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Fibrosing Organizing Pneumonia Seen in Patients with Autoimmune Features or Connective Tissue Disease Shows a Tendency of Progressive Disease

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Name	Type of File	Size	Page
Fibrosing OP_Respirology.docx	Main Document - MS Word	5.9 MB	Page 4
Figure 1.TIF	Figure	628.3 KB	Page 31
Figure 2.TIF	Figure	5.1 MB	Page 32
Figure 3.TIF	Figure	5.4 MB	Page 33
Figure 4.TIF	Figure	971.8 KB	Page 34
Fibrosing OP_Supplement.docx	Supplementary Material for Review	9.3 MB	Page 35
STROBE.doc	STROBE Statement	107.5 KB	Page 48

Fibrosing Organizing Pneumonia Seen in Patients with Autoimmune Features or Connective Tissue Disease Shows a Tendency of Progressive Disease

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Summary

- *Clinical course and baseline factors associated with progression in biopsy-proven fibrosing organizing pneumonia.*
- *Ground-glass opacity and consolidation decreased over time, whereas honeycombing increased, and approximately one-third of patients showed disease progression.*
- *Connective tissue disease or autoimmune features, rather than baseline quantitative CT findings, were associated with disease progression.*

Abstract

Background and Objective: Fibrosing organizing pneumonia (OP), the coexistence of OP and fibrosing nonspecific interstitial pneumonia on surgical lung biopsy, is underrecognized and its prognostic determinants are poorly characterized. We aimed to identify clinical and radiologic features associated with progression in biopsy-proven fibrosing OP.

Methods: We retrospectively reviewed 25 patients with biopsy-proven fibrosing OP. Deep learning-based quantitative computed tomography (qCT) lung texture analysis was adopted in quantification of ground-glass opacity (GGO), reticulation, honeycombing (HC), and consolidation. Progressive disease (PD) was defined as either a decline in forced vital capacity (FVC) of at least 10% or an increase in qCT-derived fibrosis extent of at least 3.4 percentage points. Improved disease (ID) was defined as either an increase in FVC of at least 10% or a decrease in fibrosis extent of at least 3.4 percentage points.

Results: Among 25 patients, 18 had idiopathic disease and seven had connective tissue disease (CTD) or interstitial pneumonia with autoimmune features (IPAF). Over a median follow-up of 56.8 months, eight patients (32.0%) showed PD, another eight (32.0%) had ID, and nine (36.0%) remained stable. On follow-up CT, GGO decreased in 24 patients (96.0%) and consolidation in 20 (80.0%), whereas HC increased in 18 (72.0%). CTD/IPAF etiology was associated with PD and lower baseline DLco showed a borderline association. No baseline qCT parameter helped predict PD.

Conclusion: Fibrosing OP shows diverse clinical courses despite overall resolution of inflammatory CT components. PD was associated with CTD/IPAF etiology, whereas lower baseline DLco showed a borderline association.

Keywords: Clinical biomarker, Fibrosing nonspecific interstitial pneumonia, Organizing pneumonia, Fibrosing organizing pneumonia, Prognosis

Introduction

In 2013, Travis et al., in a statement from the American Thoracic Society (ATS) and European Respiratory Society (ERS) providing an update of the international multidisciplinary classification of idiopathic interstitial pneumonias (IIPs), elaborated on a fibrosing variant of organizing pneumonia (OP) (we call it fibrosing OP), despite this entity not representing an official classification category.[1] A subsequent ERS/ATS update addressed combined patterns of interstitial pneumonia, of which combined OP and NSIP is among the most common, reported in up to 60% of patients with idiopathic inflammatory myositis.[2]

Histologically, in fibrosing OP, bands and/or nodules composed mainly of granulation plugs within alveoli, alveolar ducts and bronchioles are usually distributed randomly, but occasionally mixed with fibrotic nonspecific interstitial pneumonia (fNSIP) in local areas. Small foci of loose granulation tissue at the edge of the fibrotic bands may mimic fibroblastic foci.[3-5] On CT, lung abnormalities of fibrosing OP appear as typical OP but with areas of irregularly distributed reticular opacities.

Fibrosing OP could be idiopathic, but many cases tend to be those of OP with known causes, particularly associated with connective tissue disease, or cases of cryptogenic OP with recurrent episodes leading to residual or progressive interstitial fibrosis.[6] This progressive interstitial fibrosis is of great clinical importance, as recent studies show that new drugs offer a viable option to mitigate disease progression.[7, 8]

The pathogenesis of fibrosing OP is not well understood. In fibrosing OP, the OP process is not limited to the formation of granulation tissue within the airspaces but also involves the development of significant fibrosis in the alveolar walls. Mural incorporation refers to this fibrosis process in the alveolar walls, a term meant to indicate that the granulation tissue and other components of OP are being incorporated into or becoming part of the alveolar walls. It has been noted that these fibrotic changes can be seen in both the initial OP process or as a later development.[9]

Overlapping forms of interstitial pneumonia like fNSIP and OP, have been recognized, but may be underappreciated, because the disease manifests some disproportionate histopathologic features of the two components of OP and fNSIP on surgical lung biopsy.[10] In addition, the clinical, radiological, and prognostic characteristics of fibrosing OP are not well addressed. In this study, we aimed to characterize the clinical, radiologic, and prognostic

features of biopsy-proven fibrosing OP using serial quantitative CT and pulmonary function data, and to identify factors associated with disease progression.

Methods

Patients' selection

This retrospective study was approved by our institutional review board (IRB number; 2026-05-072), which was conducted in accordance with the Declaration of Helsinki, and the requirement for informed consent was waived.

From the histopathologic data system of the Department of Pathology at our institution, we retrieved patients histopathologically diagnosed via surgical lung biopsy as having 'mixed OP and fNSIP', 'fibrosing OP', 'overlap of OP and fNSIP', or 'combined OP and fNSIP' between March 2014 and May 2025. Among 30 patients who were initially identified, five patients were excluded. Thus, we included a total of 25 patients who were diagnosed as fibrosing OP or combined OP and fNSIP in the analysis (Figure 1, Supplementary material).

Clinical, Histopathologic, and CT Imaging Assessment

Demographic data, comorbidities including connective tissue diseases (CTD), CTD-related serologic profiles, pulmonary function test parameters, bronchoalveolar lavage (BAL) results, treatments, and outcomes were collected. Histopathologic specimens were reviewed by an experienced thoracic pathologist (J.H., with 30 years of experience in interstitial lung disease interpretation), who was blinded to the patients' clinical and radiological information, and histopathologic diagnoses were determined in accordance with the ATS/ERS multidisciplinary classification of idiopathic interstitial pneumonias.[1] IPAF was defined according to the 2015 ERS/ATS research statement, requiring an interstitial pneumonia with features from at least two of the clinical, serologic, and morphologic domains in the absence of a defined CTD or alternative etiology.[11]

Initial CT and pulmonary function studies were defined as those obtained at or around the time of biopsy-proven diagnosis, and follow-up studies were defined as the most recent available at the end of the observation period. For patients who experienced relapse, the same baseline and most recent time points were used; relapse episodes were recorded as events but were not analyzed as separate time points.

Automated quantitative CT (qCT) analysis was performed using deep learning-based

texture analysis software (AVIEW 1.1.46.22-win, Coreline Soft, Seoul, South Korea). Fibrosis extent was defined as the sum of reticulation and honeycombing (fibrosis% = reticulation% + honeycombing%), consistent with previous studies using the same software [12, 13], and the same-day measurement variability of AVIEW-derived fibrosis extent has been reported to be approximately 1% in a multicenter prospective study.[14] To validate the qCT-based progression assessment, semi-quantitative visual scoring of disease extent was independently performed by two thoracic radiologists (K.S.L. and D.Y.J., with 34 and 10 years of experience, respectively), who were blinded to the clinical, pulmonary functional, and histopathologic data and discrepancies were resolved by consensus. Further details regarding clinical data collection and CT imaging analysis are provided in the Supplementary material.

Definition of disease outcomes

In this study, disease outcomes were classified into three categories: progressive disease (PD), stable disease (SD), and improved disease (ID). PD was defined based on criteria adapted from the INBUILD trial, in which disease progression is assessed using decline in forced vital capacity (FVC) and/or radiologic worsening on high-resolution CT (HRCT). In our study, the radiologic component was defined objectively using quantitative CT (qCT).[7] Accordingly, PD was defined as either (a) a relative decline of at least 10% in percent-predicted FVC or (b) an increase in qCT-derived fibrosis extent of at least 3.4 percentage points. The 3.4–percentage point threshold corresponds to the minimal clinically important difference of a quantitative fibrosis score in idiopathic pulmonary fibrosis and has been applied with comparable qCT software. [15-17]

Because no established consensus exists for defining objective improvement in interstitial lung diseases, including fibrosing OP, we used a pre-specified operational definition in this study. ID was defined as the counterpart of the PD criteria: a relative increase in percent-predicted FVC of at least 10% or a decrease in qCT-derived fibrosis extent of at least 3.4 percentage points. Patients who met neither the PD nor the improvement criteria were classified as having SD. In cases with discordant physiologic and radiologic changes, PD classification took precedence over ID classification.

Additionally, to assess the robustness of our findings to the choice of radiologic progression threshold, we conducted a sensitivity analysis using an alternative qCT threshold. (Supplementary material and Table S1**)**

Statistical Analysis

Univariable analyses were performed to evaluate the associations of baseline clinical features and qCT findings with PD status. Because follow-up qCT changes were constituent components of the PD outcome definition, only baseline variables were evaluated as candidate predictors to avoid circularity; longitudinal interval changes are therefore reported descriptively rather than as predictors. Continuous variables are presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney U test, whereas categorical variables were compared using Fisher's exact test. Because of the small sample size and sparse data, including complete separation in some variables, univariable Firth penalized logistic regression was performed to estimate odds ratios (ORs) with 95% confidence intervals (CIs).[18] Paired changes between initial and follow-up qCT findings were assessed using the Wilcoxon signed-rank test. Agreement between qCT-based and visual radiologic PD assessment was evaluated using Cohen's kappa statistic. Three-group comparisons were performed using the Kruskal-Wallis test. All statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing), and a two-sided P value $< .05$ was considered statistically significant.

Results

Demographics and baseline characteristics

Of 30 patients initially identified, five were excluded, yielding a final cohort of 25 patients with biopsy-proven fibrosing OP. Detailed baseline characteristics are described in Table 1. The study population consisted of 14 women (56.0%) and 11 men (44.0%), with a median age of 57.5 years. Two (8.0%) were current smokers, and seven (28.0%) were ex-smokers. Among 25 patients, 18 (72.0%) had idiopathic disease (**Figures 2 and S1**), five (20.0%) had underlying CTD (**Figures 3 and S2**), and two (8.0%) had interstitial pneumonia with autoimmune features (IPAF). (Supplementary material)

The medians of initial FVC and DLco were 81.0% and 71.0%, respectively. The 6MWT was performed in 13 patients, with a median walking distance of 481 m (IQR, 408–585) and a median nadir SpO_2 of 89.0% (IQR, 86.0–92.0). BAL data were available in 14 patients, with a median lymphocyte proportion of 30.0% (IQR, 10.0–40.0).

On initial qCT, baseline honeycombing was negligible in all patients (none exceeding 1%; Table 1). Lung lesions were predominantly peripheral/subpleural (18 of 25, 72.0%) and lower-zone predominant (17 of 25, 68.0%), whereas bronchiolocentric distribution was observed in 9 of 25 patients (36.0%). Surgical lung biopsy specimens were available for review in all patients. **(**Supplementary material)

Treatment and outcomes

Among the 25 patients, disease progressed in 8 (32.0%) while 17 (68.0%) remained stable (n = 9, 36.0%) or improved (n = 8, 32.0%). (**Table S2**) Of eight PD patients, two met both physiologic and radiologic criteria, three met only the radiologic criterion, and three met only physiologic criterion.

Twenty-two patients (88.0%) received treatment, all with corticosteroids; 19 (86.4%) also received immunosuppressants (azathioprine in all, with one switch to mycophenolate mofetil). Relapse or re-treatment occurred in 5 of 22 (22.7%), with similar frequency in the PD and non-PD groups (2/8 vs 3/14; P = 1.000); all five had idiopathic disease. The three untreated patients all had idiopathic disease with preserved lung function, and none developed PD.

Detailed treatment courses are provided in the Supplementary material.

No patient died or underwent lung transplantation during follow-up. Median follow-up was 56.8 months (IQR, 30.7–103.9). Follow-up duration did not differ significantly between the PD and non-PD groups (80.8 vs. 49.6 months; P = .140).

Radiologic, physiologic, and clinical assessment according to disease progression

The median CT interval was 48.1 months (range, 7.2–128.5). The qCT-based radiologic PD assessment showed perfect agreement with visual assessment (κ = 1.000). Across the cohort, inflammatory components resolved in most patients. GGO decreased in 24 of 25 (96.0%; P < .001) and consolidation in 20 (80.0%; P < .001), whereas honeycombing increased in 18 (72.0%; P = .018) and reticulation showed no significant overall change (P = .508).

When stratified by the presence of disease progression, reticulation increased more frequently (6/8 [75.0%] vs 3/17 [17.6%]; P = .010) and to a greater extent (median change, +2.5% vs −0.6%; P = .005). The magnitude of honeycombing increase was also greater in the PD group (+1.18% vs +0.001%; P = .031), although the frequency of increase did not differ (P = .362). Significant honeycombing emergence (≥1% from a baseline <1%) was observed in 4 of 8 PD patients versus 2 of 17 non-PD patients (P = .059). Figure S3 presents patient-level characteristics.

The median PFT interval was 49.6 months (IQR, 26.8–84.5) and was relatively longer in the PD than non-PD group (72.3 vs 37.5 months; P = .066). Follow-up FVC and DLco were lower in the PD group, and symptom aggravation was observed only in PD patients. Detailed clinical, radiological, and physiological outcomes between the groups are available in Table 2.

Predictive factors for progressive disease

In the cohort, treatment rates did not differ between PD and non-PD groups (8/8 [100.0%] vs 14/17 [82.4%]; P = .527). Immunosuppressant use was numerically more frequent in the PD group but without statistical significance (8/8 [100.0%] vs 11/17 [64.7%]; P = .129).

In univariable analysis, CTD/IPAF etiology was the only baseline clinical factor significantly associated with PD (Figure 4). Five of seven patients (71.4%) with CTD/IPAF-

related disease showed progression, compared with three of 18 patients (16.7%) with idiopathic disease (OR, 9.74; 95% CI, 1.62–78.13; P = .012). Lower initial DLco showed a borderline association with progression (OR per 10% increase, 0.67; 95% CI, 0.42–1.03; P = .072).

No baseline qCT parameter, including GGO, reticulation, fibrosis extent, or consolidation, was associated with progression (all P > .160). Male sex, ever-smoker status, treatment received, and lesion distribution were also not significant predictors (all P > .300; Figure 4). The results of additional comparisons of baseline and follow-up characteristics across the three groups (ID, SD, and PD) as well as between ID and SD are presented in the Tables S2 and S3 in the Supplementary Material.

Discussion

Most patients with cryptogenic organizing pneumonia (COP) recover completely after corticosteroid therapy, but relapse is common, and a subset shows residual or progressive interstitial fibrosis with or without recurrent episodes of OP.[19-22] In this context, we characterized biopsy-proven fibrosing OP using serial quantitative CT, pulmonary function, and clinically defined outcome criteria. Our findings suggest that fibrosing OP may be better understood as a mixed inflammatory-fibrotic disorder in which reversible and irreversible components coexist within the same patient.

One of the main findings was the differential longitudinal behavior of individual qCT components in patients with fibrosing OP. GGO significantly decreased in most patients, whereas reticulation did not significantly change overall but increased preferentially in PD patients. Honeycombing increased over time in the overall cohort, and the magnitude of honeycombing increase was greater in PD patients than in non-PD patients. Consolidation decreased in 20 of 25 patients (80.0%) at a similar rate in both groups, although residual consolidation remained higher in PD patients. These findings suggest that OP component, including GGO and consolidation, may improve over time, whereas the fibrotic component may persist or progress. Accordingly, assessment based only on total ILD extent may not fully reflect these differing trajectories within the same patient, and texture-level qCT assessment may provide additional information beyond overall disease extent.[23] Although no baseline qCT parameter predicted PD, the value of serial qCT lies in its ability to track longitudinal texture-level changes that are not apparent at a single time point.

Among baseline variables, CTD/IPAF etiology was significantly associated with progression. Previous reports suggested an association between fibrosing OP and CTD/IPAF. Fischer et al. reported that some patients with a mixed pattern of fibrosis and OP have underlying polymyositis or antisynthetase syndrome.[24] Enomoto et al. similarly reported that NSIP-OP overlap was the most prevalent CT pattern in IPAF.[25] This may reflect persistent systemic inflammation and repeated lung injury in CTD/IPAF leading to fibrosis, although the mechanism remains uncertain.[26, 27] Notably, of the remaining two non-PD patients with CTD/IPAF, one with IPAF (anti-Jo-1 antibody) and one with CTD (polymyositis), the latter showed objective improvement. While previous studies reported that about 20-40% of patients with CTD-ILD or IPAF satisfy criteria for progression [28, 29], patients with IPAF showed

better survival and physiologic and radiologic improvement compared to patients without IPAF.[25] The triggers and mechanisms driving progression in these populations warrant further study. However, given that OP has been generally regarded to have a favorable treatment response, the fact that a significant proportion of patients, particularly those with CTD-ILD or IPAF, can still experience progression requires clinical attention including the consideration of whether to initiate antifibrotic therapy.[7, 8] These findings also support the inclusion of fibrosing OP in the clinical spectrum of progressive pulmonary fibrosis. Interestingly, treatment status was not significantly associated with PD, but this comparison should be interpreted cautiously because treatment was not randomized and all three untreated patients had idiopathic disease with preserved lung function, introducing confounding by indication.

Consistent with our finding, lower baseline DLco predicted progression in biopsy-proven fibrotic NSIP, possibly reflecting disease severity.[30] Lee et al. reported that prognostic impact of a decline in DLco remained significant regardless of changes in FVC.[31] Accordingly, DLco may serve as a useful complement to serial imaging in risk stratification. Nevertheless, DLco should be interpreted cautiously because it may be affected by technical variability and comorbid conditions such as pulmonary hypertension.

Among non-PD patients, ID was observed in a subset, predominantly in idiopathic disease (Supplementary Material). Greater baseline reticulation/fibrosis extent and lower DLco in improved patients may reflect greater room for measurable recovery rather than true reversal of established fibrosis. In fibrosing OP, qCT-derived reticulation may include partially reversible organizing tissue because early mural incorporation can overlap with established fibrosis on CT. [32, 33] Therefore, the observed decrease in qCT-derived fibrosis in improved patients may partly reflect resolution of the organizing component. These exploratory findings should be interpreted cautiously given the small sample size.

Our study has several limitations. First, this was a retrospective single-center study with a small sample size (n = 25), which limited statistical power and precluded multivariable modeling. We used Firth penalized regression to reduce small-sample bias; however, the resulting estimates should still be interpreted cautiously because of the limited number of patients and events. Nevertheless, this sample size reflects the rarity of biopsy-proven fibrosing OP, and our findings should therefore be regarded as hypothesis-generating. Second, the criteria used to define progression were adapted for this study and have not been specifically validated in fibrosing OP. Nevertheless, their perfect agreement with visual radiologic

assessment supports the clinical relevance of the chosen threshold. Third, GGO and reticulation may coexist within the same lesion, and their separation by qCT remains challenging. Finally, the interval between initial and follow-up pulmonary function testing tended to be longer in patients with progressive disease than in those without progressive disease, which may have provided greater opportunity to detect functional progression. However, this difference was not statistically significant, and the main findings were directionally consistent between CT-based and pulmonary function–based assessments.

In conclusion, fibrosing OP showed heterogeneous clinical and radiologic behavior, with improvement of OP components but persistence or progression of fibrotic abnormalities over time. CTD/IPAF etiology was associated with progressive disease, whereas no baseline qCT variable significantly predicted progression. These findings support fibrosing OP as a mixed inflammatory-fibrotic disorder requiring longitudinal monitoring with pulmonary function assessment and serial qCT.

Data availability: Data generated or analyzed during the study are available from the corresponding author upon reasonable request.

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Conflicts of interest: The authors declare no conflicts of interest.

Ethics Statement: This retrospective study was approved by the Institutional Review Board of Samsung Medical Center (IRB no. 2026-05-072). The requirement for written informed consent was waived by the Institutional Review Board owing to the retrospective nature of the study.

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Tables

Table 1. Baseline Characteristics by Progressive Disease Status

Variable	Non-PD (n = 17)	PD (n = 8)	P value*
Clinical characteristics			
Age at diagnosis, yr	58.5 (55.8–63.5)	55.6 (53.7–58.4)	.162
Male sex, n (%)	7/17 (41.2)	4/8 (50.0)	1.000
Ever smoker, n (%)	5/17 (29.4)	4/8 (50.0)	.394
CTD/IPAF etiology, n (%)	2/17 (11.8)	5/8 (62.5)	**.017**
Treatment received, n (%)	14/17 (82.4)	8/8 (100.0)	.527
Baseline pulmonary function			
Initial FVC, % predicted	82.0 (78.0–89.0)	67.5 (53.8–86.0)	.210
Initial FEV1, % predicted	88.0 (78.0–96.0)	74.0 (58.0–87.2)	.153
Initial FEV1/FVC, %	80.0 (79.0–82.0)	85.0 (79.8–87.8)	.169
Initial DLco, % predicted	75.0 (62.0–87.0)	51.5 (45.0–73.2)	.075
6-Minute Walk Test			
Total distance, m	496 (396–568)	474 (441–547)	1.000
SpO2, %	88.5 (86.5–91.5)	91.0 (87.5–92.5)	.611
Bronchoalveolar lavage*			
BAL lymphocyte, %	30.0 (12.2–40.0)	33.5 (6.5–60.0)	.829
Cytospin lymphocyte, %	29.5 (16.5–40.0)	7.0 (5.0–39.0)	.540
Distribution of fibrosis			
Lower zone predominant, n (%)	12/17 (70.6)	5/8 (62.5)	1.000
Peripheral/subpleural, n (%)	12/17 (70.6)	6/8 (75.0)	1.000
Bronchiolocentric, n (%)	7/17 (41.2)	2/8 (25.0)	.661
Initial qCT measurements			
Ground-glass opacity, %	2.9 (1.9–9.1)	7.7 (4.9–12.1)	.097
Reticulation, %	2.0 (0.6–4.8)	2.6 (1.7–5.4)	.588
Honeycombing, %	0.003 (0.000–0.015)	0.001 (0.000–0.013)	.791
Fibrosis extent, %	2.0 (0.6–4.9)	2.6 (1.8–5.4)	.549
Consolidation, %	0.3 (0.1–0.7)	1.0 (0.1–2.3)	.406

*Note.— * P values are from Fisher's exact test; Data are presented as medians with interquartile ranges for continuous variables, and as numbers with percentages for categorical variables. P values were calculated using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Bronchoalveolar lavage was performed in 56% of patients (14 of 25). CTD = connective tissue disease, DLco = diffusing capacity for carbon monoxide, FVC = forced vital capacity, GGO = ground-glass opacity, HC = honeycombing, IPAF = interstitial pneumonia with autoimmune features, PD = progressive disease, qCT = quantitative computed tomography.*

Table 2. Follow-up Findings by Progressive Disease Status

Variable	Non-PD (n = 17)	PD (n = 8)	P value
Follow-up qCT measurements			
GGO, %	0.6 (0.3–1.7)	0.9 (0.4–2.3)	.440
Reticulation, %	0.9 (0.4–2.1)	7.8 (2.4–9.8)	.005
Honeycombing, %	0.001 (0.000–0.017)	1.183 (0.003–4.272)	.091
Fibrosis extent, %	0.9 (0.4–2.1)	9.0 (2.4–15.3)	.004
Fibrosis change, percentage points	-0.6 (-2.6–0.0)	5.7 (1.8–9.2)	.004
HC change, percentage points	0.001 (-0.006–0.005)	1.182 (0.002–4.157)	.031
Emergence of significant HC (≥1%), n (%)	2/17 (11.8)	4/8 (50.0)	.059
FU Consolidation, %	0.018 (0.006–0.030)	0.110 (0.019–0.374)	.049
Follow-up pulmonary function			
Last FVC, % predicted	89.0 (83.0–96.0)	61.0 (45.8–78.0)	.003
Last DLco, % predicted	75.0 (66.0–84.0)	56.5 (38.5–62.0)	.031
Relative FVC decline, %	-5.1 (-19.5–-1.1)	15.1 (3.2–19.0)	.007
Symptom outcome			
Aggravated, n (%)	0/17 (0.0)	3/8 (37.5)	.024
Improved, n (%)	6/17 (35.3)	1/8 (12.5)	.362

Note.— Data are presented as medians with interquartile ranges for continuous variables, and as numbers with percentages for categorical variables. P values were calculated using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. DLco = diffusing capacity for carbon monoxide, FVC = forced vital capacity, GGO = ground-glass opacity, HC = honeycombing, PD = progressive disease, qCT = quantitative computed tomography.

Figure legends

Figure 1. Flow chart for patient enrollment.

Figure 2. Serial clinical and CT findings in a 64-year-old woman with fibrosing organizing pneumonia of idiopathic nature (**A, B**) Lung window of thin-section (1.25-mm section thickness) CT scans obtained at levels of right inferior pulmonary vein (**A**) and suprahepatic IVC (**B**), respectively, show patchy areas of ground-glass opacity (arrowheads), consolidation (arrows), and reversed halo sign (open arrows) in bilateral lower lung zones. (**C**) Coronal reformatted image (2.0-mm section thickness) demonstrates ground-glass opacity (arrowheads), consolidation (arrows) and reversed halo sign (open arrows) in bilateral lower lung zones. At this time, FVC and DLco were 111% and 112% of predicted values, respectively. qCT extents of ground-glass opacity and consolidation were 2.8% and 0.7%, respectively. (**D**) Photomicrograph (H & E, x 100) of surgical biopsy specimen obtained from right lower lobe discloses areas of organizing pneumonia with intra-alveolar granulation polyps (arrows) and some even interstitial fibrosis (arrowheads). Also note post-inflammatory varicose veins (open arrow) with thick muscular layer. (**E**) Eleven-month follow-up CT obtained at a similar level to **(B)** shows complete resolution of lung lesions without specific treatment.

Figure 3. Serial clinical and CT findings in a 55-year-old woman with rheumatoid arthritis and fibrosing organizing pneumonia (**A, B**) Lung window of thin-section (1.25-mm section thickness) CT scans obtained at levels of right inferior pulmonary vein (**A**) and suprahepatic IVC (**B**), respectively, show patchy areas of ground-glass opacity (arrows) and reticulation (open arrows) in lungs. At this time, FVC and DLco were 45% and 45% of predicted values, respectively. qCT extents of ground-glass opacity and reticulation were 5.6% and 7.4%, respectively. (**C, D**) CT scans obtained at similar levels to A and B, respectively and 10 and a half years after **A** & **B**, demonstrate patchy areas of reticulation (open arrows) and honeycombing (arrowheads). At this time, FVC and DLco were 76% and 65% of predicted value, respectively. qCT extents of reticulation and honeycombing were 9.7% and 9.4%, respectively. (**E**) Photomicrograph (H & E, x 40) of surgical specimen obtained from right lower lobe discloses area of even interstitial fibrosis (open arrows) and focal organizing pneumonia (arrow). **Inset:** organizing pneumonia with intraalveolar granulation plugs

Figure 4. Forest plot of univariable logistic regression for baseline factors associated with progressive disease

Note. — CTD = connective tissue disease, DLco = diffusing capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GGO = ground-glass opacity, HC = honeycombing, ILD = interstitial lung disease, IPAF = interstitial pneumonia with autoimmune features, OR = odds ratio, PD = progressive disease, qCT = quantitative computed tomography.

Figures

Figure 1. Flow chart for patient enrollment.

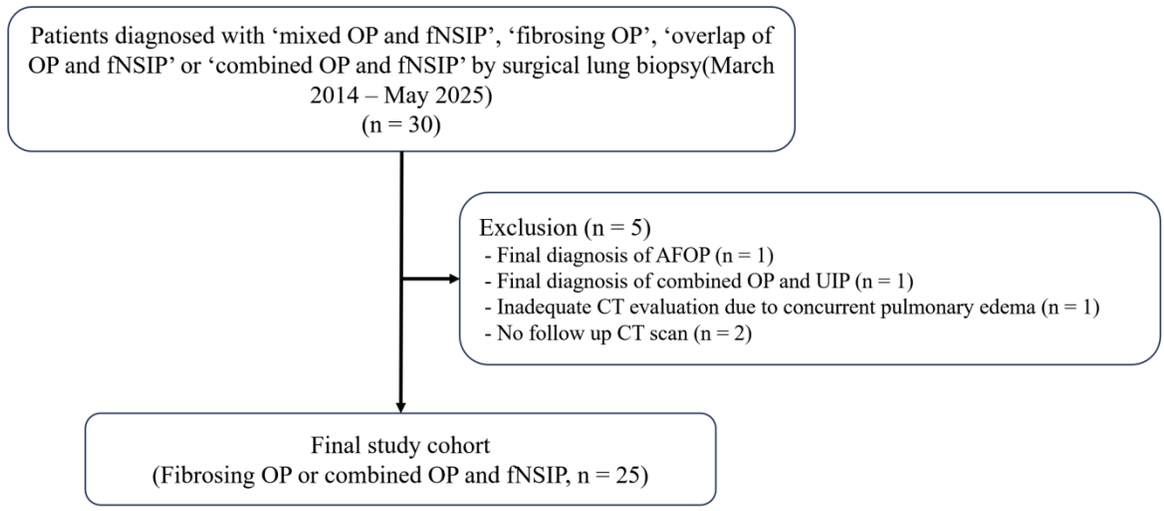
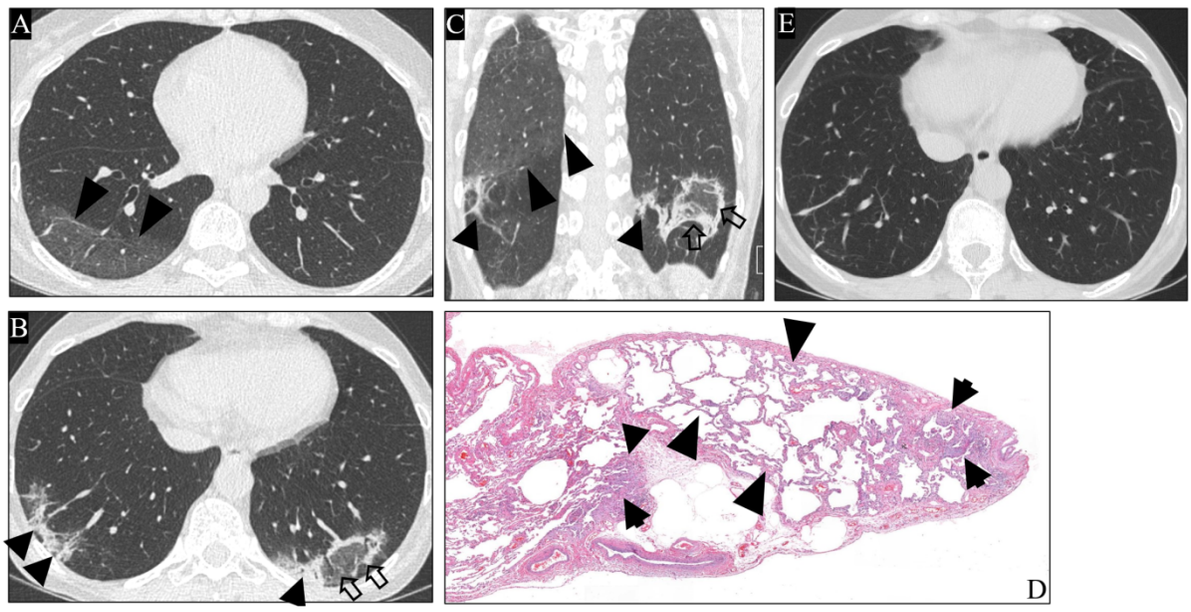


Figure 2. Serial clinical and CT findings in a 64-year-old woman with fibrosing organizing pneumonia of idiopathic nature (**A, B**) Lung window of thin-section (1.25-mm section thickness) CT scans obtained at levels of right inferior pulmonary vein (**A**) and suprahepatic IVC (**B**), respectively, show patchy areas of ground-glass opacity (arrowheads), consolidation (arrows), and reversed halo sign (open arrows) in bilateral lower lung zones. (**C**) Coronal reformatted image (2.0-mm section thickness) demonstrates ground-glass opacity (arrowheads), consolidation (arrows) and reversed halo sign (open arrows) in bilateral lower lung zones. At this time, FVC and DLco were 111% and 112% of predicted values, respectively. qCT extents of ground-glass opacity and consolidation were 2.8% and 0.7%, respectively. (**D**) Photomicrograph (H & E, x 100) of surgical biopsy specimen obtained from right lower lobe discloses areas of organizing pneumonia with intra-alveolar granulation polyps (arrows) and some even interstitial fibrosis (arrowheads). Also note post-inflammatory varicose veins (open arrow) with thick muscular layer. (**E**) Eleven-month follow-up CT obtained at a similar level to **(B)** shows complete resolution of lung lesions without specific treatment.



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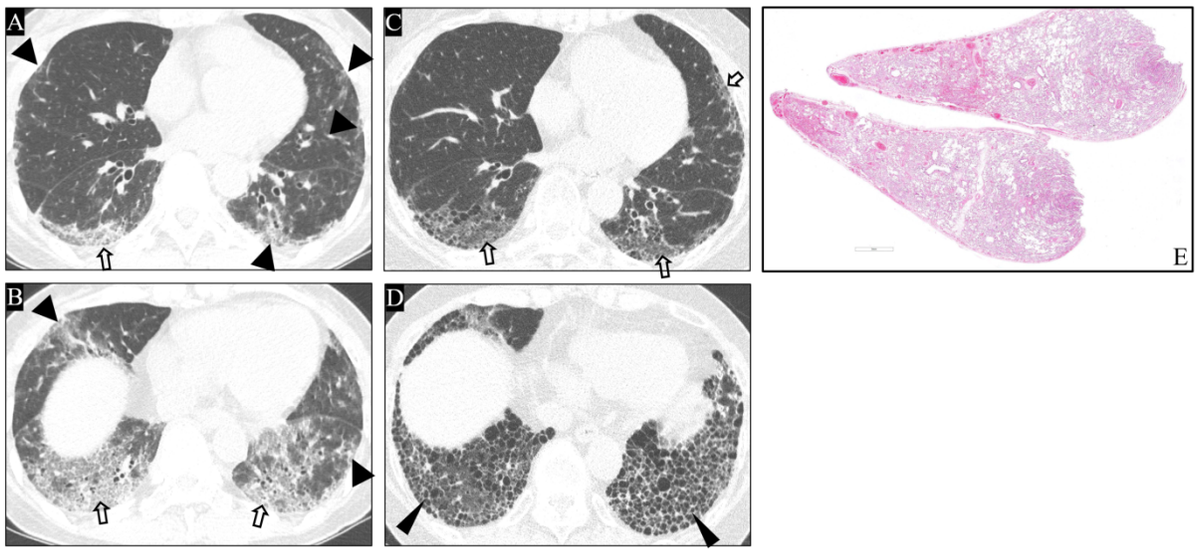
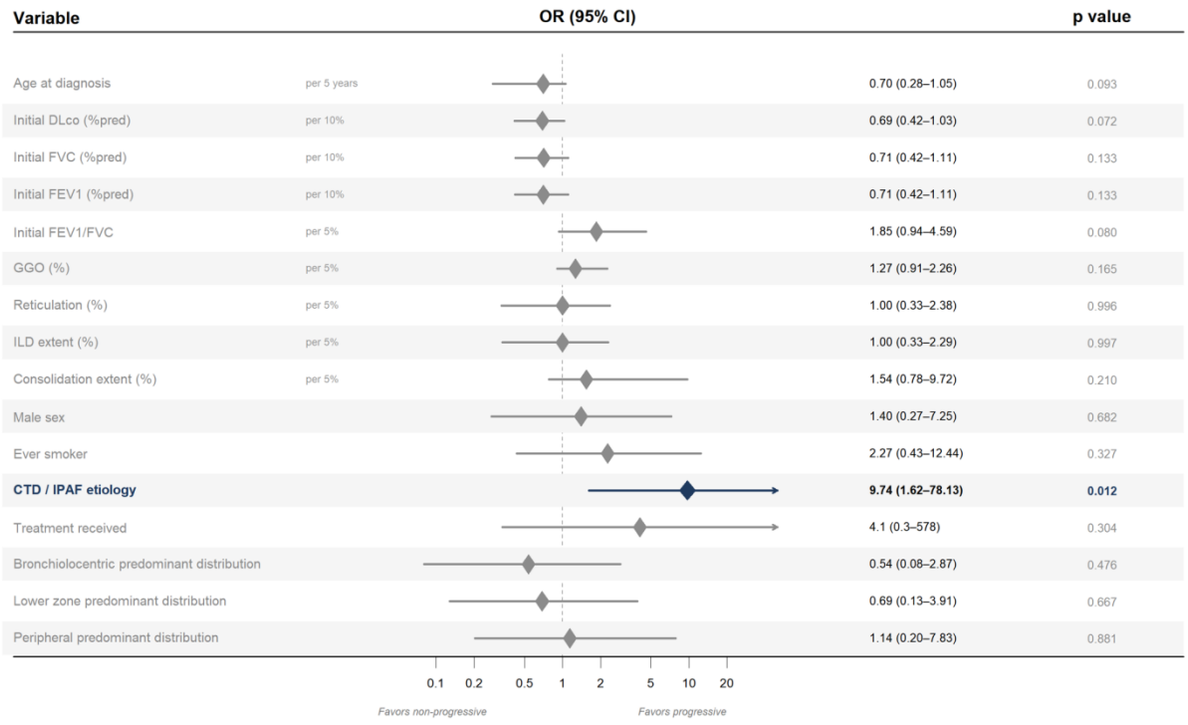


Figure 4. Forest plot of univariable logistic regression for baseline factors associated with progressive disease



Note. — CTD = connective tissue disease, DLco = diffusing capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GGO = ground-glass opacity, HC = honeycombing, ILD = interstitial lung disease, IPAF = interstitial pneumonia with autoimmune features, OR = odds ratio, PD = progressive disease, qCT = quantitative computed tomography.

Figure 1.

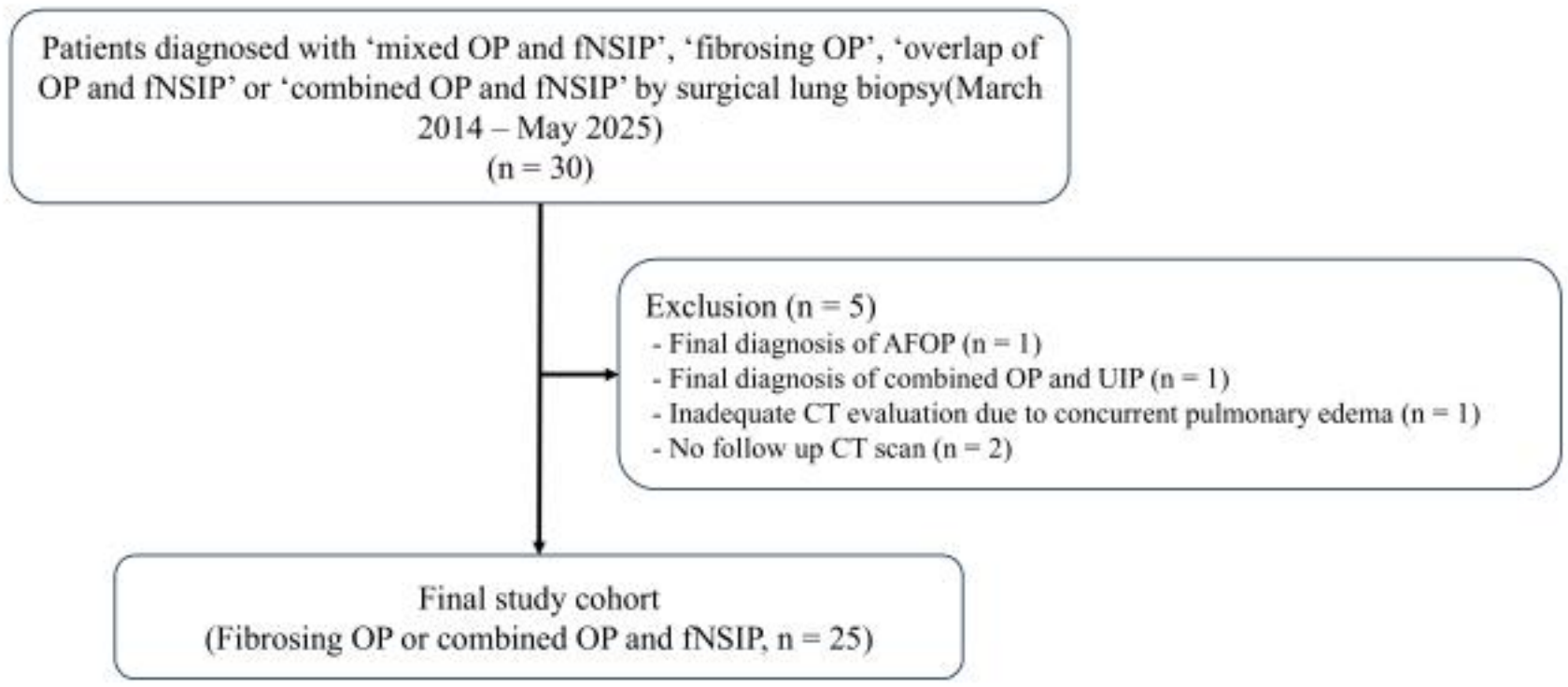

Patients diagnosed with 'mixed OP and fNSIP', 'fibrosing OP', 'overlap of OP and fNSIP' or 'combined OP and fNSIP' by surgical lung biopsy(March 2014 – May 2025)
(n = 30)
Exclusion (n = 5)
- Final diagnosis of AFOP (n = 1)
- Final diagnosis of combined OP and UIP (n = 1)
- Inadequate CT evaluation due to concurrent pulmonary edema (n = 1)
- No follow up CT scan (n = 2)
Final study cohort
(Fibrosing OP or combined OP and fNSIP, n = 25)

Figure 2

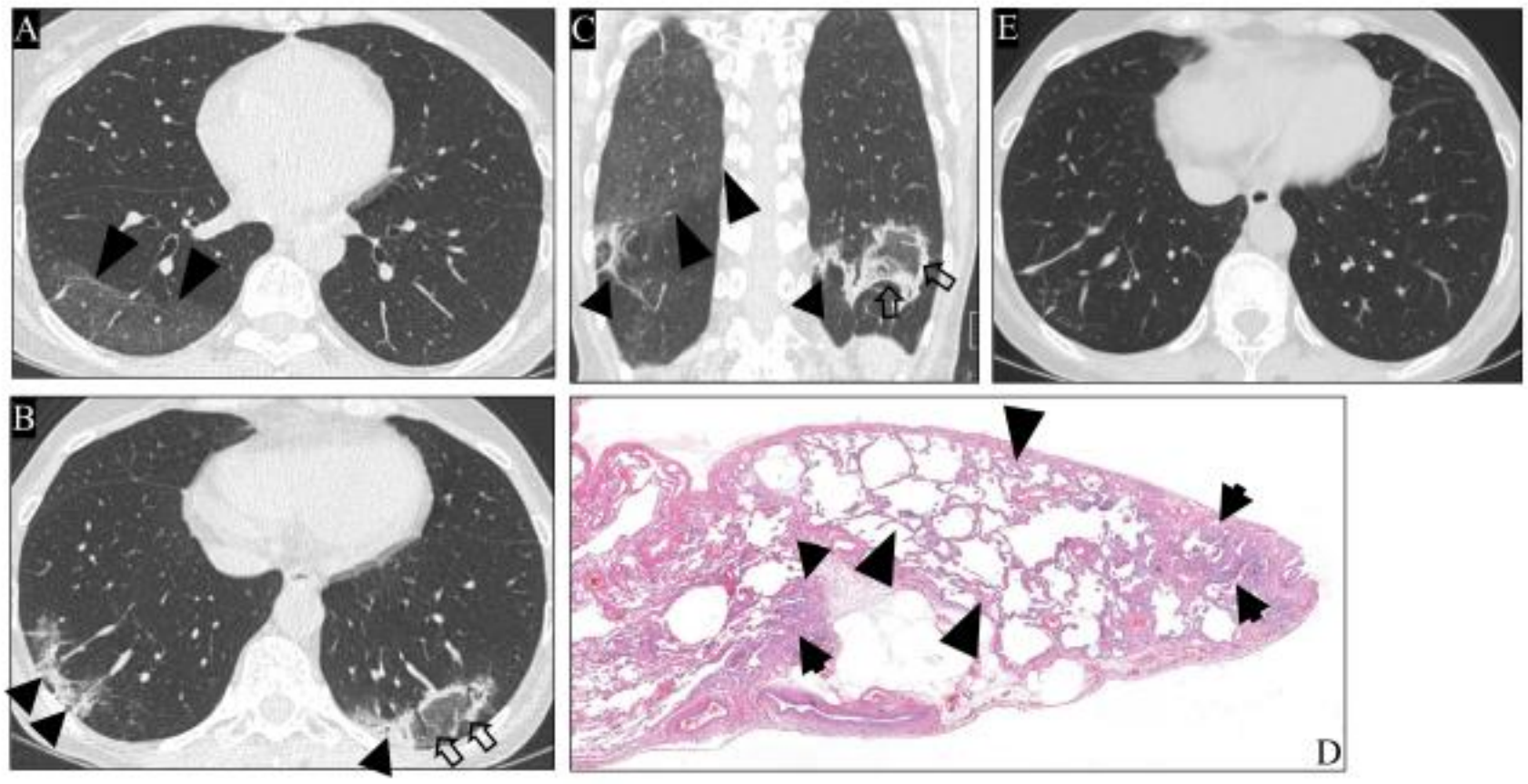


Figure 3.

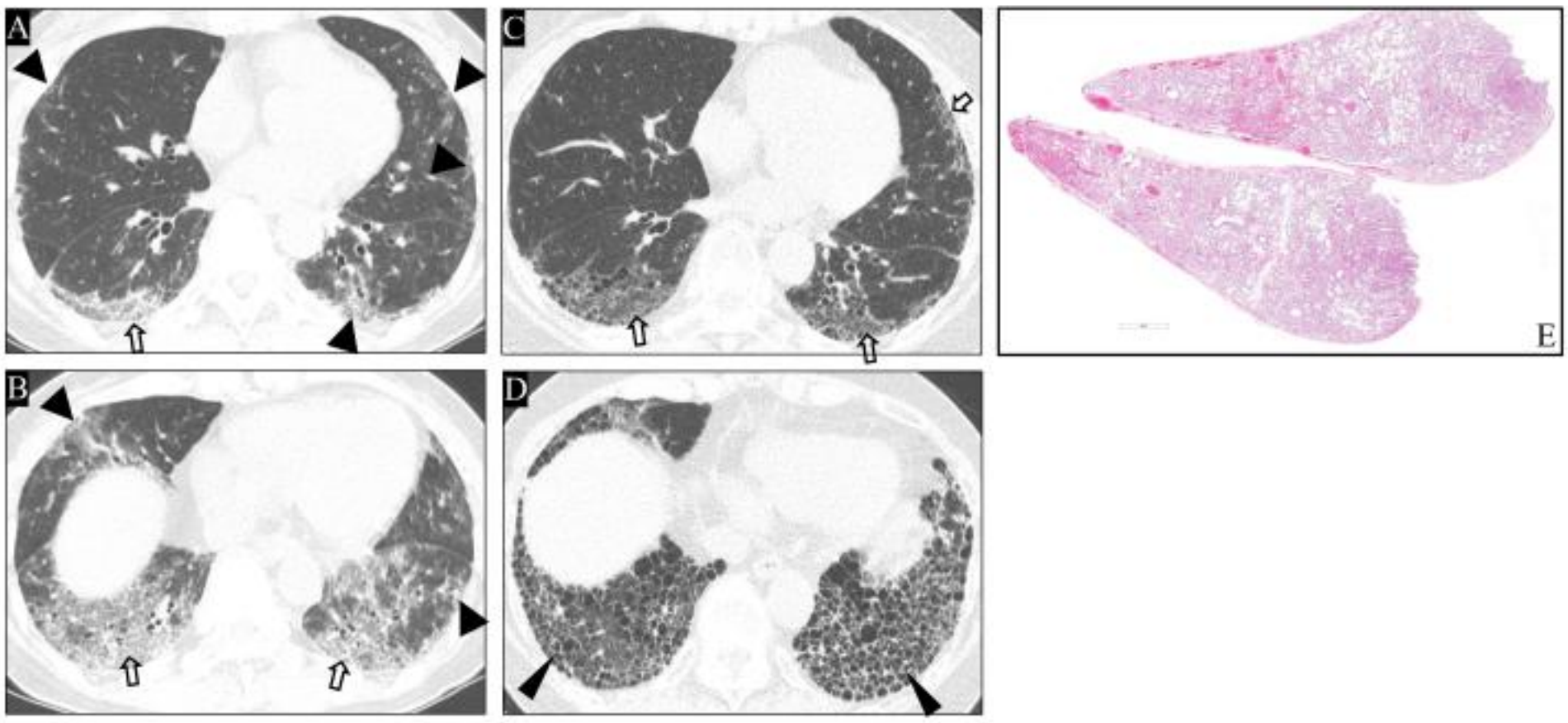
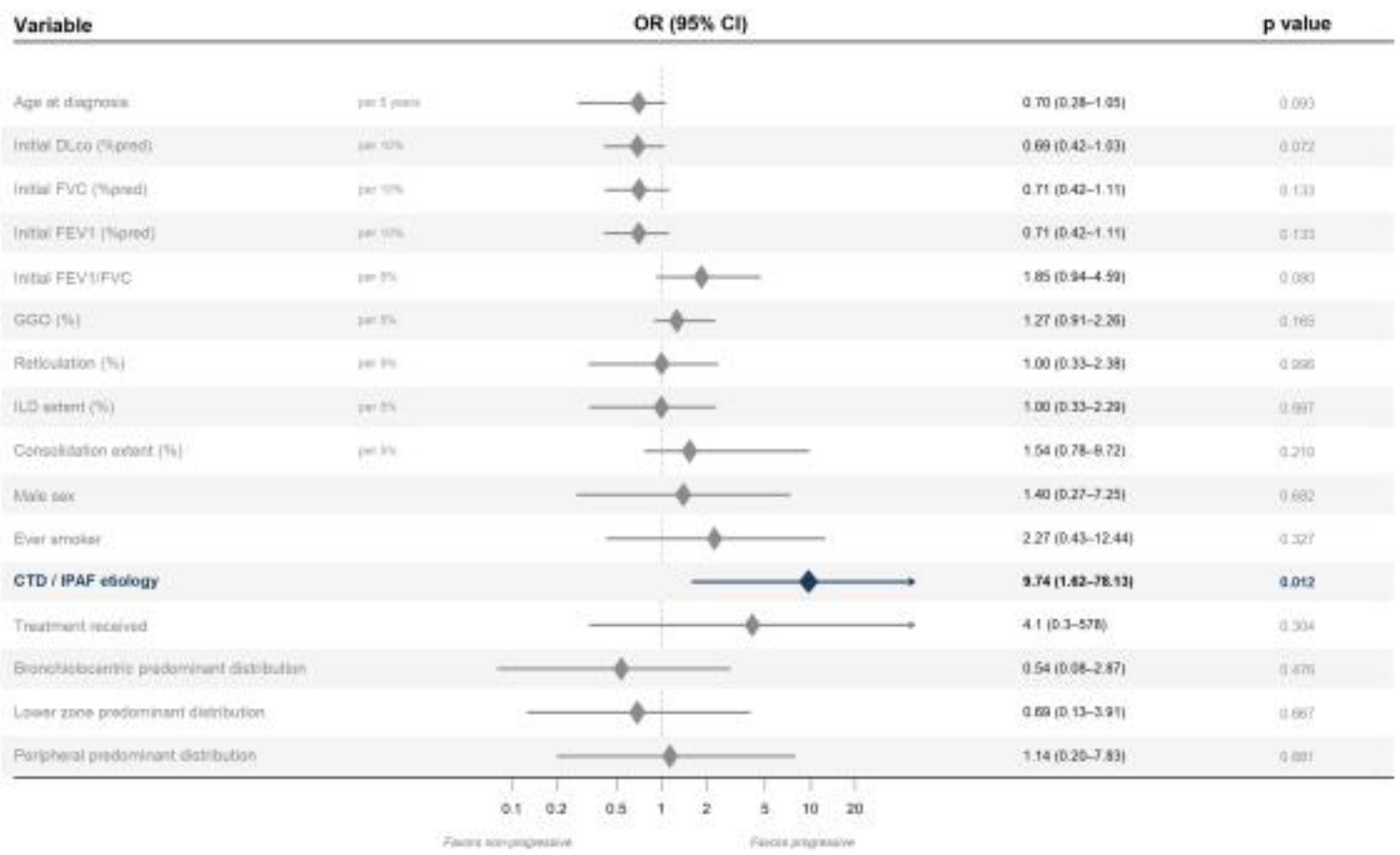


Figure 4.


Variable
OR (95% CI)
p value
Age at diagnosis
per 5 years
0.70 (0.28–1.05)
0.093
Initial DLco (%pred)
per 10%
0.69 (0.42–1.03)
0.072
Initial FVC (%pred)
per 10%
0.71 (0.42–1.11)
0.133
Initial FEV1 (%pred)
per 10%
0.71 (0.42–1.11)
0.133
Initial FEV1/FVC
per 5%
1.85 (0.94–4.59)
0.080
GGO (%)
per 5%
1.27 (0.91–2.26)
0.165
Reticulation (%)
per 5%
1.00 (0.33–2.38)
0.998
ILD extent (%)
per 5%
1.00 (0.33–2.29)
0.997
Consolidation extent (%)
per 5%
1.54 (0.78–8.72)
0.210
Male sex
1.40 (0.27–7.25)
0.682
Ever smoker
2.27 (0.43–12.44)
0.327
CTD / IPAF eSology
9.74 (1.62–78.13)
0.012
Treatment received
4.1 (0.3–578)
0.304
Bronchiolocentric predominant distribution
0.54 (0.08–2.87)
0.476
Lower zone predominant distribution
0.69 (0.13–3.91)
0.667
Peripheral predominant distribution
1.14 (0.20–7.83)
0.881
0.1
0.2
0.5
1
2
5
10
20
Favors non-progressive
Favors progressive

[Supplementary material]

Fibrosing Organizing Pneumonia Seen in Patients with Autoimmune Features or Connective Tissue Disease Shows a Tendency of Progressive Disease

Methods

Patients' selection

Five patients were excluded for the following reasons: (1) final diagnosis of acute fibrinous and organizing pneumonia (AFOP) was made upon histopathological review, but the initial CT obtained at the time of SLBx demonstrated unilateral disease (n = 1); (2) final diagnosis of combined OP and UIP upon pathology review, as the initial biopsy showed a mixture of OP, fNSIP, and UIP (n = 1); (3) inability to accurately evaluate the pattern and extent of interstitial lung disease on CT, as the SLBx was obtained after managing concurrent pulmonary edema (n = 1); and (4) lack of follow-up CT scans (n = 2).

Clinical Data Collection and evaluation

Patient demographics, smoking history, and underlying comorbidities—including specific connective tissue diseases (e.g., rheumatoid arthritis, systemic sclerosis, myositis), interstitial pneumonia with autoimmune features (IPAF), and other chronic or neoplastic conditions—were extracted from electronic medical records. Concurrently, serologic profiles [e.g., fluorescent antinuclear antibody (FANA), rheumatoid factor, anti-CCP antibody, and myositis-specific antibodies] were evaluated. The total number of positive serologic markers per patient was calculated to assess potential associations with treatment outcomes and follow-up CT findings, such as complete resolution or the extent of residual reticulation.

Initial and follow-up pulmonary function test parameters, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, and diffusing capacity of the lung for carbon monoxide (DLco), were recorded. Six-minute walk test (6MWT) distance, and nadir SpO2 were also recorded, along with bronchoalveolar lavage (BAL) fluid differential cell counts. Finally, we documented the clinical course of patient treatment, detailing the initiation, cessation, and modification of corticosteroid or immunosuppressant therapies, including specific agents administered during disease recurrence.

CT acquisition

CT examinations were performed using various multidetector CT scanners, including the Discovery CT 750HD, Revolution Frontier, and Revolution Apex (GE Healthcare, Chicago,

IL, USA); the SOMATOM Force (Siemens Healthineers, Erlangen, Germany); and the Aquilion ONE Genesis and Prism (Canon Medical Systems, Otawara, Japan). After scanning the whole thorax with a helical technique, thin-section CT images were reconstructed with a 1.25-mm section thickness from the lung apices to the bases at end-inspiration. Images were reconstructed using a high-spatial-frequency (bone) algorithm and viewed on standard lung window settings (window width, 1500 HU; window level, -700 HU).

CT imaging analyses

Automated quantitative CT (qCT) analysis was conducted by the use of deep learning-based texture analysis software (AVIEW 1.1.46.22-win, Coreline Soft). This tool helps perform fully automatic segmentation of the lung parenchyma and classify ILD features into being ground-glass opacity (GGO), consolidation, reticulation, and honeycombing, providing quantification results as absolute percentages of total lung volume.

The observers (K.S.L. and D.Y.J., with 34 and 10 years of experience, respectively) subjectively assessed the overall and relative extent of pulmonary parenchymal abnormalities, including consolidation, GGO, reticulation, and honeycombing, defined according to the Fleischner Society glossary of terms and at six levels of CT scans as described previously.[1, 2] The distribution of lung abnormalities was classified on axial images as being subpleural, central, bronchocentric/bronchiolocentric, or random, and on coronal reformation images as being upper- (above the aortic arch), middle- (between the aortic arch and the right inferior pulmonary vein), or lower-zone (below the right inferior pulmonary vein to the lung base) predominant.

Sensitivity analysis

In the sensitivity analysis using an alternative qCT threshold to assess the robustness of our findings to the choice of radiologic progression threshold, the radiologic component of PD was redefined as an increase in qCT-derived fibrosis extent of at least 2.2 percentage points, while the FVC criterion remained unchanged. This lower threshold was chosen, based on a recent qCT study where a smaller increase in fibrosis extent could represent a clinically meaningful change in progressive pulmonary fibrosis.[3] According to another recent study, the 1-year minimal clinically important difference for qCT fibrosis score was also reported to

be 2.24%, and exceeding this threshold was associated with reduced transplant-free survival. Therefore, this sensitivity analysis was performed to determine whether the main findings were preserved when applying a more sensitive qCT-based definition of radiologic progression.[4]

Results

Demographics and baseline characteristics

Five patients with CTD included one with rheumatoid arthritis, three with dermatomyositis/polymyositis, and one with Sjögren syndrome. The two patients with IPAF had anti-RNP antibody with FANA 1:640 and anti-Jo-1 antibody, respectively. Five of the seven patients with CTD/IPAF were women and two were men.

Surgical lung biopsy specimens were obtained at multiple sites (≥2 lobes) in 14 patients and at a single site in 11 patients (one patient had unspecified biopsy sites in pathology records). Among 39 biopsy sites, the right lower lobe was the most frequently biopsied site (n = 19), followed by the right middle lobe (n = 13), left lower lobe (n = 3), right upper lobe (n = 2), left upper lobe (n = 1), and right lung with unspecified lobar location (n = 1). The median interval between the initial CT study and surgical lung biopsy was 5 days (mean, 29.3 days; range, 0–196 days).

The 6-minute walk test was performed in 13 patients, with a median walking distance of 481 m (IQR, 408–585) and a median nadir SpO_2 of 89.0% (IQR, 86.0–92.0). BAL data were available in 14 patients, with a median lymphocyte proportion of 30.0% (IQR, 10.0–40.0).

Treatment and disease outcomes

Of eight PD patients, two met both physiologic and radiologic criteria, three met only the radiologic criterion, and three met only the physiologic criterion. Among the 19 patients who received immunosuppressants, seven (36.8%) started on the same day as corticosteroids, while 12 (63.2%) had immunosuppressants added subsequently. Follow-up duration did not differ significantly between the PD and non-PD groups (median, 80.8 vs. 49.6 months; $p = 0.140$).

Objective improvement within non-progressive patients

Among the 17 non-PD patients, eight (47.1%) met criteria for objective improvement and nine (52.9%) remained stable under the strict main criteria. Among eight improved patients, four met only the FVC increase criterion, two met only the fibrosis decrease criterion, and 2 met both criteria. Seven of 8 improved patients had idiopathic disease, and 1 had CTD. Because progression took precedence over improvement in the outcome hierarchy, one patient who met both improvement criterion and progression criterion (FVC change, +68.9%; fibrosis change, +11.77%) was classified as PD rather than ID. Across three outcome groups, baseline DLco differed significantly (p = 0.017), and CTD/IPAF etiology was observed predominantly in the progressive group (5/8 [62.5%] in PD, 1/9 [11.1%] in SD, and 1/8 [12.5%] in ID; p = 0.068). Follow-up findings also differed across three groups, including last FVC (p = 0.009), last DLco (p = 0.048), FVC change (p = 0.009), follow-up reticulation (p = 0.024), follow-up fibrosis extent (p = 0.020), and fibrosis change (p = 0.001), whereas GGO change did not differ significantly (p = 0.285).

In the direct comparison between stable and improved patients, initial reticulation extent (p = 0.046) and fibrosis extent (p = 0.046) were significantly higher in improved than stable patients. Lower initial DLco showed an association with improvement on Firth penalized logistic regression (OR per 10%, 0.52; 95% CI, 0.19–0.91; p = 0.017), although this finding should be interpreted cautiously given the small sample size (n = 17). Reticulation extent (OR per 5%, 3.44; 95% CI, 0.89–36.96; p = 0.088) and fibrosis extent (OR per 5%, 3.32; 95% CI, 0.88–35.40; p = 0.094) showed trends but did not reach significance on Firth regression. Among follow-up variables, improved patients showed a greater decrease in fibrosis extent (OR, 0.41; 95% CI, 0.09–0.79; p = 0.002), greater FVC improvement (p = 0.043), and more frequent symptom improvement (62.5% vs 11.1%; p = 0.050). The concordance between the objective three-group classification and subjective symptom outcome was 64.0% (16/25). Detailed results were summarized in Supplementary Tables 1 and 2.

Sensitivity analysis

Because the main analysis used strict outcome criteria, we performed additional sensitivity analyses using alternative definitions of improvement and radiologic progression. In the sensitivity analysis using a lower radiologic progression threshold of 2.2%, two

additional patients were reclassified as PD, increasing the number of PD patients to 10 of 25 (40.0%). With this threshold, CTD/IPAF showed a trend (P = .075), whereas DLco was no longer significant (p = 0.212; AUC, 0.653). Follow-up qCT measures became more strongly associated with PD, including fibrosis change (p = 0.001), honeycombing change (p = 0.005), and significant honeycombing emergence (p = 0.023). FVC decline (p = 0.002) and last FVC (p = 0.001) remained significant. qCT–visual agreement decreased from $\kappa = 1.000$ to $\kappa = 0.694$. (Supplementary Table 3)

In an additional sensitivity analysis applying the INBUILD criteria, defining PD as (a) relative FVC decline (percent-predicted) ≥10%, (b) relative FVC decline (percent-predicted) 5%–10% with symptom worsening, or (c) relative FVC decline (percent-predicted) 5%–10% with concurrent qCT fibrosis increase ≥ 3.4 percentage points, PD decreased from 8 to 5 patients (20.0%). No patient met criterion (b) or (c); all 5 PD patients met criterion (a) alone. Under these criteria, the three patients with isolated qCT fibrosis increase ≥ 3.4 percentage points but FVC decline <5% were reclassified as non-PD, and the associations between PD and qCT fibrosis change (p = 0.192), honeycombing change (p = 0.447), baseline DLco (p = 0.475), and CTD/IPAF (p = 0.113) were no longer significant. Only FVC decline (p = 0.001) and last FVC (p = 0.008) remained significant, reflecting the tautological relationship with the FVC-only PD definition. When the INBUILD criteria were applied with a 2.2% qCT threshold for criterion (c), one additional patient met this criterion, increasing PD to 6 (24.0%), but qCT-related associations remained largely nonsignificant (fibrosis change p = 0.121; honeycombing change p = 0.198). These findings underscore the added value of qCT fibrosis extent as an independent progression criterion for detecting subclinical radiologic progression not captured by FVC-based criteria alone.

Table S1. Sensitivity Analysis Using Alternative Radiologic Threshold (≥2.2%)

Variable	Non-PD (n = 15)	PD (n = 10)	P value
Baseline			
CTD/IPAF etiology, n (%)	2/15 (13.3)	5/10 (50.0)	0.075
Initial DLco, % predicted	75.0 (61.5–88.0)	62.0 (46.2–73.8)	0.212
Follow-up			
FU fibrosis extent, %	0.8 (0.2–1.4)	7.3 (2.8–13.8)	0.001
qCT fibrosis change, %	-1.4 (-3.2–-0.2)	4.1 (2.5–7.8)	0.001
HC change, %	0.000 (-0.009–0.003)	1.182 (0.063–3.358)	0.005
Emergence of significant HC (≥1%), n (%)	1/15 (6.7)	5/10 (50.0)	0.023
Last FVC, % predicted	92.0 (83.0–97.0)	67.0 (49.2–81.2)	0.001
Last DLco, % predicted	75.0 (65.5–85.0)	60.0 (44.2–66.5)	0.046
Relative FVC decline, %	-6.4 (-20.9–-3.4)	11.8 (2.6–16.8)	0.002
Symptom aggravated, n (%)	0/15 (0.0)	3/10 (30.0)	0.052

Note.— P values were calculated using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. CTD = connective tissue disease, DLco = diffusing capacity for carbon monoxide, FVC = forced vital capacity, HC = honeycombing, IPAF = interstitial pneumonia with autoimmune features, PD = progressive disease, qCT = quantitative computed tomography.

Table S2. Baseline and Follow-up Findings Across Three Outcome Groups

Variable	Improved (n = 8)	Stable (n = 9)	Progressive (n = 8)	P value
Baseline				
Age, yr	57.8 (52.2–59.4)	61.8 (56.5–67.7)	55.6 (53.7–58.4)	0.157
CTD/IPAF, n (%)	1/8 (12)	1/9 (11)	5/8 (62)	0.068
Treatment, n (%)	7/8 (88)	7/9 (78)	8/8 (100)	0.750
Initial DLco, % predicted	61.5 (51.5–79.2)	87.0 (71.0–95.0)	51.5 (45.0–73.2)	0.017
Initial FVC, % predicted	81.5 (62.8–87.5)	83.0 (78.0–89.0)	67.5 (53.8–86.0)	0.335
Reticulation (qCT), %	4.7 (2.3–7.3)	0.6 (0.5–1.6)	2.6 (1.7–5.4)	0.071
Fibrosis extent (qCT), %	4.7 (2.3–7.3)	0.6 (0.5–1.7)	2.6 (1.8–5.4)	0.074
GGO (qCT), %	6.8 (1.8–12.7)	2.4 (1.9–5.4)	7.7 (4.9–12.1)	0.112
Consolidation (qCT), %	0.5 (0.3–1.3)	0.1 (0.0–0.3)	1.0 (0.1–2.3)	0.123
Follow-up				
GGO change, %	-6.1 (-10.9–-1.3)	-1.9 (-3.7–-0.7)	-5.2 (-6.9–-1.5)	0.285
Fibrosis change, %	-3.2 (-5.0–-1.8)	-0.1 (-0.5–0.5)	5.7 (1.8–9.2)	0.001
HC change, %	0.002 (-0.012–0.011)	0.001 (-0.000–0.002)	1.182 (0.002–4.157)	0.098
FVC change (+ = improved), %	17.5 (11.0–21.8)	3.4 (0.0–5.1)	-15.1 (-19.0–-3.2)	0.009
FU Reticulation, %	0.8 (0.3–1.6)	1.0 (0.5–3.1)	7.8 (2.4–9.8)	0.024
FU Fibrosis extent, %	0.8 (0.3–1.6)	1.0 (0.5–3.3)	9.0 (2.4–15.3)	0.020
Last FVC, % predicted	92.5 (84.5–99.5)	83.0 (83.0–92.0)	61.0 (45.8–78.0)	0.009
Last DLco, % predicted	65.5 (44.5–88.0)	75.0 (70.0–82.0)	56.5 (38.5–62.0)	0.048

Note.— Continuous variables are presented as median (interquartile range), and categorical variables as number (%). P values from Kruskal-Wallis test. CTD = connective tissue disease, DLco = diffusing capacity for carbon monoxide, FVC = forced vital capacity, GGO = ground-glass opacity, HC = honeycombing, IPAF = interstitial pneumonia with autoimmune features, qCT = quantitative computed tomography.

Table S3. Direct Comparison Between Stable and Improved Patients

Variable	Stable (n = 9)	Improved (n = 8)	P value	OR (95% CI)	P value
Baseline characteristics					
Age, per 5 years	61.8 (56.5–67.7)	57.8 (52.2–59.4)	0.229	0.60 (0.25–1.21)	0.162
Initial FVC, per 10%	83.0 (78.0–89.0)	83.0 (62.8–95.8)	0.531	0.79 (0.41–1.34)	0.380
Initial FEV1, per 10%	88.0 (81.0–98.0)	87.0 (60.8–94.8)	0.630	0.78 (0.43–1.30)	0.345
Initial FEV1/FVC, per 5%	80.0 (79.0–82.0)	80.0 (78.0–83.5)	1.000	1.15 (0.52–2.83)	0.728
Initial DLco, per 10%	87.0 (71.0–95.0)	61.5 (51.5–79.2)	0.024	0.52 (0.19–0.91)	0.017
BAL lymphocyte, per 10%	19.5 (12.2–35.0)	40.0 (32.5–47.5)	0.316	1.50 (0.81–3.78)	0.210
Cytospin lymphocyte, per 10%	29.0 (16.5–40.0)	29.5 (22.2–40.5)	0.914	1.21 (0.62–2.68)	0.574
Male, n (%)	4/9 (44.4)	3/8 (37.5)	1.000		
Ever smoker, n (%)	2/9 (22.2)	3/8 (37.5)	0.620		
CTD/IPAF, n (%)	1/9 (11.1)	1/8 (12.5)	1.000		
Treatment, n (%)	7/9 (77.8)	7/8 (87.5)	1.000		
Baseline qCT					
GGO, per 5%	2.4 (1.9–5.4)	6.8 (1.8–12.7)	0.321	1.74 (0.84–6.41)	0.154
Reticulation, per 5%	0.6 (0.5–1.6)	4.7 (2.3–7.3)	0.046	3.44 (0.89–36.96)	0.088
Honeycombing	0.00 (0.00–0.01)	0.01 (0.00–0.02)	0.350	3.94 (0.10–5208.39)	0.467
Fibrosis extent, per 5%	0.6 (0.5–1.7)	4.7 (2.3–7.3)	0.046	3.32 (0.88–35.40)	0.094
Distribution					
Lower predominant, n (%)	6/9 (66.7)	6/8 (75.0)	1.000		
Peripheral, n (%)	6/9 (66.7)	6/8 (75.0)	1.000		
Bronchiolocentric, n (%)	4/9 (44.4)	3/8 (37.5)	1.000		
Follow-up					
Follow-up GGO	0.6 (0.3–2.7)	0.5 (0.3–1.4)	0.423		
Follow-up reticulation	1.0 (0.5–3.1)	0.8 (0.3–1.6)	0.888		
Follow-up fibrosis extent	1.0 (0.5–3.3)	0.8 (0.3–1.6)	0.888		
Fibrosis change, %	−0.1 (−0.5–0.5)	−3.2 (−5.0–−1.8)	0.004	0.41 (0.09–0.79)	0.002
GGO change, %	−1.9 (−3.7–−0.7)	−6.1 (−10.9–−1.3)	0.236		
HC change, %	0.001 (−0.000–0.002)	0.002 (−0.012–0.011)	0.963		
Last FVC, % predicted	83.0 (83.0–92.0)	92.5 (84.5–99.5)	0.412		
Last DLco, % predicted	75.0 (70.0–82.0)	65.5 (44.5–88.0)	0.413		
FVC change (+ = improved), %	3.4 (0.0–5.1)	17.5 (11.0–21.8)	0.043		
HC emergence ≥1%, n (%)	1/9 (11.1)	1/8 (12.5)	1.000		
Symptom improved, n (%)	1/9 (11.1)	5/8 (62.5)	0.050		

Note.— Progressive patients were excluded. Continuous variables are median (IQR). P values: Mann-Whitney U test or Fisher's exact test. Firth penalized logistic regression for baseline variables; follow-up variables descriptive only. Fibrosis change Firth OR included as it was predefined in the analysis plan.

Figure S1. Serial clinical and CT findings in a 54-year-old man with fibrosing organizing pneumonia of idiopathic nature (A, B) Lung window of thin-section (1.25-mm section thickness) CT scans obtained at levels of the distal bronchus intermedius (A) and right inferior pulmonary vein (B), respectively, show patchy areas of ground-glass opacity (arrows) and reticular lesions (open arrows) in bilateral lungs. At this time, FVC and DLco were 58% and 45% of predicted values, respectively. qCT extents of ground-glass opacity and reticulation were 9.8% and 4.7%, respectively. (C) Photomicrograph (H & E, x 40) of surgical biopsy specimen obtained from right middle lobe discloses areas of organizing pneumonia with intra-alveolar granulation polyps (arrows) and even interstitial fibrosis (open arrows). Inset = areas of organizing pneumonia; RML =right middle lobe (D) Photomicrograph (H & E, x 40) of surgical biopsy specimen obtained from right lower lobe reveals mainly areas of even fibrous alveolar thickening (open arrows). RLL = right lower lobe (E, F) Lung window of thin-section (1.25-mm section thickness) CT scans obtained at similar levels to (A) and (B), respectively, approximately 8 years after (A) and (B), demonstrate patchy and extensive areas of reticulation. At this time, FVC and DLco were 56% and 31% of predicted values, respectively. qCT extent of reticulation was 9.5%.

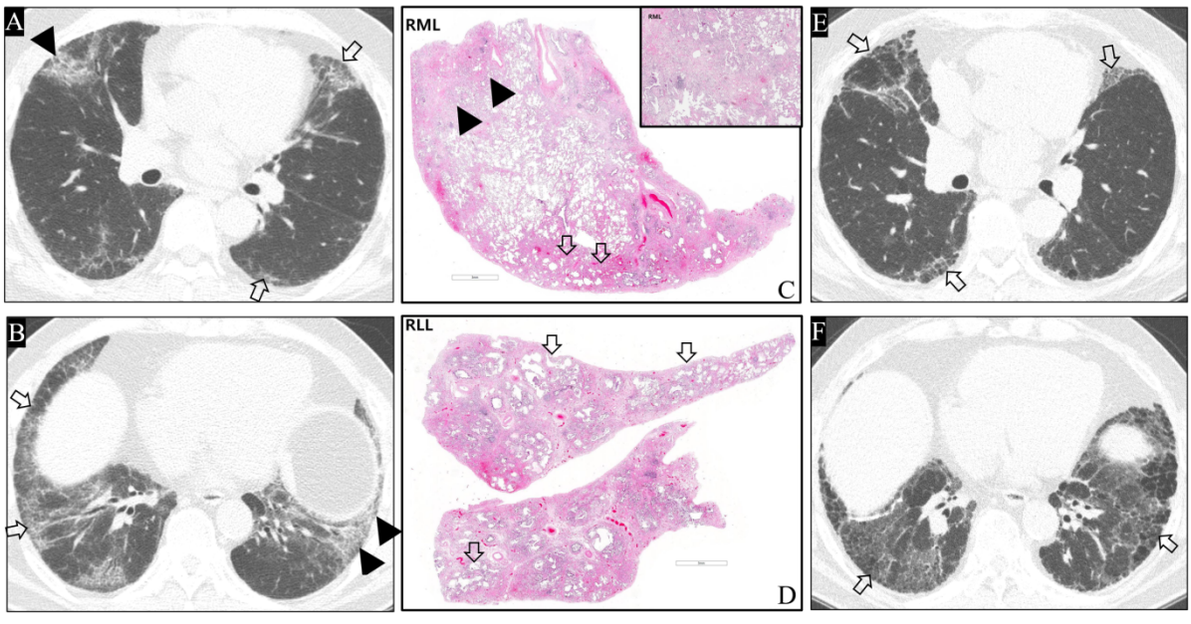


Figure S2. Serial clinical and CT findings in a 58-year-old woman with dermatomyositis/polymyositis and fibrosing organizing pneumonia (A, B) Lung window of thin-section (1.25-mm section thickness) CT scans obtained at levels of distal bronchus intermedius (A) and suprahepatic IVC (B), respectively, show subpleural reticulation (open arrows in A), consolidation (arrows in B) and juxtapleural bands (arrowhead in B). At this time, FVC and DLco were 56% and 50% of predicted value, respectively. qCT extents of consolidation and reticulation were 2.5% and 7.8%, respectively. (C, D) Photomicrographs of surgical biopsy specimen obtained from right lower lobe reveals areas of organizing pneumonia (arrows in C; H& E, x 100) and even interstitial fibrosis (open arrow in RLL part I). Also note dense interstitial fibrosis (open arrows in RLL part II; H& E, x 100) and lymphoid aggregates (arrowhead in D). (E, F) CT scans obtained at similar levels to A and B, respectively, and eight and a half years after A & B, demonstrate subpleural dense band-like fibrosis (open arrows E) containing internal calcifications (small arrow E). Also note areas of honeycombing (open arrows in F) and coarse reticulation (open arrows in F). At this time, FVC, FEV1 and DLco were 42%, 48% and 54% of predicted value, respectively. qCT extents of reticulation and honeycombing were 10.1% and 6.2%, respectively.

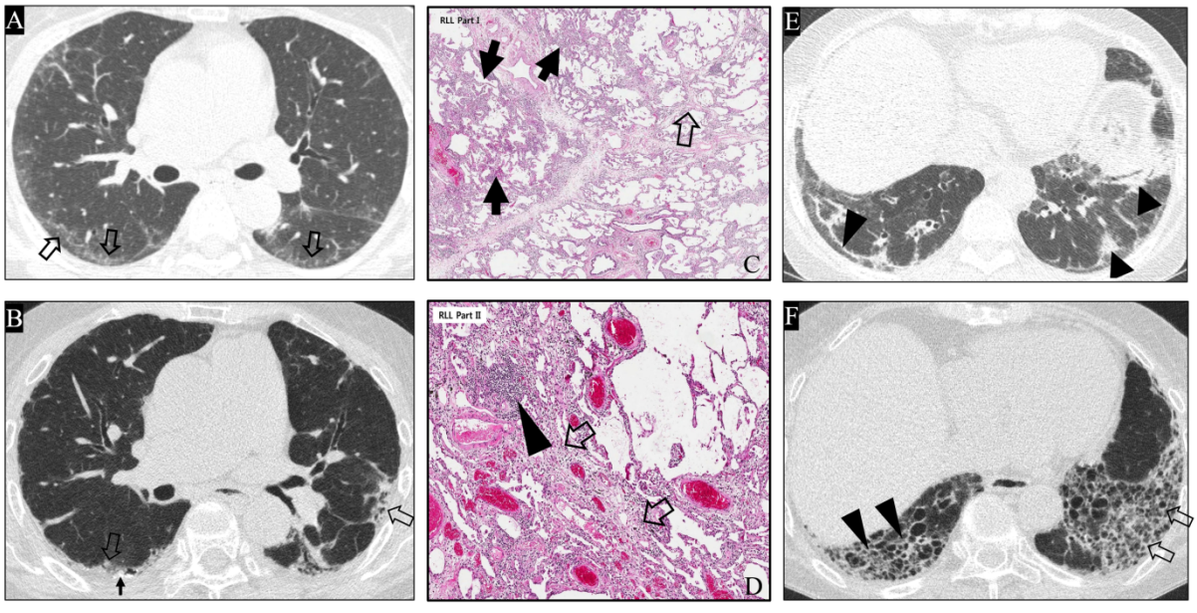
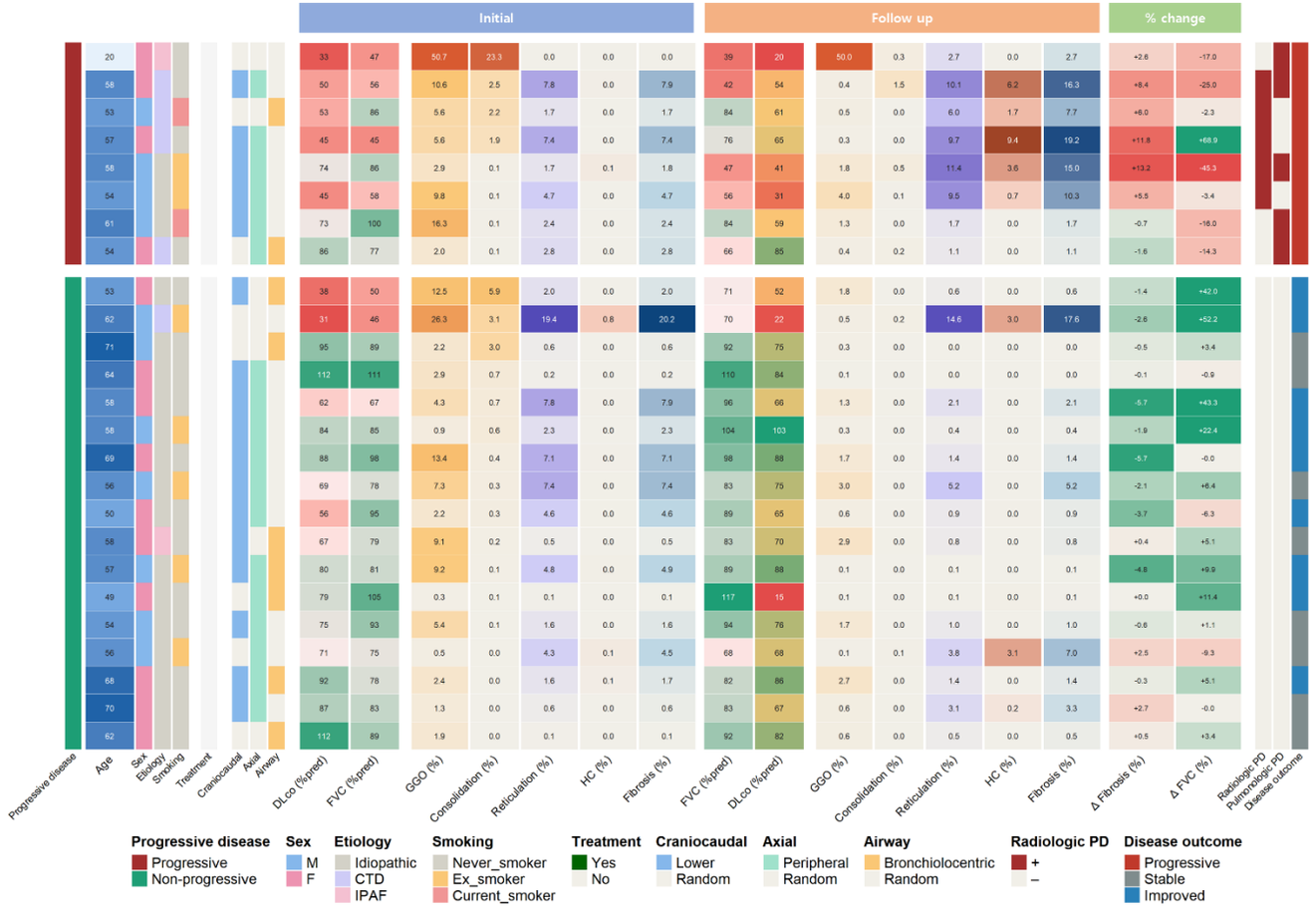


Figure S3. Individual patient characteristics and outcomes



Note. — Each column represents one patient, sorted by disease outcome (progressive → stable → improved) and baseline DLco. Sections from left to right: demographics; initial PFT (DLco, FVC); initial CT (qCT-derived GGO, reticulation, HC, fibrosis, and visual consolidation); distribution pattern; follow-up PFT (FVC, DLco); follow-up qCT; quantitative changes (Δ fibrosis, Δ FVC); and outcome (HC emergence, radiologic/pulmonologic PD, symptom, disease outcome). All CT texture percentages represent qCT-derived values unless otherwise specified. DLco = diffusing capacity of the lung for carbon monoxide; Dist = distribution; FU = follow-up; FVC = forced vital capacity; GGO = ground-glass opacity; HC = honeycombing; PD = progressive disease; Δ = change.

Reference

1. A. A. Bankier, H. MacMahon, T. Colby, et al., "Fleischner Society: glossary of terms for thoracic imaging," *Radiology* 310, no. 2 (2024): e232558.
2. K. M. Shin, K. S. Lee, M. P. Chung, et al., "Prognostic determinants among clinical, thin-section CT, and histopathologic findings for fibrotic idiopathic interstitial pneumonias: tertiary hospital study," *Radiology* 249, no. 1 (2008): 328–337.
3. Y. Ahn, H. C. Kim, J. K. Lee, et al., "Usefulness of CT quantification-based assessment in defining progressive pulmonary fibrosis," *Academic Radiology* 31, no. 11 (2024): 4696–4708.
4. S. Park, M.-J. Kim, J. H. Lee, et al., "Quantitative CT Imaging in Progressive Pulmonary Fibrosis: Clinical Usefulness and Meaningful Threshold Definition," *Chest* 169, no. 5 (2026): 1255–1266.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	✔ (N/A)
Title and abstract			
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✔
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✔
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✔
Objectives	3	State specific objectives, including any prespecified hypotheses	✔
Methods			
Study design	4	Present key elements of study design early in the paper	✔
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✔
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	✔
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	✔
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✔
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✔
Bias	9	Describe any efforts to address potential sources of bias	✔
Study size	10	Explain how the study size was arrived at	✔
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✔
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✔
		(*b*) Describe any methods used to examine subgroups and interactions	✔
		(*c*) Explain how missing data were addressed	✔
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	✔
		(*e*) Describe any sensitivity analyses	✔

Results			✔ (N/A)
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✔
		(b) Give reasons for non-participation at each stage	✔
		(c) Use a flow diagram and include the figure number (preferably figure 1) or page number	✔
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✔
		(b) Indicate number of participants with missing data for each variable of interest	✔
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	✔
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	✔
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	✔
		Cross-sectional study—Report numbers of outcome events or summary measures	✔
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✔
		(*b*) Report category boundaries when continuous variables were categorized	✔
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	✔
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✔
Discussion			
Key results	18	Summarise key results with reference to study objectives	✔
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✔
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✔
Generalisability	21	Discuss the generalisability (external validity) of the study results	✔
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✔

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

*N/A stands for not applicable and may be a reasonable choice depending on the type of study performed