l/year] | 95% Confidence Interval [l/year] | p-value | Model $R^2$ value |
|---|---|---|---|---|---|---|
| IPF (n = 290) | FVC (l) | Δ-PPFE | -0.09 | -0.14, -0.05 | 0.00001 | 0.33 |
| FHP (n = 67) | FVC (l) | Δ-PPFE | -0.04 | -0.09, 0.005 | 0.070 | 0.60 |

**Supplementary Table 11**. **Univariable Cox regression models showing mortality in the IPF cohort and in the FHP cohort.** IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, AF = antifibrotic, ILD = interstitial lung disease, Δ-ILD = annualised change in ILD extent between scans, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, Δ-PPFE-adj = Δ-PPFE above scan noise.

| Cohort | Variable | Hazard ratio | 95% Confidence Interval | p-value | Model C-index |
|---|---|---|---|---|---|
| IPF | Age at baseline (years) | 1.01 | 0.99, 1.03 | 0.26 | 0.60 |
| | Male gender | 1.38 | 0.98, 1.94 | 0.068 | 0.60 |
| | Ever smoker | 1.30 | 0.96, 1.76 | 0.096 | 0.60 |
| | AF treatment (never/ever) | 0.81 | 0.60, 1.08 | 0.15 | 0.60 |
| | Baseline DLco% predicted | 0.95 | 0.94, 0.96 | < 0.0001 | 0.70 |
| | Baseline FVC% predicted | 0.98 | 0.97, 0.99 | < 0.0001 | 0.66 |
| | Baseline ILD extent (%) | 1.04 | 1.03, 1.05 | < 0.0001 | 0.68 |
| | Δ-ILD (%/year) | 1.01 | 1.00, 1.02 | 0.058 | 0.61 |
| | Baseline emphysema presence | 1.01 | 0.76, 1.35 | 0.93 | 0.59 |
| | Baseline PPFE extent (%) | 1.17 | 1.12, 1.22 | < 0.0001 | 0.67 |
| | Baseline clinically important PPFE presence (PPFE >2.5%) | 2.52 | 1.92, 3.31 | < 0.0001 | 0.67 |
| | Δ-PPFE (%/year) | 1.27 | 1.20, 1.35 | < 0.0001 | 0.66 |
| | Δ-PPFE-adj (%/year) | 1.33 | 1.25, 1.42 | < 0.0001 | 0.66 |
| FHP | Age at baseline (years) | 1.05 | 1.02, 1.08 | 0.004 | 0.69 |
| | Male gender | 1.33 | 0.73, 2.42 | 0.36 | 0.64 |
| | Ever smoker | 1.28 | 0.70, 2.34 | 0.43 | 0.64 |
| | Baseline DLco% predicted | 0.96 | 0.93, 0.99 | 0.006 | 0.74 |
| | Baseline FVC% predicted | 0.98 | 0.96, 1.00 | 0.11 | 0.67 |
| | Baseline ILD extent (%) | 1.06 | 1.04, 1.09 | < 0.0001 | 0.77 |
| | Δ-ILD (%/year) | 1.04 | 0.98, 1.09 | 0.21 | 0.68 |
| | Baseline emphysema presence | 0.85 | 0.43, 1.67 | 0.63 | 0.64 |
| | Baseline PPFE extent (%) | 1.20 | 1.06, 1.36 | 0.003 | 0.73 |
| | Baseline clinically important PPFE presence (PPFE >2.5%) | 1.43 | 0.73, 2.81 | 0.30 | 0.67 |
| | Δ-PPFE (%/year) | 1.30 | 1.17, 1.44 | < 0.0001 | 0.73 |
| | Δ-PPFE-adj (%/year) | 1.30 | 1.15, 1.46 | < 0.0001 | 0.72 |

**Supplementary Table 12: Association of Δ-PPFE with mortality in multivariable Cox regression models in the IPF cohort and in the FHP cohort**. Models in all cohorts were adjusted for patient age, gender, smoking history (never/ever), baseline emphysema presence (absent/present), baseline DLco% predicted, baseline presence of clinically important PPFE, and Δ-PPFE. Models in the IPF cohort were additionally adjusted for antifibrotic treatment (never/ever). IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, AF = antifibrotic, Δ-PPFE = annualised change in computerised upper-lung PPFE between scans.

| Cohort | Variable | Hazard ratio | 95% Confidence Interval | p-value | Model C-index |
|---|---|---|---|---|---|
| IPF (n = 414) | Baseline age (years) | 1.00 | 0.99, 1.02 | 0.72 | 0.75 |
| | Male gender | 1.53 | 1.05, 2.24 | 0.028 | |
| | Ever smoker | 1.13 | 0.80, 1.57 | 0.49 | |
| | Baseline emphysema presence | 0.98 | 0.70, 1.36 | 0.88 | |
| | AF treatment (never/ever) | 0.72 | 0.53, 0.96 | 0.027 | |
| | Δ-ILD (%/year) | 1.01 | 0.99, 1.02 | 0.22 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.80 | 1.33, 2.43 | 0.00015 | |
| | Baseline DLco% predicted | 0.96 | 0.94, 0.97 | < 0.0001 | |
| | Δ-PPFE (%/year) | 1.20 | 1.13, 1.28 | < 0.0001 | |
| FHP (n = 98) | Baseline age (years) | 1.06 | 1.02, 1.10 | 0.003 | 0.81 |
| | Male gender | 1.26 | 0.53, 2.98 | 0.59 | |
| | Ever smoker | 0.97 | 0.43, 2.19 | 0.95 | |
| | Baseline emphysema presence | 0.65 | 0.27, 1.57 | 0.33 | |
| | Δ-ILD (%/year) | 1.05 | 0.99, 1.12 | 0.12 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.32 | 0.56, 3.13 | 0.51 | |
| | Baseline DLco% predicted | 0.97 | 0.94, 1.00 | 0.028 | |
| | Δ-PPFE (%/year) | 1.21 | 1.07, 1.38 | 0.004 | |

**Supplementary Table 13: Association of Δ-PPFE with mortality in non-imputed multivariable Cox regression models in the IPF cohort and in the FHP cohort**. Models in all cohorts were adjusted for patient age, gender, smoking history (never/ever), baseline emphysema presence (absent/present), baseline DLco% predicted, baseline presence of clinically important PPFE, and Δ-PPFE. Models in the IPF cohort were additionally adjusted for antifibrotic treatment (never/ever). In non-imputed models, patients with missing DLco% predicted within 3 months of baseline CT were excluded. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, AF = antifibrotic, Δ-PPFE = annualised change in computerised upper-lung PPFE between scans.

| Cohort | Variable | Hazard ratio | 95% Confidence Interval | p-value | Model C-index |
|---|---|---|---|---|---|
| IPF (n = 319) | Baseline age (years) | 1.00 | 0.98, 1.02 | 0.93 | 0.75 |
| | Male gender | 1.59 | 1.04, 2.44 | 0.034 | |
| | Ever smoker | 1.21 | 0.84, 1.75 | 0.31 | |
| | Baseline emphysema presence | 1.04 | 0.72, 1.51 | 0.82 | |
| | AF treatment (never/ever) | 0.65 | 0.47, 0.90 | 0.008 | |
| | Δ-ILD (%/year) | 1.00 | 0.99, 1.02 | 0.63 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.73 | 1.24, 2.41 | 0.001 | |
| | Baseline DLco% predicted | 0.95 | 0.94, 0.97 | < 0.0001 | |
| | Δ-PPFE (%/year) | 1.26 | 1.18, 1.35 | < 0.0001 | |
| FHP (n = 66) | Baseline age (years) | 1.06 | 1.01, 1.12 | 0.020 | 0.83 |
| | Male gender | 0.82 | 0.31, 2.15 | 0.69 | |
| | Ever smoker | 2.13 | 0.71, 6.44 | 0.18 | |
| | Baseline emphysema presence | 1.08 | 0.42, 2.78 | 0.88 | |
| | Δ-ILD (%/year) | 1.10 | 1.01, 1.19 | 0.035 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 2.24 | 0.83, 6.09 | 0.11 | |
| | Baseline DLco% predicted | 0.96 | 0.93, 0.99 | 0.010 | |
| | Δ-PPFE (%/year) | 1.33 | 1.11, 1.59 | 0.002 | |

**Supplementary Table 14: Multivariable Cox regression models in the IPF cohort and in the FHP cohort without adjustment for Δ-PPFE**. Models in all cohorts were adjusted for patient age, gender, smoking history (never/ever), baseline emphysema presence (absent/present), baseline DLco% predicted, and baseline presence of clinically important PPFE. Models in the IPF cohort were additionally adjusted for antifibrotic treatment (never/ever). IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, AF = antifibrotic.

| Cohort | Variable | Hazard ratio | 95% Confidence Interval | p-value | Model C-index |
|---|---|---|---|---|---|
| IPF (n = 414) | Baseline age (years) | 1.00 | 0.99, 1.02 | 0.78 | 0.74 |
| | Male gender | 1.34 | 0.92, 1.95 | 0.12 | |
| | Ever smoker | 1.26 | 0.90, 1.77 | 0.18 | |
| | Baseline emphysema presence | 0.83 | 0.59, 1.16 | 0.27 | |
| | AF treatment (never/ever) | 0.72 | 0.53, 0.97 | 0.031 | |
| | Δ-ILD (%/year) | 1.02 | 1.00, 1.03 | 0.031 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.87 | 1.39, 2.52 | 0.00005 | |
| | Baseline DLco% predicted | 0.95 | 0.94, 0.97 | < 0.0001 | |
| FHP (n = 98) | Baseline age (years) | 1.06 | 1.02, 1.11 | 0.002 | 0.77 |
| | Male gender | 1.61 | 0.70, 3.69 | 0.26 | |
| | Ever smoker | 0.90 | 0.40, 2.03 | 0.80 | |
| | Baseline emphysema presence | 0.53 | 0.23, 1.24 | 0.14 | |
| | Δ-ILD (%/year) | 1.06 | 0.99, 1.13 | 0.09 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.84 | 0.86, 3.91 | 0.11 | |
| | Baseline DLco% predicted | 0.96 | 0.93, 0.99 | 0.016 | |

**Supplementary Table 15**. **Demographic data comparing IPF patients without clinically important PPFE at baseline and without progressive PPFE, patients with clinically important PPFE at baseline and without progressive PPFE, and patients with progressive PPFE.** Baseline demographic data, pulmonary function indices and disease severity metrics in IPF patients a) without clinically important PPFE at baseline and without progressive PPFE, b) with clinically important PPFE at baseline and without progressive PPFE, and c) with progressive PPFE. Clinically important PPFE at baseline was defined as baseline PPFE extent >2.5%. Progressive PPFE (i.e., longitudinal increase in PPFE above scan noise) was defined as Δ-PPFE >1.25%/year. Statistical tests were made to test for independence (categorical variables) and differences in means/medians (continuous variables) across the three groups. IPF = idiopathic pulmonary fibrosis, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, ILD = interstitial lung disease, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, Δ-PPFE-adj = Δ-PPFE above scan noise.

| Variable | No clinically important PPFE at baseline, no progressive PPFE | Clinically important PPFE at baseline, no progressive PPFE | Progressive PPFE | p-value |
|---|---|---|---|---|
| IPF cohort: | (n = 256) | (n = 69) | (n = 89) | |
| Median baseline age in years (range) | 68.5 (32.0 - 95.0) | 69.0 (42.0 - 83.0) | 70.0 (37.0 - 84.0) | 0.95 |
| Male / female | 73.4% / 26.6% | 84.1% / 15.9% | 76.4% / 23.6% | 0.19 |
| Survival (alive / dead) | 55.1% / 44.9% | 30.4% / 69.6% | 24.7% / 75.3% | <0.0001 |
| Median years of follow-up (range) | 3.0 (0.0 - 9.0) | 1.7 (0.0 - 8.2) | 1.2 (0.0 - 5.9) | <0.0001 |
| Median years between CT scans (range) | 1.2 (0.5 - 3.0) | 1.1 (0.5 - 2.8) | 1.0 (0.5 - 2.9) | 0.002 |
| Never / ever smokers | 32.8% / 67.2% | 29.0% / 71.0% | 25.8% / 74.2% | 0.44 |
| Antifibrotic (never / ever) | 28.9% / 71.1% | 31.9% / 68.1% | 34.8% / 65.2% | 0.57 |
| Baseline FVC% predicted | 86.1 +/- 18.3 | 74.1 +/- 18.3 | 72.2 +/- 20.2 | <0.0001 |
| Baseline DLco% predicted | 51.8 +/- 14.1 | 41.4 +/- 14.0 | 44.1 +/- 14.1 | <0.0001 |
| Baseline emphysema (absent/present) | 27.3% / 72.7% | 33.3% / 66.7% | 46.1% / 53.9% | 0.005 |
| Baseline ILD extent (%) | 36.0 +/- 11.5 | 45.3 +/- 12.8 | 42.8 +/- 11.3 | <0.0001 |
| Δ-ILD (%/year) | 6.2 +/- 6.5 | 8.2 +/- 7.8 | 11.5 +/- 12.9 | <0.0001 |
| Baseline PPFE extent (%) | 0.8 +/- 0.7 | 4.8 +/- 2.5 | 3.5 +/- 2.8 | <0.0001 |
| Δ-PPFE (%/year) | 0.2 +/- 0.4 | -0.5 +/- 1.5 | 3.5 +/- 2.7 | <0.0001 |
| Clinically important baseline PPFE prevalence | 0.0% | 100.0% | 59.6% | <0.0001 |
| Progressive PPFE prevalence | 0.0% | 0.0% | 100.0% | <0.0001 |
| Δ-PPFE-adj (progressive PPFE patients, %/year) | – | – | 2.3 +/- 2.7 | – |

**Supplementary Table 16**. **Demographic data comparing FHP patients without clinically important PPFE at baseline and without progressive PPFE, patients with clinically important PPFE at baseline and without progressive PPFE, and patients with progressive PPFE.** Baseline demographic data, pulmonary function indices and disease severity metrics in FHP patients a) without clinically important PPFE at baseline and without progressive PPFE, b) with clinically important PPFE at baseline and without progressive PPFE, and c) with progressive PPFE. Clinically important PPFE at baseline was defined as baseline PPFE extent >2.5%. Progressive PPFE (i.e., longitudinal increase in PPFE above scan noise) was defined as Δ-PPFE >1.25%/year. Statistical tests were made to test for independence (categorical variables) and differences in means/medians (continuous variables) across the three groups. FHP = fibrotic hypersensitivity pneumonitis, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, ILD = interstitial lung disease, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, Δ-PPFE-adj = Δ-PPFE above scan noise.

| Variable | No clinically important PPFE at baseline, no progressive PPFE | Clinically important PPFE at baseline, no progressive PPFE | Progressive PPFE | p-value |
|---|---|---|---|---|
| FHP cohort: | (n = 56) | (n = 17) | (n = 25) | |
| Median baseline age in years (range) | 64.5 (28.0 - 85.0) | 67.0 (40.0 - 81.0) | 61.0 (41.0 - 82.0) | 0.72 |
| Male / female | 37.5% / 62.5% | 35.3% / 64.7% | 40.0% / 60.0% | 0.95 |
| Survival (alive / dead) | 64.3% / 35.7% | 58.8% / 41.2% | 28.0% / 72.0% | 0.009 |
| Median years of follow-up (range) | 3.3 (0.4 - 10.4) | 2.6 (0.0 - 12.0) | 1.8 (0.0 - 6.0) | 0.0001 |
| Never / ever smokers | 48.2% / 51.8% | 41.2% / 58.8% | 60.0% / 40.0% | 0.45 |
| Baseline FVC% predicted | 68.3 +/- 21.3 | 62.8 +/- 16.0 | 56.2 +/- 15.3 | 0.066 |
| Baseline DLco% predicted | 53.1 +/- 16.4 | 50.7 +/- 19.4 | 44.7 +/- 15.5 | 0.23 |
| Baseline emphysema (absent/present) | 66.1% / 33.9% | 64.7% / 35.3% | 80.0% / 20.0% | 0.41 |
| Baseline ILD extent (%) | 28.8 +/- 13.3 | 39.9 +/- 12.7 | 39.0 +/- 12.8 | 0.0007 |
| Δ-ILD (%/year) | 2.8 +/- 5.7 | 4.5 +/- 4.7 | 6.3 +/- 5.0 | 0.027 |
| Median years between CT scans (range) | 1.2 (0.5 - 2.8) | 1.2 (0.7 - 2.9) | 1.0 (0.5 - 2.8) | 0.28 |
| Baseline PPFE extent (%) | 0.7 +/- 0.6 | 4.2 +/- 1.9 | 3.1 +/- 3.0 | <0.0001 |
| Δ-PPFE (%/year) | 0.0 +/- 0.5 | -0.6 +/- 0.9 | 3.6 +/- 3.3 | <0.0001 |
| Clinically important baseline PPFE prevalence | 0.0% | 100.0% | 36.0% | <0.0001 |
| Progressive PPFE prevalence | 0.0% | 0.0% | 100.0% | <0.0001 |
| Δ-PPFE-adj (progressive PPFE patients, %/year) | – | – | 2.4 +/- 3.3 | – |

**Supplementary Table 17: Association of Δ-PPFE-adj with mortality in non-imputed multivariable Cox regression models in the IPF cohort and in the FHP cohort**. Models in all cohorts were adjusted for patient age, gender, smoking history (never/ever), baseline emphysema presence (absent/present), baseline DLco% predicted, and Δ-PPFE-adj. Models in the IPF cohort were additionally adjusted for antifibrotic treatment (never/ever). In non-imputed models, patients with missing DLco% predicted within 3 months of baseline CT were excluded. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, AF = antifibrotic, Δ-PPFE-adj = annualised change in computerised upper-zone PPFE above scan noise.

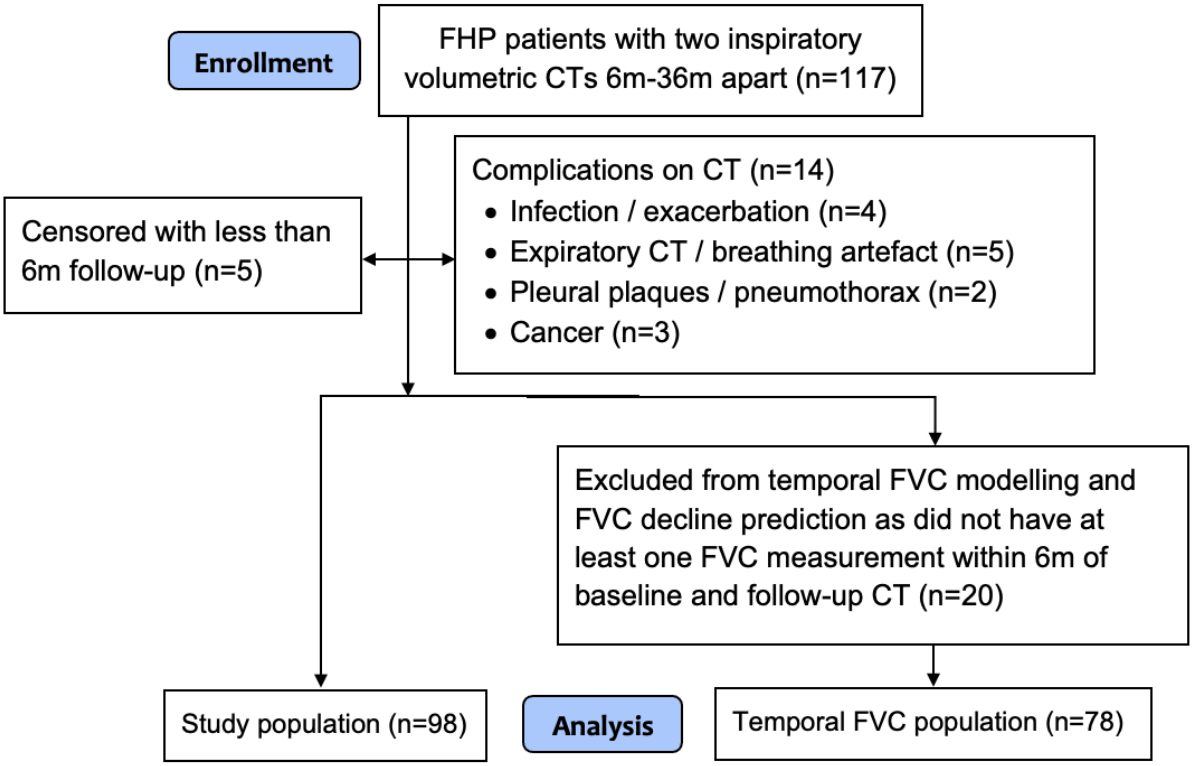
| Cohort | Variable | Hazard ratio | 95% Confidence Interval | p-value | Model C-index |
|---|---|---|---|---|---|
| IPF (n = 319) | Baseline age (years) | 1.00 | 0.98, 1.02 | 0.86 | 0.75 |
| | Male gender | 1.50 | 0.97, 2.30 | 0.067 | |
| | Ever smoker | 1.32 | 0.91, 1.93 | 0.15 | |
| | Baseline emphysema presence | 0.99 | 0.68, 1.43 | 0.95 | |
| | AF treatment (never/ever) | 0.65 | 0.47, 0.90 | 0.009 | |
| | Δ-ILD (%/year) | 1.00 | 0.99, 1.02 | 0.54 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.67 | 1.19, 2.33 | 0.003 | |
| | Baseline DLco% predicted | 0.96 | 0.94, 0.97 | < 0.00001 | |
| | Δ-PPFE-adj (%/year) | 1.32 | 1.22, 1.43 | < 0.00001 | |
| FHP (n = 66) | Baseline age (years) | 1.05 | 1.00, 1.11 | 0.037 | 0.81 |
| | Male gender | 0.88 | 0.34, 2.28 | 0.79 | |
| | Ever smoker | 2.16 | 0.72, 6.51 | 0.17 | |
| | Baseline emphysema presence | 0.91 | 0.36, 2.33 | 0.84 | |
| | Δ-ILD (%/year) | 1.10 | 1.01, 1.19 | 0.028 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 2.12 | 0.79, 5.67 | 0.13 | |
| | Baseline DLco% predicted | 0.96 | 0.93, 0.99 | 0.008 | |
| | Δ-PPFE-adj (%/year) | 1.30 | 1.07, 1.57 | 0.008 | |

**Supplementary Table 18: Association of Δ-PPFE-adj with mortality in multivariable Cox regression models in the IPF cohort and in the FHP cohort, without adjustment for baseline presence of clinically important PPFE**. Models in all cohorts were adjusted for patient age, gender, smoking history (never/ever), baseline emphysema presence (absent/present), baseline DLco% predicted, and Δ-PPFE. Models in the IPF cohort were additionally adjusted for antifibrotic treatment (never/ever). IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, AF = antifibrotic, Δ-PPFE-adj=annualised change in computerised upper-zone PPFE between scans above scan noise.

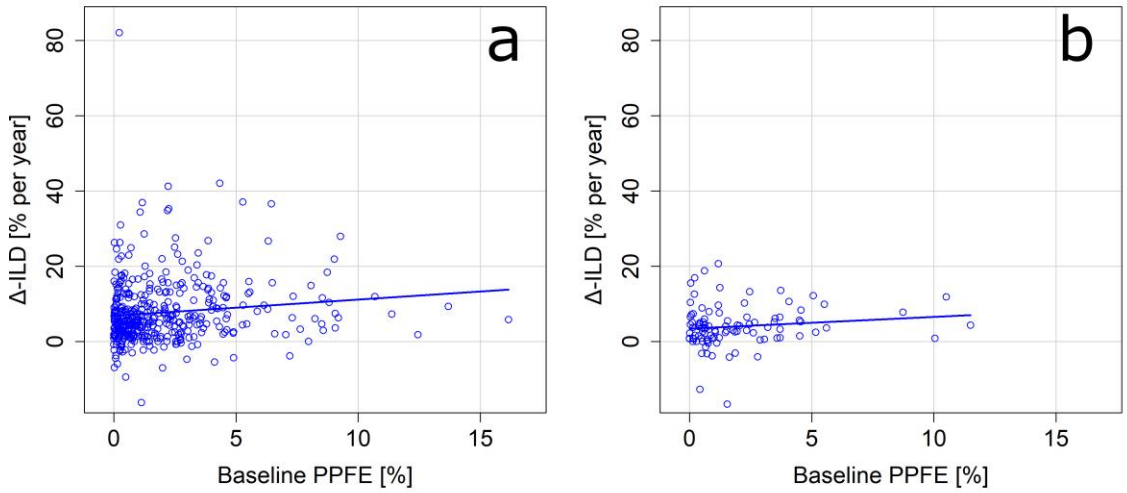
| Cohort | Variable | Hazard ratio | 95% Confidence Interval | p-value | Model C-index |
|---|---|---|---|---|---|
| IPF (n = 414) | Baseline age (years) | 1.00 | 0.99, 1.02 | 0.58 | 0.74 |
| | Male gender | 1.48 | 1.00, 2.17 | 0.047 | |
| | Ever smoker | 1.21 | 0.86, 1.71 | 0.27 | |
| | Baseline emphysema presence | 0.85 | 0.61, 1.18 | 0.33 | |
| | AF treatment (never/ever) | 0.72 | 0.53, 0.97 | 0.030 | |
| | Δ-ILD (%/year) | 1.01 | 1.00, 1.03 | 0.094 | |
| | Baseline DLco% predicted | 0.95 | 0.94, 0.96 | <0.00001 | |
| | Δ-PPFE-adj (%/year) | 1.28 | 1.18, 1.37 | <0.00001 | |
| FHP (n = 98) | Baseline age (years) | 1.06 | 1.02, 1.10 | 0.004 | 0.79 |
| | Male gender | 1.35 | 0.58, 3.13 | 0.47 | |
| | Ever smoker | 0.94 | 0.42, 2.09 | 0.87 | |
| | Baseline emphysema presence | 0.66 | 0.28, 1.51 | 0.31 | |
| | Δ-ILD (%/year) | 1.05* | 0.99, 1.12 | 0.11 | |
| | Baseline DLco% predicted | 0.96 | 0.94, 0.99 | 0.020 | |
| | Δ-PPFE-adj (%/year) | 1.23 | 1.07, 1.40 | 0.004 | |

**Supplementary Table 19: Association of Δ-PPFE-adj with mortality in multivariable Cox regression models in the IPF cohort (n = 414), with varying threshold of scan noise**. Models were adjusted for patient age, gender, smoking history (never/ever), baseline emphysema presence (absent/present), antifibrotic treatment (never/ever), baseline DLco% predicted, baseline presence of clinically important PPFE, and Δ-PPFE-adj. The threshold of scan noise was varied between models. IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, AF = antifibrotic, Δ-PPFE-adj=annualised change in computerised upper-zone PPFE between scans above scan noise.

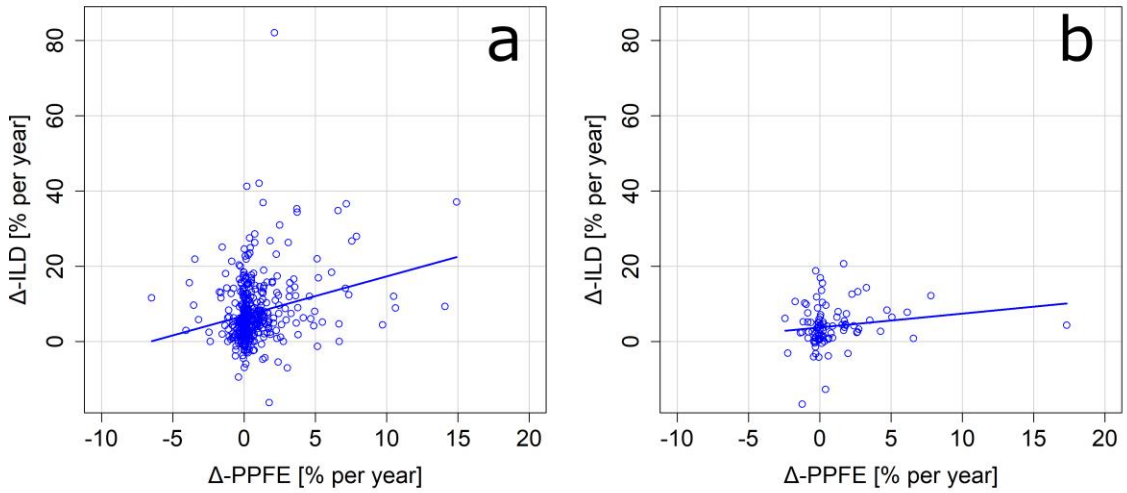
| Threshold used to determine scan noise (%/year) | Variable | Hazard ratio | 95% Confidence Interval | p-value | Model C-index |
|---|---|---|---|---|---|
| 0.5 | Baseline age (years) | 1.00 | 0.99, 1.02 | 0.75 | 0.75 |
| | Male gender | 1.48 | 1.01, 2.16 | 0.046 | |
| | Ever smoker | 1.19 | 0.85, 1.66 | 0.32 | |
| | Baseline emphysema presence | 0.95 | 0.68, 1.33 | 0.77 | |
| | AF treatment (never/ever) | 0.72 | 0.53, 0.97 | 0.030 | |
| | Δ-ILD (%/year) | 1.01 | 1.00, 1.02 | 0.20 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.68 | 1.24, 2.27 | 0.0009 | |
| | Baseline DLco% predicted | 0.96 | 0.94, 0.97 | <0.00001 | |
| | Δ-PPFE-adj (%/year) | 1.23 | 1.15, 1.32 | <0.00001 | |
| 0.75 | Baseline age (years) | 1.00 | 0.99, 1.02 | 0.76 | 0.75 |
| | Male gender | 1.47 | 1.00, 2.15 | 0.048 | |
| | Ever smoker | 1.20 | 0.85, 1.68 | 0.29 | |
| | Baseline emphysema presence | 0.94 | 0.67, 1.32 | 0.74 | |
| | AF treatment (never/ever) | 0.72 | 0.54, 0.97 | 0.031 | |
| | Δ-ILD (%/year) | 1.01 | 1.00, 1.02 | 0.18 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.69 | 1.25, 2.29 | 0.0008 | |
| | Baseline DLco% predicted | 0.96 | 0.94, 0.97 | <0.00001 | |
| | Δ-PPFE-adj (%/year) | 1.24 | 1.15, 1.33 | <0.00001 | |
| 1.0 | Baseline age (years) | 1.00 | 0.99, 1.02 | 0.75 | 0.75 |
| | Male gender | 1.46 | 1.00, 2.14 | 0.051 | |
| | Ever smoker | 1.21 | 0.86, 1.69 | 0.27 | |
| | Baseline emphysema presence | 0.94 | 0.67, 1.31 | 0.70 | |
| | AF treatment (never/ever) | 0.72 | 0.54, 0.97 | 0.032 | |
| | Δ-ILD (%/year) | 1.01 | 1.00, 1.02 | 0.16 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.70 | 1.26, 2.30 | 0.0006 | |
| | Baseline DLco% predicted | 0.96 | 0.94, 0.97 | <0.00001 | |
| | Δ-PPFE-adj (%/year) | 1.24 | 1.15, 1.33 | <0.00001 | |
| 1.5 | Baseline age (years) | 1.00 | 0.99, 1.02 | 0.72 | 0.75 |
| | Male gender | 1.44 | 0.98, 2.11 | 0.061 | |
| | Ever smoker | 1.23 | 0.88, 1.72 | 0.23 | |
| | Baseline emphysema presence | 0.92 | 0.66, 1.29 | 0.64 | |
| | AF treatment (never/ever) | 0.73 | 0.54, 0.98 | 0.036 | |
| | Δ-ILD (%/year) | 1.01 | 1.00, 1.03 | 0.13 | |
| | Baseline clinically important PPFE (PPFE extent >2.5%) | 1.73 | 1.28, 2.33 | 0.0005 | |
| | Baseline DLco% predicted | 0.96 | 0.94, 0.97 | 0.00001 | |
| | Δ-PPFE-adj (%/year) | 1.25 | 1.16, 1.35 | 0.00001 | |



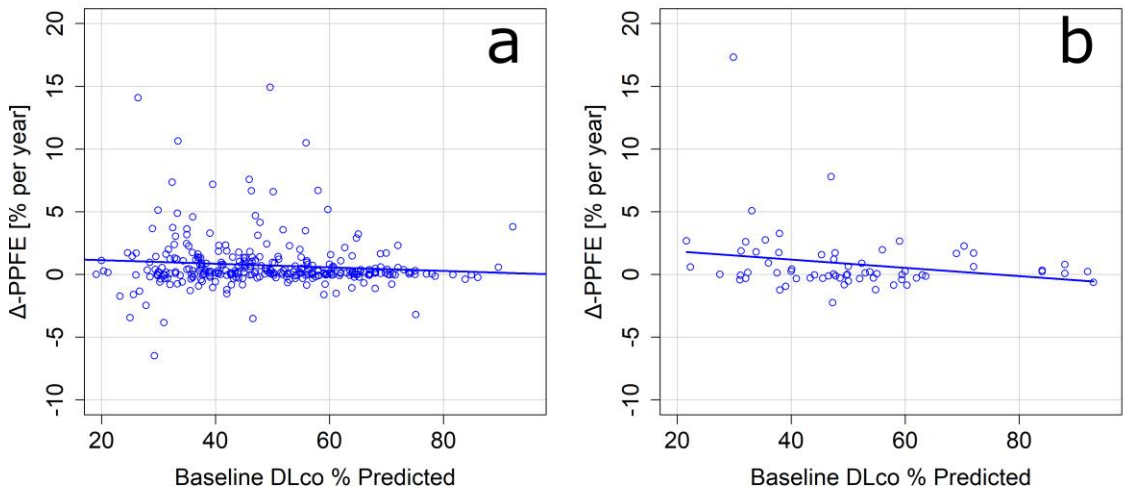

**Supplementary Figure 1**. **CONSORT diagram showing patient exclusions for FHP patients in the study.** CONSORT flow diagrams for all FHP patients in the study. FHP = fibrotic hypersensitivity pneumonitis, CT = computed tomography, FVC = forced vital capacity.



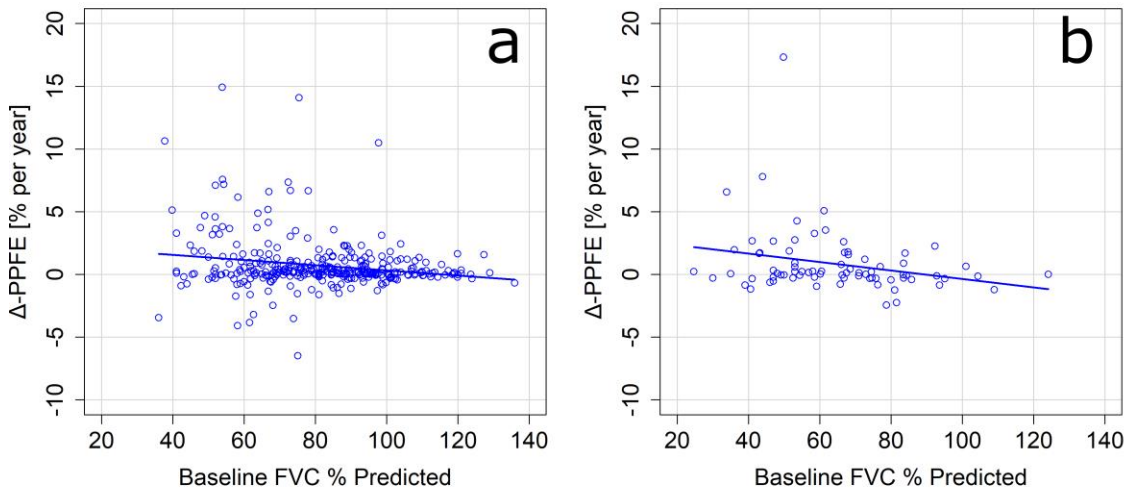

**Supplementary Figure 2**. **Association between Δ-ILD and baseline PPFE in the IPF cohort (a) and the FHP cohort (b).** a) Relationship between Δ-ILD and baseline PPFE in the IPF cohort, with a line of best fit shown (effect=0.36 %/year, 95% CI= 0.01–0.70 %/year, p=0.043, $R^2$=0.01). b) Relationship between Δ-ILD and baseline PPFE in the FHP cohort, with a line of best fit shown (effect=0.32 %/year, 95% CI= -0.17–0.80 %/year, p=0.20, $R^2$=0.02). ILD = interstitial lung disease, Δ-ILD = annualised change in ILD extent between scans, PPFE = pleuroparenchymal fibroelastosis, baseline PPFE = baseline computerised upper-zone PPFE extent, IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis.



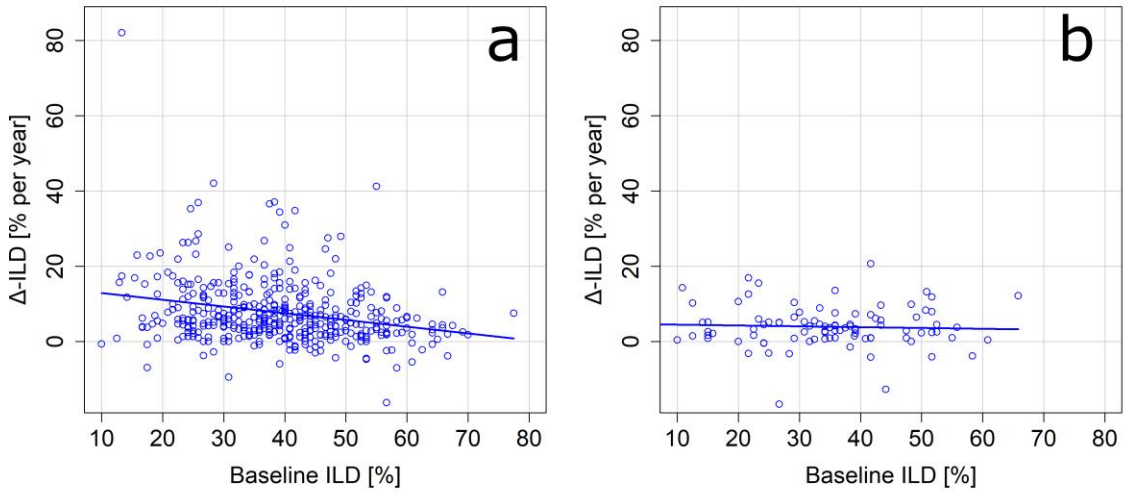

**Supplementary Figure 3: Association between Δ-ILD and Δ-PPFE in the IPF cohort (a) and FHP cohort (b).** a) Relationship between Δ-ILD and Δ-PPFE in the IPF cohort, with a line of best fit shown (effect=1.05 %/year, 95% CI=0.66–1.44 %/year, p<0.0001, $R^2$=0.06). b) Relationship between Δ-ILD and Δ-PPFE in the FHP cohort, with a line of best fit shown (effect=0.37 %/year, 95% CI= -0.08–0.82 %/year, p=0.11, $R^2$=0.03). IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis, ILD = interstitial lung disease, Δ-ILD = annualised change in ILD extent between CT scans, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between CT scans.



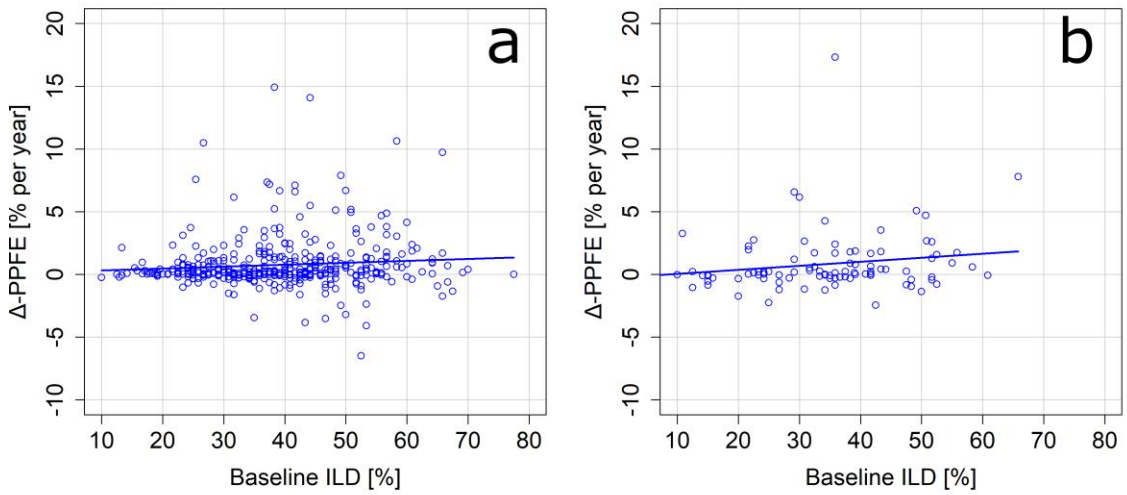

**Supplementary Figure 4**. **Association between Δ-PPFE and baseline DLco in the IPF cohort (a) and the FHP cohort (b).** a) Relationship between Δ-PPFE and baseline DLco% predicted in the IPF cohort, with a line of best fit shown (effect= -0.01 %/year, 95% CI= -0.03–0.0001 %/year, p=0.051, $R^2$=0.01). b) Relationship between Δ-PPFE and baseline DLco% predicted in the FHP cohort, with a line of best fit shown (effect= -0.03 %/year, 95% CI= -0.07–0.003 %/year, p=0.076, $R^2$=0.05). DLco = diffusing capacity for carbon monoxide, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis.



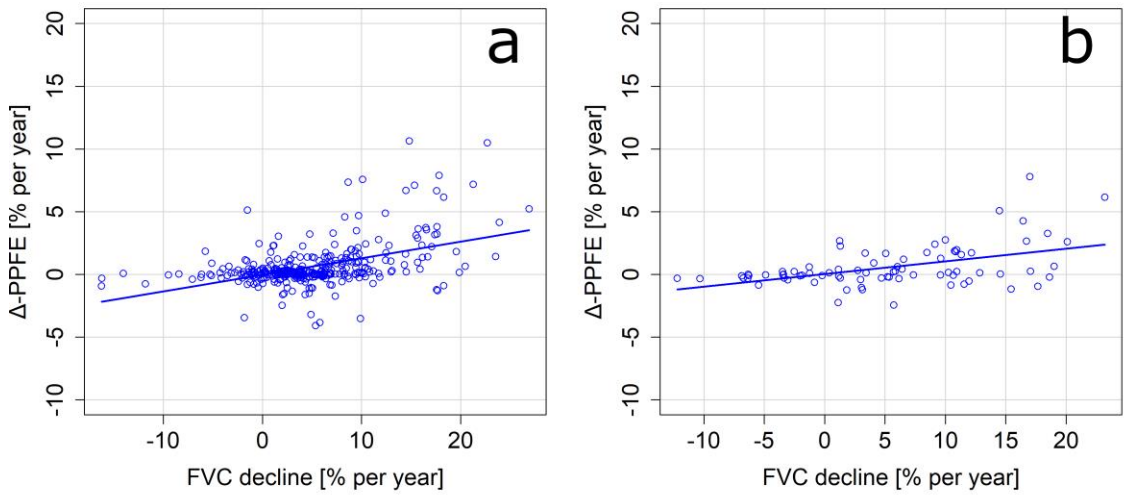

**Supplementary Figure 5**. **Association between Δ-PPFE and baseline FVC in the IPF cohort (a) and the FHP cohort (b).** a) Relationship between Δ-PPFE and baseline FVC% predicted in the IPF cohort, with a line of best fit shown (effect= -0.02 %/year, 95% CI= -0.03– -0.01 %/year, p=0.0003, $R^2$=0.04). b) Relationship between Δ-PPFE and baseline FVC% predicted in the FHP cohort, with a line of best fit shown (effect= -0.03 %/year, 95% CI= -0.06– -0.005 %/year, p=0.023, $R^2$=0.07). FVC = forced vital capacity, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis.




**Supplementary Figure 6**. **Association between Δ-ILD and baseline ILD extent in the IPF cohort (a) and the FHP cohort (b).** a) Relationship between Δ-ILD and baseline ILD extent in the IPF cohort, with a line of best fit shown (effect= -0.15 %/year, 95% CI= -0.22– -0.09 %/year, p<0.0001, $R^2$=0.05). b) Relationship between Δ-ILD and baseline ILD extent in the FHP cohort, with a line of best fit shown (effect= -0.02 %/year, 95% CI= -0.10–0.06 %/year, p=0.59, $R^2$ = 0.003). ILD = interstitial lung disease, Δ-ILD = annualised change in ILD extent between scans, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis.




**Supplementary Figure 7**. **Association between Δ-PPFE and baseline ILD extent in the IPF cohort (a) and the FHP cohort (b).** Relationship between Δ-PPFE and baseline ILD extent in the IPF cohort, with a line of best fit shown (effect=0.02 %/year, 95% CI= -0.001–0.03 %/year, p=0.064, $R^2$=0.01). b) Relationship between Δ-PPFE and baseline ILD extent in the FHP cohort, with a line of best fit shown (effect=0.03 %/year, 95% CI= -0.002–0.07 %/year, p=0.063, $R^2$=0.04). ILD = interstitial lung disease, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis.




**Supplementary Figure 8**. **Association between Δ-PPFE and FVC decline per year in the IPF cohort (a) and the FHP cohort (b).** Relationship between Δ-PPFE and FVC decline per year in the IPF cohort, with a line of best fit shown (effect=0.13 %/year, 95% CI= 0.11–0.16 %/year, p<0.0001, $R^2$=0.22). b) Relationship between Δ-PPFE and baseline ILD extent in the FHP cohort, with a line of best fit shown (effect=0.10 %/year, 95% CI= 0.06–0.14 %/year, p<0.0001, $R^2$=0.23). ILD = interstitial lung disease, PPFE = pleuroparenchymal fibroelastosis, Δ-PPFE = annualised change in computerised upper-zone PPFE between scans, FVC = forced vital capacity, IPF = idiopathic pulmonary fibrosis, FHP = fibrotic hypersensitivity pneumonitis.

**Supplementary References**


1 Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. *Prevention Science* 2007; **8**: 206–213.

2 Gudmundsson E, Zhao A, Mogulkoc N, *et al.* Pleuroparenchymal fibroelastosis in idiopathic pulmonary fibrosis: Survival analysis using visual and computer-based computed tomography assessment. *EClinicalMedicine* 2021; **38**: 101009.