인제대학교
INJE UNIVERSITY

"호흡기내과 의사를 위한 Respiratory Review of 2022"

Interstitial lung disease

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- IPF
  - Risk factors: maternal smoking
  - Diagnosis: cryobiopsy
  - The visual tool for the assessment: R-scale
  - Prognosis: monocyte count
  - Treatment: antifibrotics, pirfenidone + inhaled N-acetylcysteine, antimicrobial therapy
  - Acute exacerbation: cyclophosphamide + glucocorticoid

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- Drug induced ILD
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Tobacco Smoking and Risk for Pulmonary Fibrosis

A Prospective Cohort Study From the UK Biobank

CHEST 2021; 160(3):983-993

Vanesa Bellou, MD; Lazaros Belbasis, MD, PhD; and Evangelos Evangelou, MPH, PhD

Maternal smoking around birth
Smoking statue
Age stared smoking
Age stopped smoking
Presence of smokers in the household
Number of cigarettes smoked per day

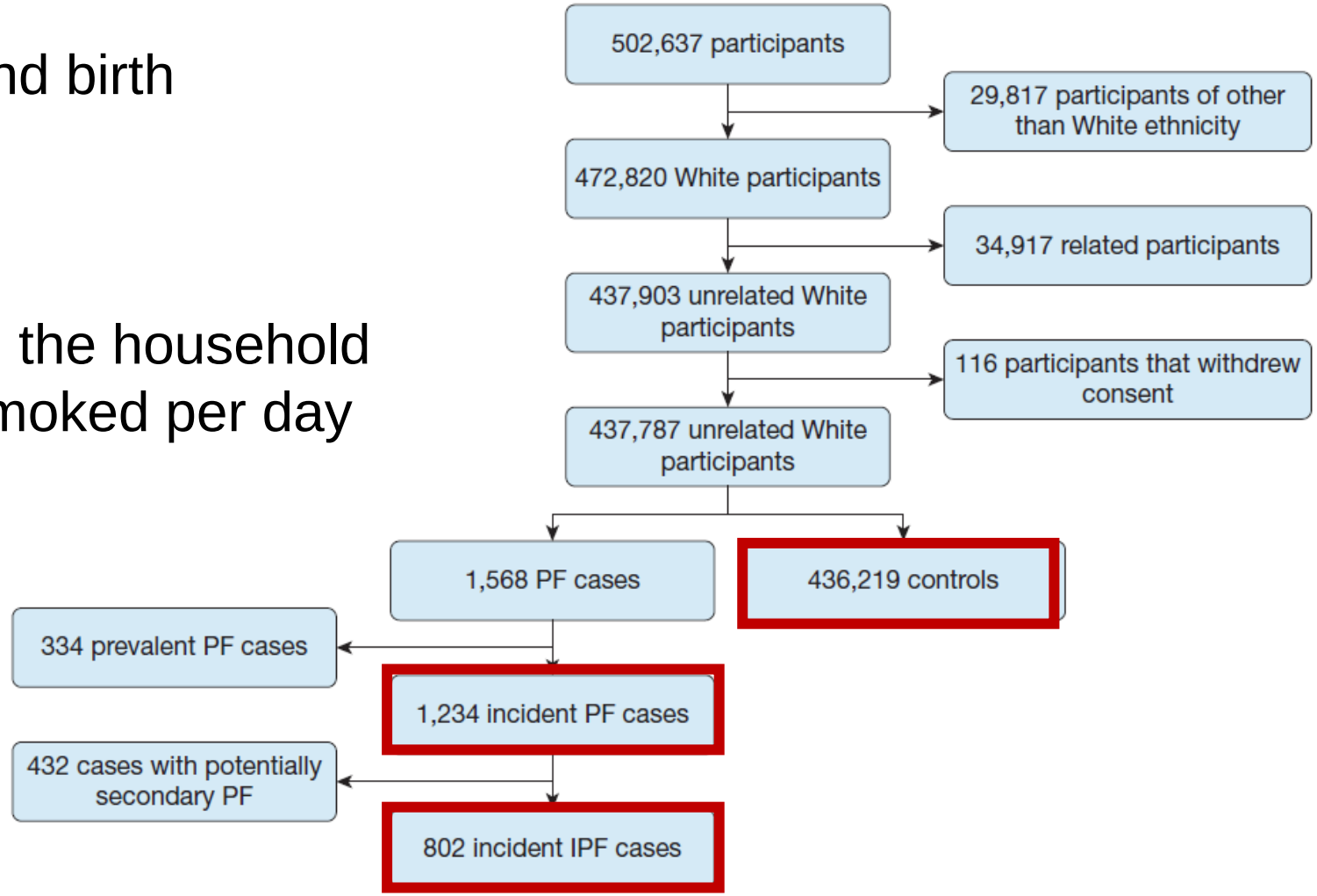


TABLE 2] Multivariable Analysis of Smoking Status and Maternal and Household Smoking for Risk of Pulmonary Fibrosis and IPF in Imputed Data

Exposure	Level of Exposure	Pulmonary Fibrosis			IPF		
		HR (95% CI)	*P* Value	E Value[a]	HR (95% CI)	*P* Value	E Value[a]
Age at recruitment	Per 1-y increase	1.129 (1.117-1.140)	9.98×10^{-125}	NA	1.145 (1.130-1.160)	1.86×10^{-92}	NA
Sex	Male vs female	1.460 (1.302-1.638)	9.84×10^{-11}	NA	1.861 (1.607-2.156)	1.06×10^{-16}	NA
Townsend index	Per 1-unit increase	1.056 (1.037-1.074)	1.61×10^{-9}	NA	1.063 (1.040-1.086)	3.66×10^{-8}	NA
Home area population density	Urban vs rural	1.091 (0.922-1.292)	.311	NA	1.077 (0.873-1.327)	.489	NA
Ever smoking	Yes vs no	2.132 (1.882-2.414)	1.04×10^{-32}	3.686 (3.170)	2.116 (1.810-2.472)	4.16×10^{-21}	3.653 (3.021)
Maternal smoking	Yes vs no	1.341 (1.181-1.523)	7.60×10^{-6}	2.017 (1.643)	1.383 (1.181-1.621)	6.62×10^{-5}	2.111 (1.643)
Household smoking	Yes vs no	1.259 (1.051-1.508)	.013	1.830 (1.283)	1.264 (1.016-1.572)	.036	1.842 (1.143)

HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; NA = not applicable.

[a]For each association, we present the E value for the mean effect and the lower limit of 95% CI. For the adjustment variables (ie, age, sex, Townsend index, and home area population density), we did not calculate an E value because we did not aim to examine their association with risk for pulmonary fibrosis and IPF.

TABLE 3] Multivariable Analysis of Pack-Years of Smoking and Maternal and Household Smoking for Risk of Pulmonary Fibrosis and IPF in Imputed Data

Exposure	Level of Exposure	Pulmonary Fibrosis			IPF		
		HR (95% CI)	*P* Value	E Value[a]	HR (95% CI)	*P* Value	E Value[a]
Age at recruitment	Per 1-y increase	1.124 (1.109-1.138)	5.95×10^{-73}	NA	1.135 (1.117-1.154)	1.49×10^{-53}	NA
Sex	Male vs female	1.354 (1.176-1.560)	2.66×10^{-5}	NA	1.674 (1.397-2.007)	2.49×10^{-8}	NA
Townsend index	Per 1-unit increase	1.038 (1.017-1.060)	4.30×10^{-4}	NA	1.043 (1.017-1.070)	.001	NA
Home area population density	Urban vs rural	1.139 (0.923-1.405)	.224	NA	1.123 (0.867-1.454)	.378	NA
Pack-years of smoking	Per 1-unit increase	1.012 (1.009-1.015)	4.44×10^{-16}	1.122 (1.104)	1.012 (1.008-1.016)	1.08×10^{-11}	1.122 (1.098)
Maternal smoking	Yes vs no	1.327 (1.143-1.540)	2.12×10^{-4}	1.986 (1.547)	1.455 (1.212-1.747)	6.33×10^{-5}	2.269 (1.719)
Household smoking	Yes vs no	1.117 (0.901-1.384)	.310	1.000	1.139 (0.882-1.473)	.318	1.000

HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; NA = not applicable.

[a]For each association, we presented the E value for the mean effect and the lower limit of 95% CI. For the adjustment variables (ie, age, sex, Townsend index, and home area population density), we did not calculate an E value because we did not aim to examine their association with risk of pulmonary fibrosis.

TABLE 4] Interaction of Maternal Smoking and Smoking Status for Risk of Pulmonary Fibrosis in Imputed Data

Variable	Maternal Smoking		HR (95% CI) for Maternal Smoking Within Strata of Smoking Status
	No	Yes	
Never smokers	Reference	1.24 (0.98-1.57) $P = .069$	1.24 (0.98-1.56) $P = .074$
Ever smokers	2.07 (1.78-2.42) $P = 1.90 \times 10^{-20}$	2.89 (2.43-3.45) $P = 1.69 \times 10^{-32}$	1.40 (1.20-1.62) $P = 1.08 \times 10^{-5}$
HR (95% CI) for smoking status within strata of maternal smoking	2.05 (1.76-2.40) $P = 1.51 \times 10^{-19}$	2.38 (1.91-2.96) $P = 1.62 \times 10^{-14}$	

Data are presented as HR (95% CI), unless otherwise indicated. HR = hazard ratio. The effect estimates are adjusted for age at recruitment, sex, Townsend index, and home population area density.

- Exposure to maternal smoking

  could impact fetal growth and lung development in the prenatal or postnatal period

Cryobiopsy for Identification of Usual Interstitial Pneumonia and Other Interstitial Lung Disease Features

Further Lessons from COLDICE, a Prospective Multicenter Clinical Trial

Wendy A. Cooper[1,2,3], Annabelle Mahar[1], Jeffrey L. Myers[4], Christopher Grainge[5], Tamera J. Corte[2,6,7], Jonathan P. Williamson[8,9], Michael P. Vallely[2], Simon Lai[10], Ellie Mulyadi[10], Paul J. Torzillo[2,6], Martin J. Phillips[9,11], Edmund M. T. Lau[2,6], Ganesh Raghu[12*], and Lauren K. Troy[2,6*]

Am J Respir Crit Care Med Vol 203, Iss 10, pp 1306–1313, May 15, 2021

- In COLDICE study in nine Australian tertiary hospitals

  histopathological agreement between TBLC and SLB was 70.8%

  diagnostic agreement at MDD was 76.9%

Lancet Respir Med 2020;8:171-81

- To characterize specific features of TBLC predictive of UIP in corresponding SLB and to identify clinical indices predictive of biopsy concordance

  (the overall agreement for idiopathic UIP in TBLC and SLB was 81.5%)

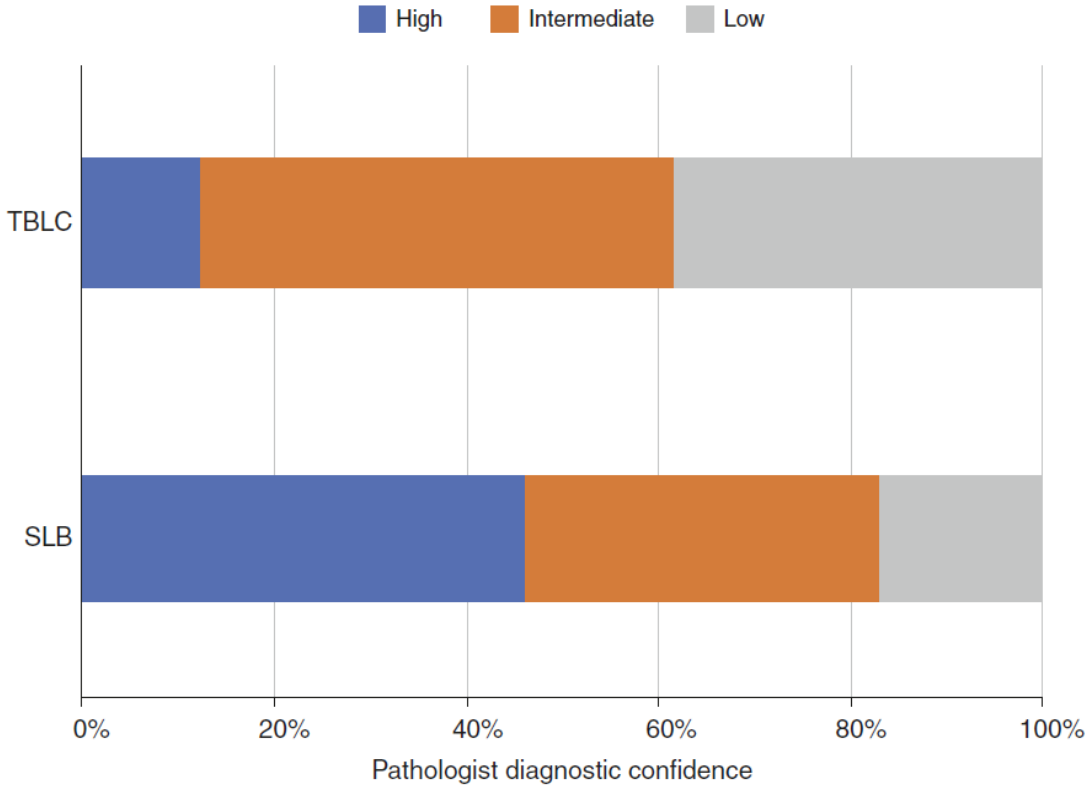
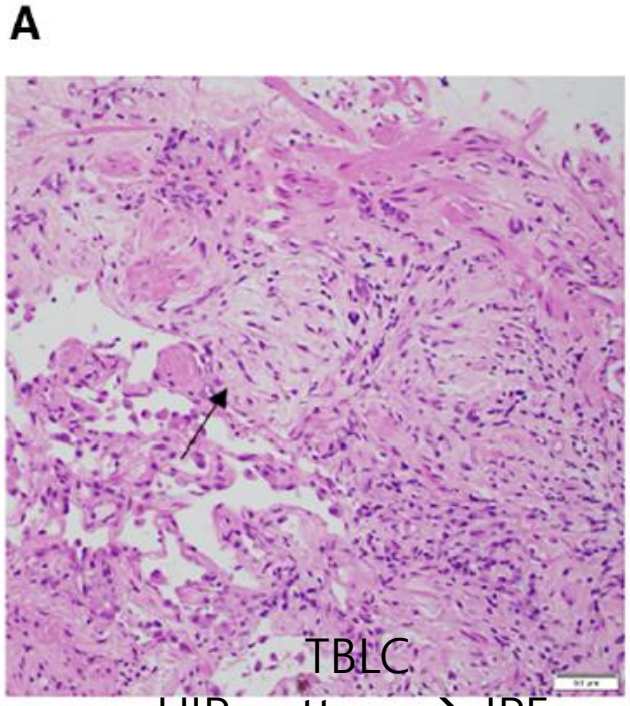
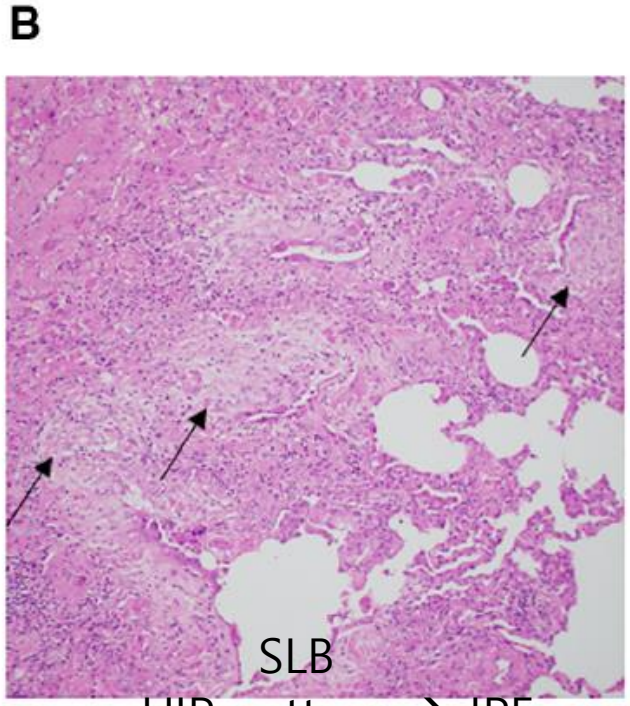


Table 1. Histopathological Criteria for Usual Interstitial Pneumonia Pattern

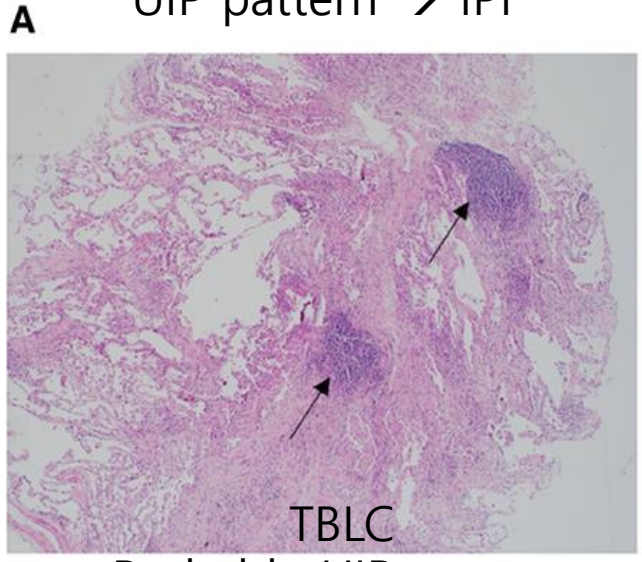
Usual Interstitial Pneumonia Criteria
• Evidence of marked fibrosis and/or architectural distortion (i.e., destructive scarring and/or honeycombing) in a predominantly subpleural or paraseptal distribution
• Patchy involvement of lung parenchyma by fibrosis
• Fibroblast foci
• Absence of features to suggest an alternative diagnosis (e.g., granulomas, hyaline membranes, prominent airway-centered changes, organizing pneumonia, marked inflammatory cell infiltrate, prominent lymphoid hyperplasia, vasculitis, eosinophils)



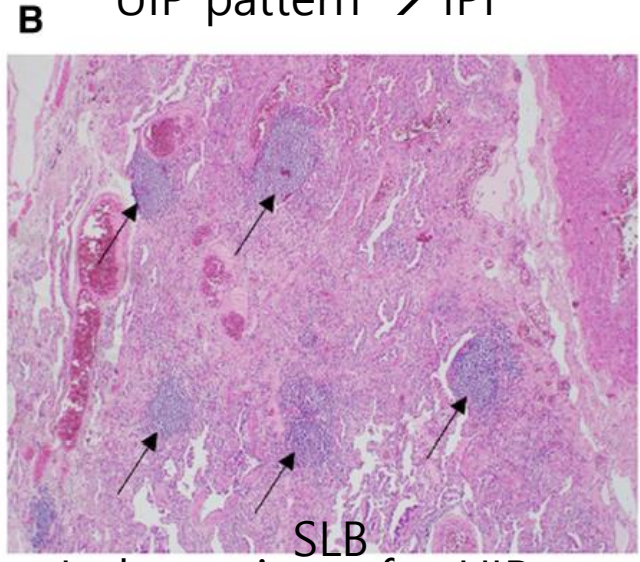
UIP pattern → IPF



UIP pattern → IPF



Probable UIP
→ Unclassifiable ILD



Indeterminate for UIP
→ CTD associated ILD

Table 5. Histopathologic Features of Usual Interstitial Pneumonia on Cryobiopsy

Usual Interstitial Pneumonia Criteria for Cryobiopsy
Required
• Patchy involvement of lung parenchyma by fibrosis
• Fibroblast foci
• Absence of features to suggest an alternative diagnosis (e.g., granulomas, hyaline membranes, prominent airway-centered changes, organizing pneumonia, marked inflammatory cell infiltrate, prominent lymphoid hyperplasia, vasculitis, eosinophils)
May be present in some, but not all, cases
• Marked fibrosis/architectural distortion (i.e., destructive scarring and/or honeycombing) in a predominantly subpleural or paraseptal distribution

Japanese Respiratory Society/Latin American Thoracic Association idiopathic pulmonary fibrosis guidelines (3, 8).
†Pleura was detected in 3/33 (9.1%) of TBLC.
‡Honeycomb change as a specific feature was seen in 5/33 (15.2%) of TBLC.

nd Surgical Lung Biopsy Concordance

OR	95% CI	*P* Value
0.86	**0.77–0.96**	**0.006**
0.42	0.14–1.31	0.135
0.15	**0.03–0.69**	**0.02**
3.98	**1.22–12.92**	**0.02**
0.20	**0.04–0.92**	**0.04**
0.60	0.15–2.44	0.47
1.24	0.21–7.39	0.82
0.39	0.13–1.18	0.10
2.70	0.30–24.10	0.374
1.80	**1.08–3.01**	**0.03**
1.06	0.79–1.43	0.68
0.67	0.29–1.55	0.36

Definition of abbreviations: CI = confidence interval; ILD = interstitial lung disease; OR = odds ratio. Bold values are those that were statistically significant.
*Including occupational, environmental, and iatrogenic exposures relevant to the development of interstitial lung disease.
†As measured by the longest axis of cryobiopsy in millimeters.

Increased numbers of TBLC samples predicted histopathologic concordance with SLB

The predictors of discordance included older age, family history, and radiologic asymmetry

Am J Respir Crit Care Med Vol 203, Iss 10, pp 1306–1313, May 15, 2021

R-scale for pulmonary fibrosis: a simple, visual tool for the assessment of health-related quality of life

Ciaran Scallan [1,2], Lauren Strand[3], Jennifer Hayes[1], Suha Kadura [1], Bridget Collins[1], Lawrence Ho[1], Carolyn Spada[1], Will Canestaro[3,4], Martin Kolb [2] and Ganesh Raghu[1]

Eur Respir J 2022; 59: 2100917

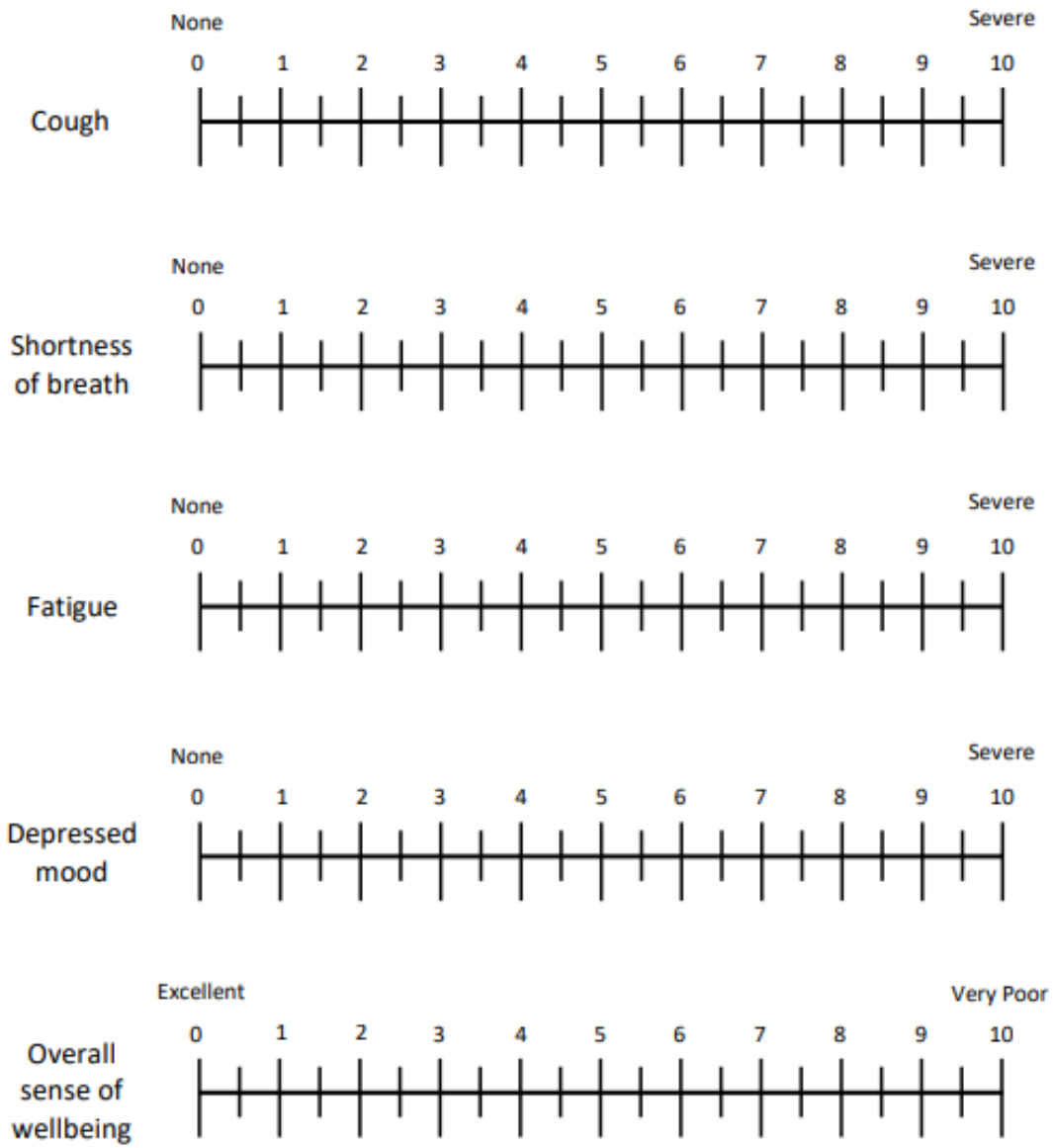
TABLE 6 Summary of health-related quality of life tools previously used in clinical studies in patients with idiopathic pulmonary fibrosis (IPF)

Name of tool	Domains assessed	Number of items
IPF-specific		
King's Brief Interstitial Lung Disease questionnaire (K-BILD) [5]	Breathlessness and activities, chest symptoms and psychological impact	15
IPF-specific version of St George's Respiratory Questionnaire (SGRQ-I) [13]	Symptoms, activity and psychosocial impact	34
A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF) [14]	Cough, shortness of breath, planning, sleep, mortality, energy, mental health, spirituality, social activities, finances, independence, sexuality, relationships and treatments	41–86[#]
Living with Idiopathic Pulmonary Fibrosis Questionnaire (L-IPF) [15]	Dyspnoea, cough and energy	44
Respiratory-specific		
St George's Respiratory Questionnaire (SGRQ) [16]	Symptoms, activity and psychosocial impact	50
University of California San Diego Shortness of Breath Questionnaire (UCSD-SOBQ) [17]	Shortness of breath	24
Cough and Sputum Assessment Questionnaire (CASA-Q) [18]	Cough	20
COPD Assessment Test (CAT) [19]	Cough, sputum, dyspnoea and chest tightness	8
Medical Research Council Scale (MRC) [20]	Dyspnoea	5
Modified Medical Research Council Scale (mMRC) [21]	Dyspnoea	5
General		
EuroQol Five-Dimensional Five-Level questionnaire (EQ-5D-5L) [3]	Mobility, self-care, usual activities, pain/discomfort and anxiety/depression	5
World Health Organization-Five Well-Being Index (WHO-5) [22]	Psychological well-being	5
Short-Form 36 Health Status Questionnaire (SF-36) [23]	Physical functioning, physical role, emotional role, bodily pain, general health, vitality, social functioning and mental health	36

[#]: varies for different versions of the tool.

1. R Scale-PF Numerical Rating Scale

This questionnaire is designed to assess the impact of your lung disease on your quality of life. Please select one location along each scale according to how you have been feeling over the last 2 weeks.



Expert revi
group sess

Open discu
concept eli
design.

Semi-structured interviews.
Likert scale:

I feel that "..." is an important contributor to my overall quality of life:
1. Strongly agree
2. Agree somewhat
3. Neither agree nor disagree
4. Disagree somewhat
5. Strongly disagree

Top five ranked items included in final tool:

1. Cough
2. Shortness of breath
3. Fatigue
4. Depressed mood
5. Overall well-being

Study participation.
Completion of RQ-LIFE-ILD, K-BILD, EQ-5D-5L.

Post tool completion questionnaire.
"Which tool did you find most accurately reflected your quality of life?"
"Which tool did you find the easiest to complete and understand?"

Eur Respir J 2022; 59: 2100917

TABLE 3 Correlation between impaired health-related quality of life tools and lung function

N=100

	R-Scale-PF total	K-BILD total	K-BILD breath	K-BILD psych	K-BILD chest	EQ-5D-5L VAS	EQ-5D-5L index score	6MWT distance	D_{LCO} % pred	FVC % pred
R-Scale-PF total	1									
K-BILD total	−0.713	1								
K-BILD breath	−0.674	0.888	1							
K-BILD psych	−0.553	0.877	0.619	1						
K-BILD chest	−0.674	0.733	0.683	0.545	1					
EQ-5D-5L VAS	−0.642	0.646	0.64	0.527	0.529	1				
EQ-5D-5L index score	−0.665	0.624	0.64	0.429	0.621	0.634	1			
6MWT distance	−0.383	0.528	0.599	0.358	0.457	0.459	0.56	1		
D_{LCO} % pred	−0.274	0.471	0.5	0.373	0.328	0.386	0.314	0.674	1	
FVC % pred	−0.307	0.421	0.421	0.342	0.347	0.277	0.213*	0.369	0.495	1

R-Scale-PF: Raghu scale for pulmonary fibrosis; K-BILD: King's Brief Interstitial Lung Disease questionnaire; EQ-5D-5L: EuroQol Five-Dimensional Five-Level questionnaire; VAS: visual analogue scale; 6MWT: 6-min walk test; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity. Correlation shown as Pearson's coefficients (*r*); all p<0.01, unless indicated. *: p<0.05.

Moderate to strong negative correlation with K-BILD, EQ-5D-5L index score, and the VAS
Moderate negative correlation between FVC % predicted and 6MWT
Weak correlation with DLCO % predicted

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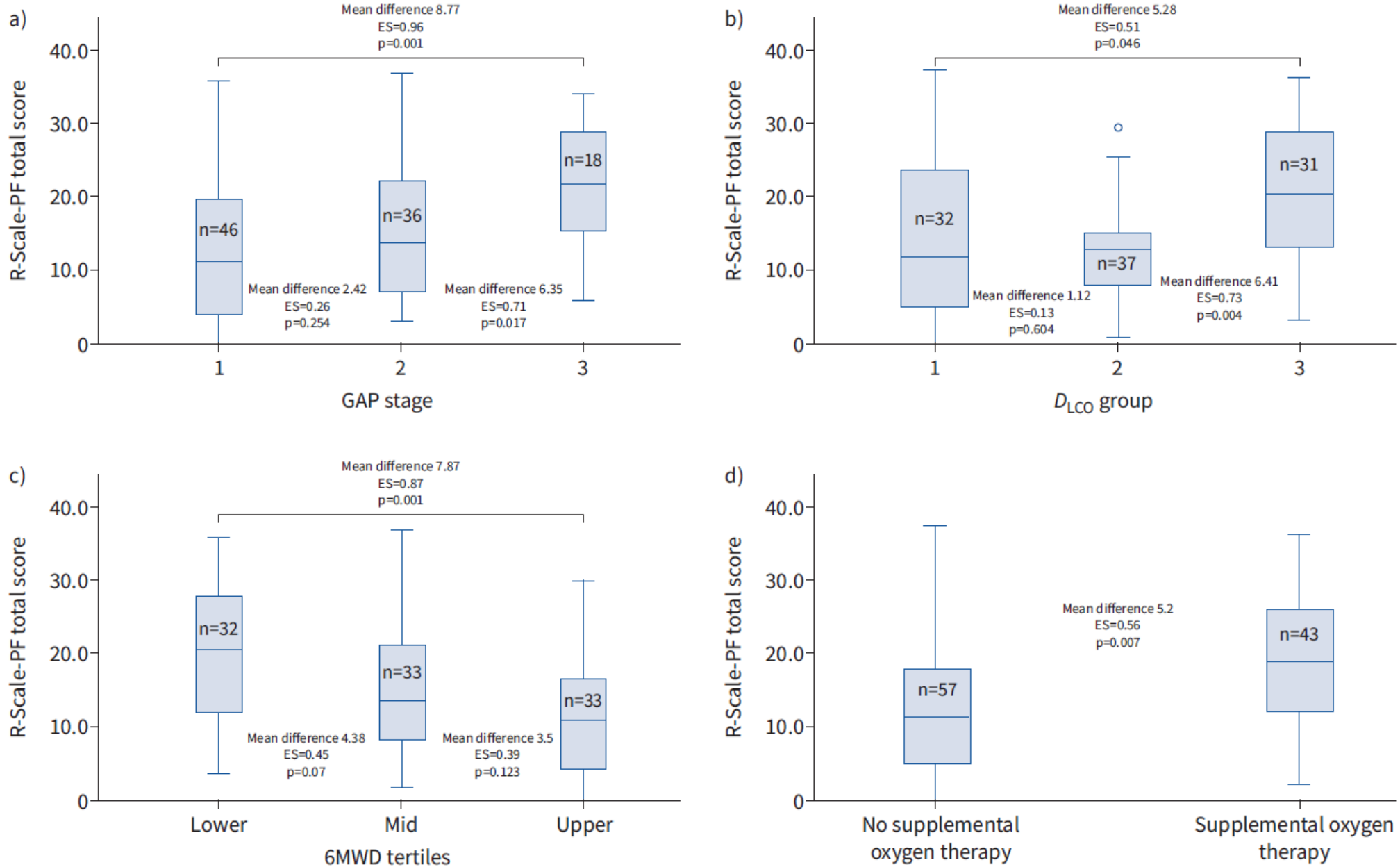

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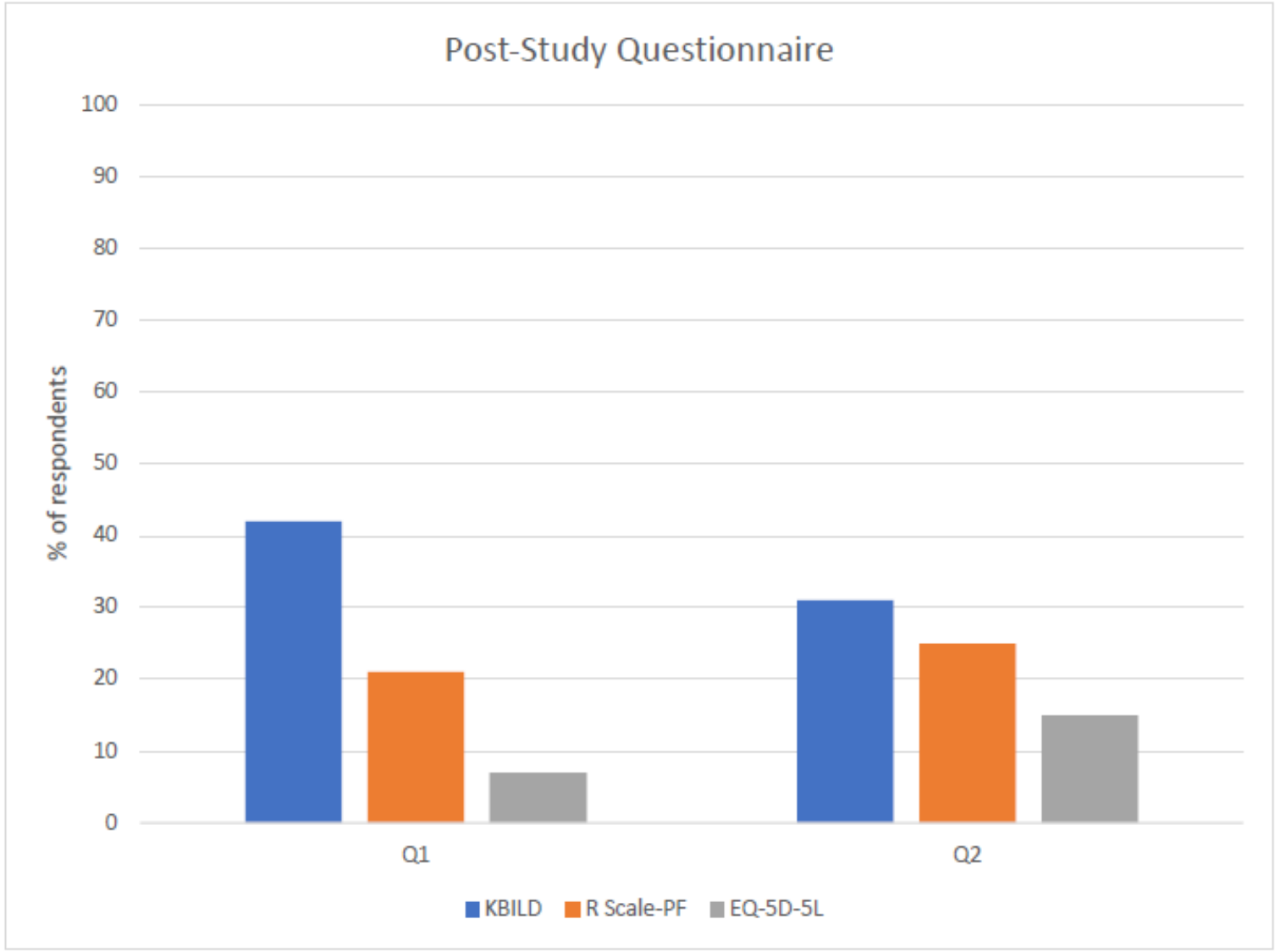


Question 1	Which questionnaire did you feel most accurately reflected the factors impacting your quality of life?
Question 2	Which questionnaire did you feel was the easiest to understand and complete?

Eur Respir J 2022; 59: 2100917

Monocyte Count as a Prognostic Biomarker in Patients with Idiopathic Pulmonary Fibrosis

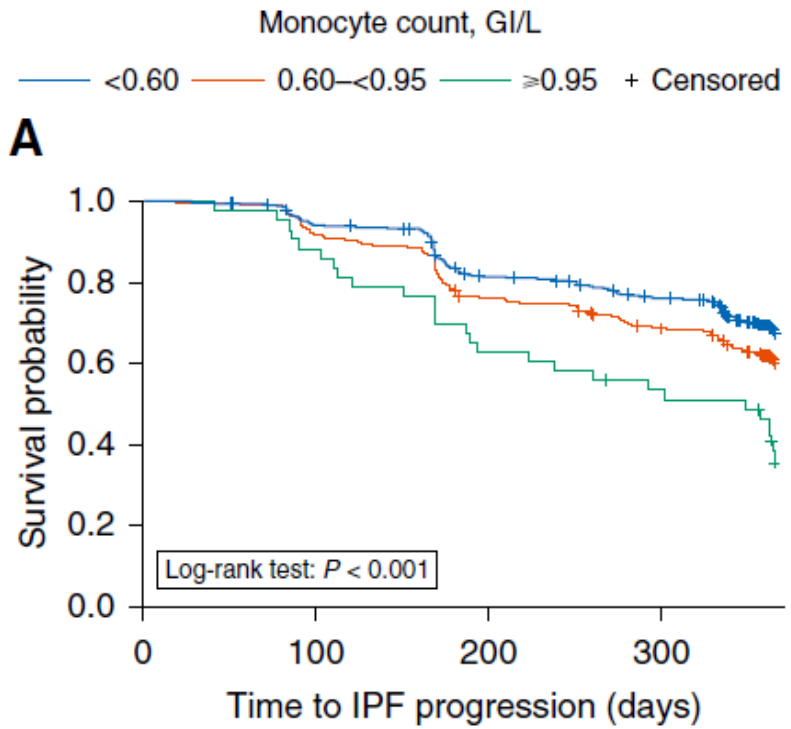
Michael Kreuter[1,2], Joyce S. Lee[3], Argyrios Tzouvelekis[4], Justin M. Oldham[5], Philip L. Molyneaux[6,7], Derek Weycker[8], Mark Atwood[8], Klaus-Uwe Kirchgaessler[9], and Toby M. Maher[6,7,10*]

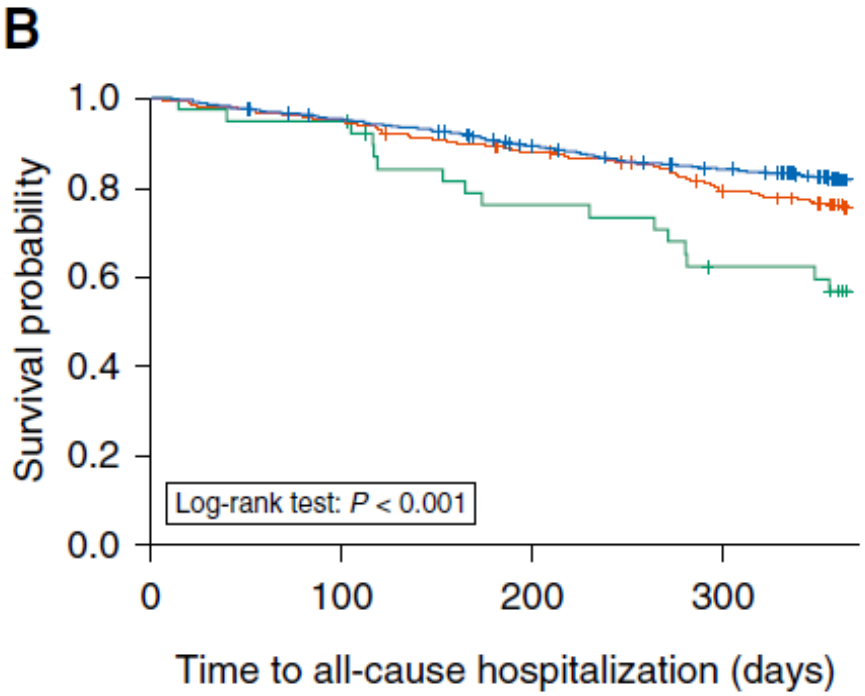
Am J Respir Crit Care Med Vol 204, Iss 1, pp 74–81, Jul 1, 2021

Table 1. Summary of Patient Baseline Characteristics in the Pooled ASCEND, CAPACITY, and INSPIRE Population by Monocyte Count

600 cells/μℓ 600-950 cells/μℓ 950 cells/μℓ

		Patients, by Monocyte Count		
	All Patients (*n* = 2,067)	**<0.60 × 10^9 cells/L (*n* = 1,609)**	**0.60 to <0.95 × 10^9 cells/L (*n* = 408)**	**≥0.95 × 10^9 cells/L (*n* = 50)**
Age, mean (SD), yr	66.7 (7.6)	66.4 (7.7)	67.8 (7.3)	67.7 (8.1)
Sex, *n* (%)				
M	1,508 (73.0)	1,136 (70.6)	328 (80.4)	44 (88.0)
Monocytes, × 10^9 cells/L				
Mean* (SD)	0.49 (0.18)	0.41 (0.10)	0.71 (0.09)	1.14 (0.29)
FVC% predicted, mean (SD)	69.0 (15.0)	69.7 (15.1)	67.4 (14.3)	63.1 (14.3)
D_{LCO}% predicted, mean (SD)	43.6 (11.4)	44.1 (11.4)	41.9 (11.2)	41.4 (9.4)
6MWD, mean (SD), m	382.0 (120.6)	385.3 (120.5)	374.7 (119.6)	336.3 (122.8)
UCSD-SOBQ total score, mean (SD)	39.1 (24.6)	38.6 (24.4)	39.7 (24.9)	47.0 (26.8)
CV risk factors, *n* (%)				
Smoker‡	1,372 (66.4)	1,064 (66.1)	276 (67.6)	32 (64.0)
Hypertension	1,068 (51.7)	815 (50.7)	230 (56.4)	23 (46.0)
Obesity§	897 (43.4)	686 (42.6)	187 (45.8)	24 (48.0)
Hypercholesterolemia	864 (41.8)	650 (40.4)	190 (46.6)	24 (48.0)
Diabetes	454 (22.0)	348 (21.6)	95 (23.3)	11 (22.0)
Chronic immunosuppressant use,‖ *n* (%)				
Steroid (systemic)	135 (6.5)	102 (6.3)	24 (5.9)	9 (18.0)
Nonsteroid	33 (1.6)	25 (1.6)	7 (1.7)	1 (2.0)
Neither	1,918 (92.8)	1,496 (93.0)	382 (93.6)	40 (80.0)





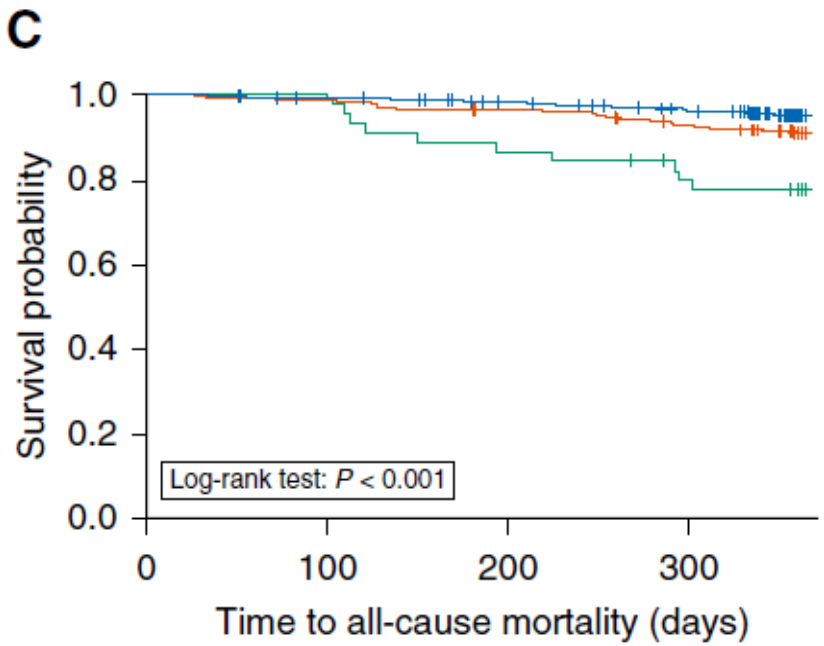


Figure 1. Kaplan-Meier curves for time to first (*A*) IPF progression (⩾10% absolute decline in FVC% predicted, ⩾50 m decline in 6-minute-walk distance, or death), (*B*) all-cause hospitalization, and (*C*) all-cause mortality over 1 year by monocyte count, in which monocyte count was defined as a time-dependent variable. IPF = idiopathic pulmonary fibrosis.

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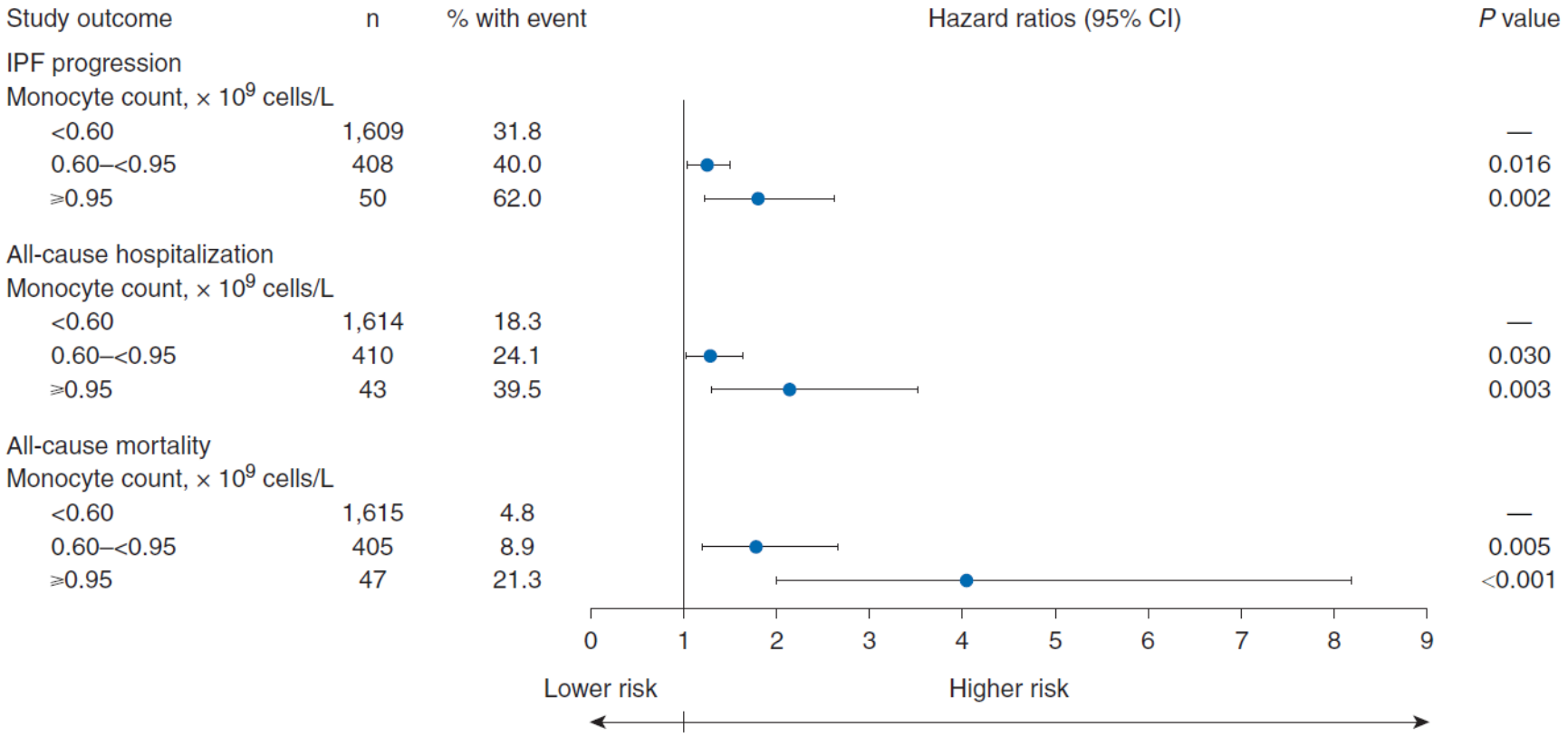

Figure 2. Adjusted hazard ratios for IPF progression, all-cause hospitalization, and all-cause mortality by monocyte count. Monocyte count and other model covariates were defined as time-dependent variables, as appropriate. CI = confidence interval; IPF = idiopathic pulmonary fibrosis.

- IPF is based on repeated epithelial injury leading to aberrant repair and the formation of fibrotic tissue. Immune cells (including monocytes) migrate to the site of injury to aid repair, where they differentiate
- The fibrocytes, a specialized cell derived from the monocyte cell lineage, has been postulated to be a precursor of the myofibroblast and has been implicated in the pathogenesis of IPF

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Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis

A Systematic Review and Meta-Analysis

Tananchai Petnak, MD; Ploypin Lertjitbanjong, MD; Charat Thongprayoon, MD; and Teng Moua, MD

- Phase III RCT for pirfenidone and nintedanib have demonstrated similar degrees of slowing lung function decline compared with placebo. ASCEND and INPULSIS studies

- 12,959 patients across 26 studies (8 RCT and 18 cohort studies)

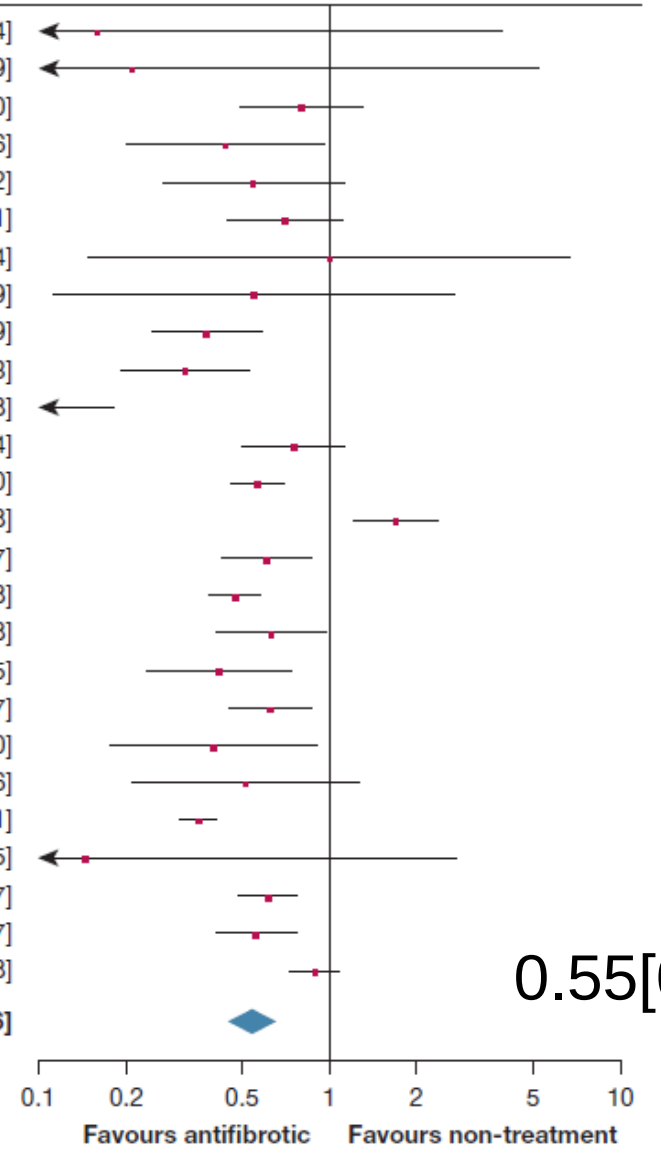
CHEST 2021; 160(5):1751-1763

All cause mortality

8 RCTs, 18 cohorts

Study or Subgroup	log[Relative Risk]	SE	Antifibrotic Total	Non-treatment Total	Weight	Relative Risk IV, Random, 95% CI
Azuma 2005	–1.8326	1.6346	72	35	0.3%	0.16 [0.01, 3.94]
Taniguchi 2010	–1.5606	1.6364	163	104	0.3%	0.21 [0.01, 5.19]
Noble 2011	–0.2231	0.2464	345	347	4.5%	0.80 [0.49, 1.30]
Richeldi 2011	–0.8197	0.3987	343	85	3.1%	0.44 [0.20, 0.96]
King 2014	–0.6014	0.3657	278	277	3.4%	0.55 [0.27, 1.12]
Richeldi 2014	–0.3521	0.2344	638	423	4.6%	0.70 [0.44, 1.11]
Huang 2015	0	0.9733	38	38	0.9%	1.00 [0.15, 6.74]
Hosein 2017	–0.5978	0.809	20	22	1.2%	0.55 [0.11, 2.69]
Jo 2017	–0.9676	0.2245	146	501	4.7%	0.38 [0.24, 0.59]
Margaritopoulos 2018	–1.1394	0.2574	75	136	4.4%	0.32 [0.19, 0.53]
Zubari 2018	–2.6689	0.4921	88	151	2.4%	0.07 [0.03, 0.18]
Cerri 2019	–0.2814	0.2082	106	36	4.9%	0.75 [0.50, 1.14]
Dempsey 2019	–0.5683	0.1097	1,255	1,255	5.8%	0.57 [0.46, 0.70]
Fernandez 2019	0.5269	0.1734	231	377	5.2%	1.69 [1.21, 2.38]
Kuanisto 2019	–0.4914	0.1821	95	358	5.2%	0.61 [0.43, 0.87]
Zurkova 2019	–0.7442	0.1047	383	218	5.9%	0.48 [0.39, 0.58]
Adegunsoya 2020	–0.4583	0.2212	68	172	4.8%	0.63 [0.41, 0.98]
Alhamad 2020	–0.8675	0.2952	64	148	4.0%	0.42 [0.24, 0.75]
Behr 2020	–0.462	0.1647	298	290	5.3%	0.63 [0.46, 0.87]
Dhooria 2020	–0.9152	0.4142	59	21	3.0%	0.40 [0.18, 0.90]
Feng 2020	–0.6604	0.4546	36	31	2.7%	0.52 [0.21, 1.26]
Kang 2020	–1.0333	0.0753	474	474	6.0%	0.36 [0.31, 0.41]
Lancaster 2020	–1.9285	1.5003	56	57	0.4%	0.15 [0.01, 2.75]
Moon 2020	–0.4846	0.1171	656	689	5.8%	0.62 [0.49, 0.77]
Nathan 2020	–0.5798	0.1625	230	206	5.4%	0.56 [0.41, 0.77]
Suzuki 2020	–0.1136	0.0984	208	80	5.9%	0.89 [0.74, 1.08]
Total (95% CI)			**6,425**	**6,531**	**100.0%**	**0.55 [0.45, 0.66]**

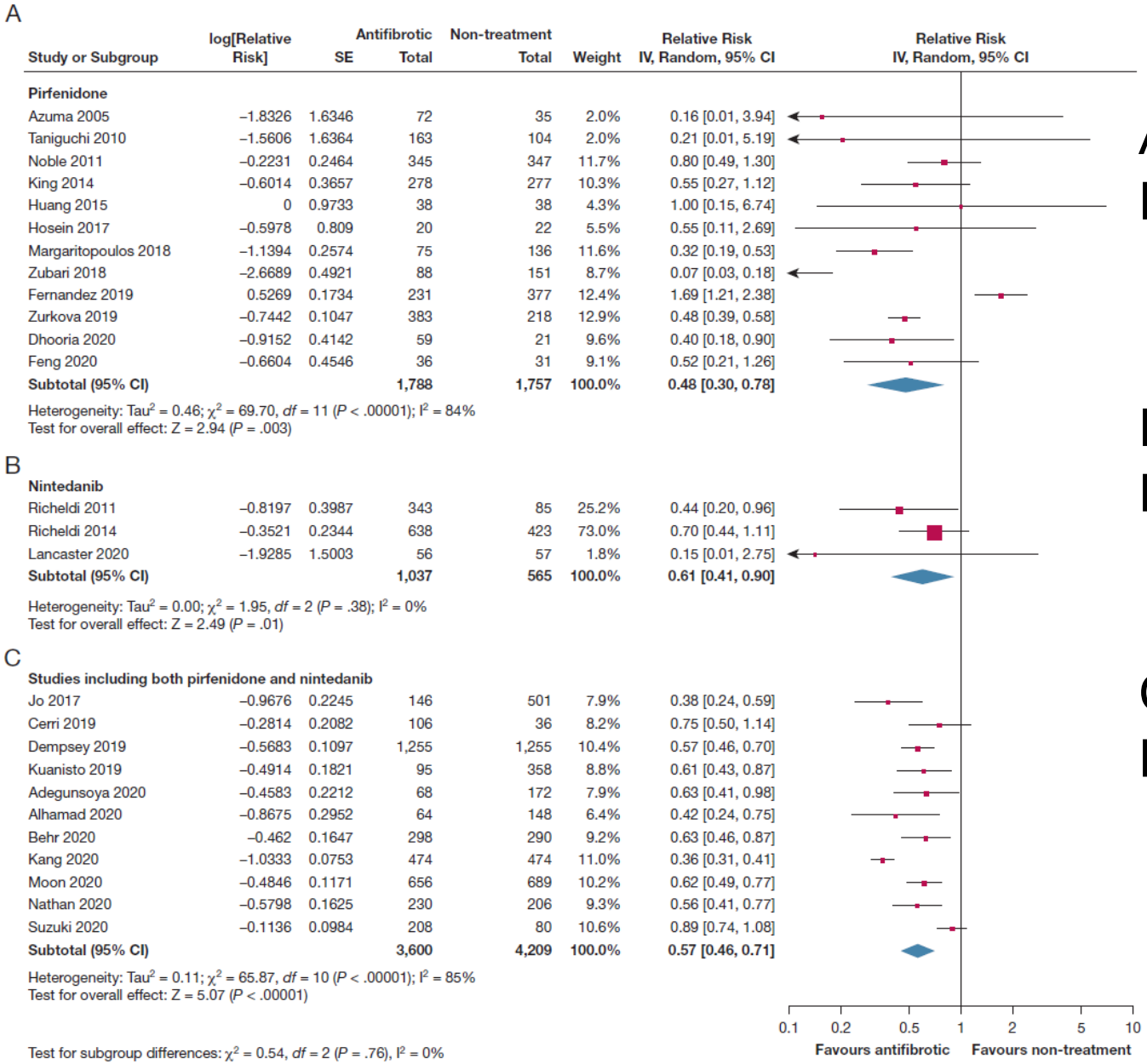
Heterogeneity: Tau² = 0.15; χ^2 = 138.49, *df* = 25 (*P* < .00001); I² = 82%
Test for overall effect: Z = 6.12 (*P* < .00001)



0.55[0.45,0.66]

CHEST 2021; 160(5):1751-1763

All cause mortality



A. Pirfenidone
Relative risk 0.55 [0.45,0.66]

B. Nintedanib
Relative risk 0.61 [0.41,0.90]

C. Pirfenidone and nintedanib
Relative risk 0.57 [0.46,0.71]

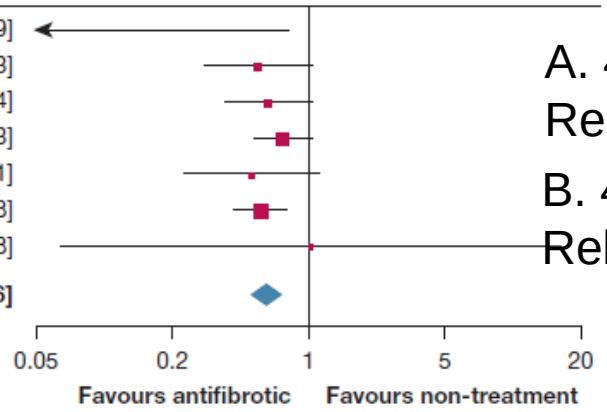
CHEST 2021; 160(5):1751-1763

Acute exacerbation

A

Study or Subgroup	log[Relative Risk]	SE	Antifibrotic Total	Non-treatment Total	Weight	Relative Risk IV, Random, 95% CI
Azuma 2005	–3.1048	1.463	72	35	0.4%	0.04 [0.00, 0.79]
Richeldi 2011	–0.5621	0.3019	343	85	9.1%	0.57 [0.32, 1.03]
Richeldi 2014	–0.4427	0.2441	638	423	14.0%	0.64 [0.40, 1.04]
Zurkova 2019	–0.2853	0.1611	383	218	32.1%	0.75 [0.55, 1.03]
Feng 2020	–0.635	0.3767	36	31	5.9%	0.53 [0.25, 1.11]
Kang 2020	–0.5335	0.1476	474	474	38.2%	0.59 [0.44, 0.78]
Lancaster 2020	0.0177	1.4016	56	57	0.4%	1.02 [0.07, 15.88]
Total (95% CI)			**2,002**	**1,323**	**100.0%**	**0.63 [0.53, 0.76]**

Heterogeneity: Tau² = 0.00; χ^2 = 5.14, *df* = 6 (*P* = .53); I^2 = 0%
Test for overall effect: Z = 5.02 (*P* < .00001)

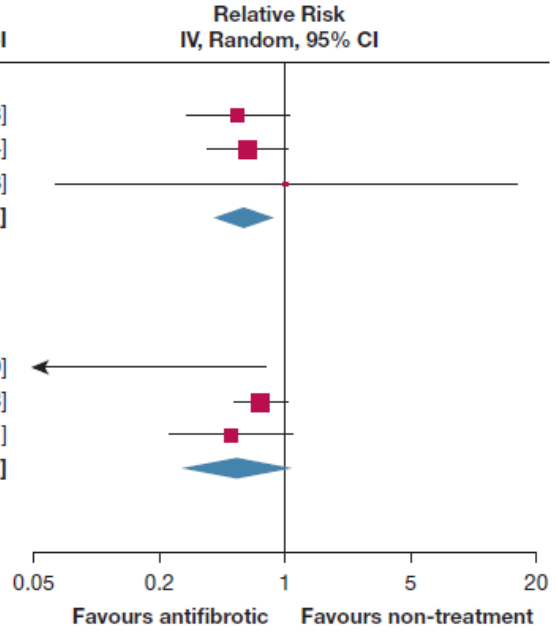


A. 4 RCTs, 3 cohorts
Relative risk 0.63 [0.53,0.76]

B. 4 RCTs
Relative risk 0.58 [0.38,0.89]

C

Study or Subgroup	log[Relative Risk]	SE	Antifibrotic Total	Non-treatment Total	Weight	Relative Risk IV, Random, 95% CI
Nintedanib						
Richeldi 2011	–0.5621	0.3019	343	85	38.8%	0.57 [0.32, 1.03]
Richeldi 2014	–0.4427	0.2441	638	423	59.4%	0.64 [0.40, 1.04]
Lancaster 2020	0.0177	1.4016	56	57	1.8%	1.02 [0.07, 15.88]
Subtotal (95% CI)			**1,037**	**565**	**100.0%**	**0.62 [0.43, 0.89]**
Heterogeneity: Tau² = 0.00; χ^2 = 0.22, *df* = 2 (*P* = .89); I^2 = 0%						
Test for overall effect: Z = 2.56 (*P* = .01)						
Pirfenidone						
Azuma 2005	–3.1048	1.463	72	35	5.1%	0.04 [0.00, 0.79]
Zurkova 2019	–0.2853	0.1611	383	218	57.9%	0.75 [0.55, 1.03]
Feng 2020	–0.635	0.3767	36	31	37.0%	0.53 [0.25, 1.11]
Subtotal (95% CI)			**491**	**284**	**100.0%**	**0.57 [0.29, 1.12]**
Heterogeneity: Tau² = 0.18; χ^2 = 4.27, *df* = 2 (*P* = .12); I^2 = 53%						
Test for overall effect: Z = 1.62 (*P* = .10)						
Test for subgroup differences: χ^2 = 0.04, *df* = 1 (*P* = .84), I^2 = 0%						



C. nintedanib
Relative risk 0.62 [0.43,0.89]

Pirfenidone
Relative risk 0.57 [0.29,1.12]

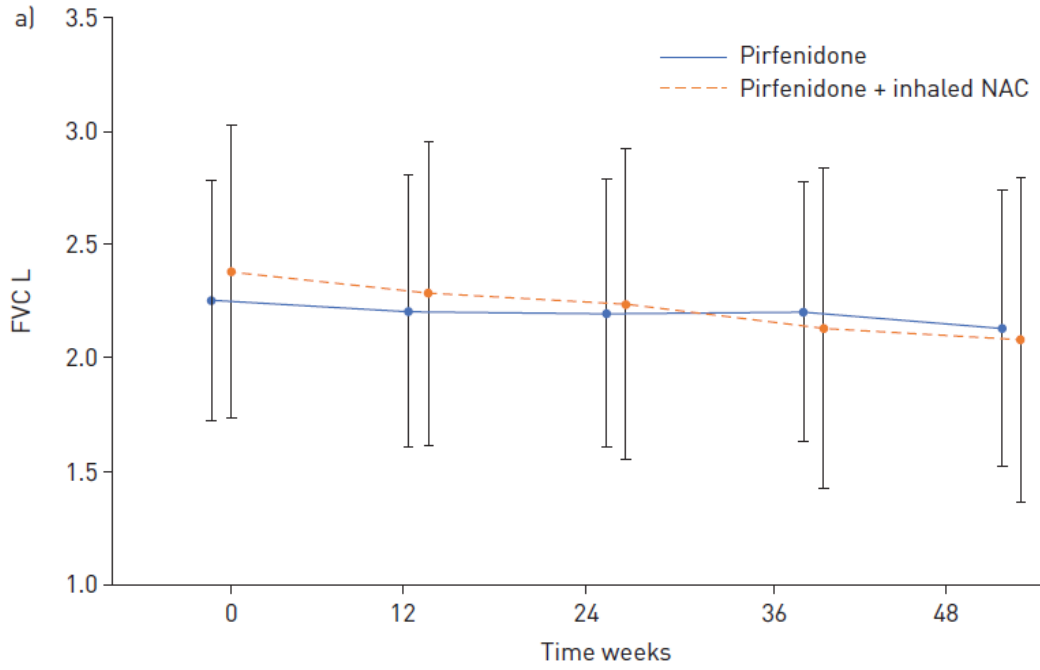
CHEST 2021; 160(5):1751-1763

Pirfenidone plus inhaled N-acetylcysteine for idiopathic pulmonary fibrosis: a randomised trial

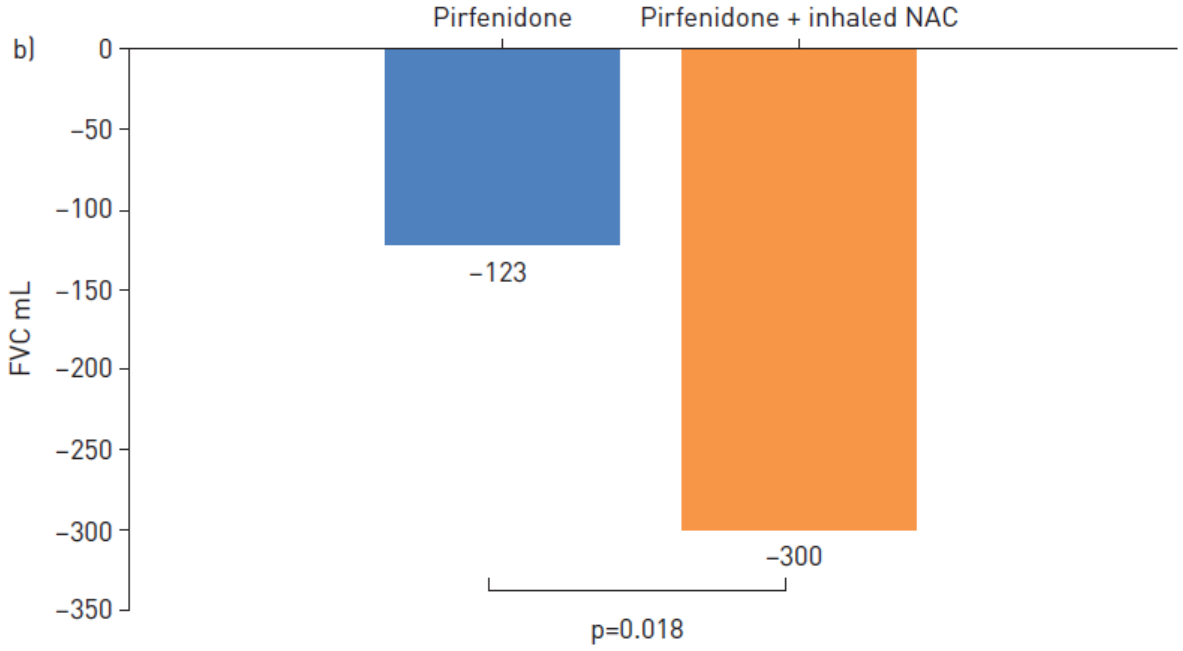
Susumu Sakamoto[1], Kensuke Kataoka[2], Yasuhiro Kondoh[2], Motoyasu Kato[3], Masaki Okamoto[4], Hiroshi Mukae[5], Masashi Bando[6], Takafumi Suda[7], Kazuhiro Yatera[8], Yoshinori Tanino[9], Tomoo Kishaba[10], Noboru Hattori[11], Yoshio Taguchi[12], Takefumi Saito[13], Yasuhiko Nishioka[14], Kazuyoshi Kuwano[15], Kazuma Kishi[1,16], Naohiko Inase[17], Shinichi Sasaki[18], Hajime Takizawa[19], Takeshi Johkoh[20], Fumikazu Sakai[21], Sakae Homma[1,22] and the Diffuse Lung Diseases Research Group of the Ministry of Health, Labour and Welfare, Japan

- N-acetylcysteine: antioxidants
- 48 week, randomized, open-label phase 3
- Pirfenidone plus inhaled N-acetylcysteine (352.4mg twice daily) (n=40) vs. pirfenidone (n=41)
- FVC >50% and D_{LCO} >35% and had been receiving pirfenidone 1200-1800mg/day before randomization
- Severe or unstable concomitant disease were excluded

Susumu Sakamoto et al. Eur Respi J 2021;57:2000348



		0	12	24	36	48	Difference L
Pirfenidone	FVC	2.254±0.529	2.205±0.603	2.199±0.587	2.203±0.574	2.131±0.612	
	Change in FVC		−0.049±0.177	−0.055±0.214	−0.051±0.179	−0.123±0.226	−0.178 p=0.0184
Pirfenidone + inhaled NAC	FVC	2.382±0.646	2.286±0.669	2.240±0.686	2.131±0.706	2.082±0.719	
	Change in FVC		−0.095±0.206	−0.142±0.220	−0.251±0.302	−0.300±0.360	



		0	48 weeks	Difference L
Pirfenidone	FVC L	2.254±0.529	2.131±0.612	
	Change in FVC L		−0.123±0.226 (−0.201 – −0.046)	−0.178
	Relative change in FVC %		−6.2±10.5 (−9.8 – −2.6)	(−0.324 – −0.031)
Pirfenidone + inhaled NAC	FVC L	2.382±0.646	2.082±0.719	p=0.0184
	Change in FVC L		−0.300±0.360 (−0.427 – −0.172)	
	Relative change in FVC %		−12.9±15.5 (−18.4 – −7.4)	

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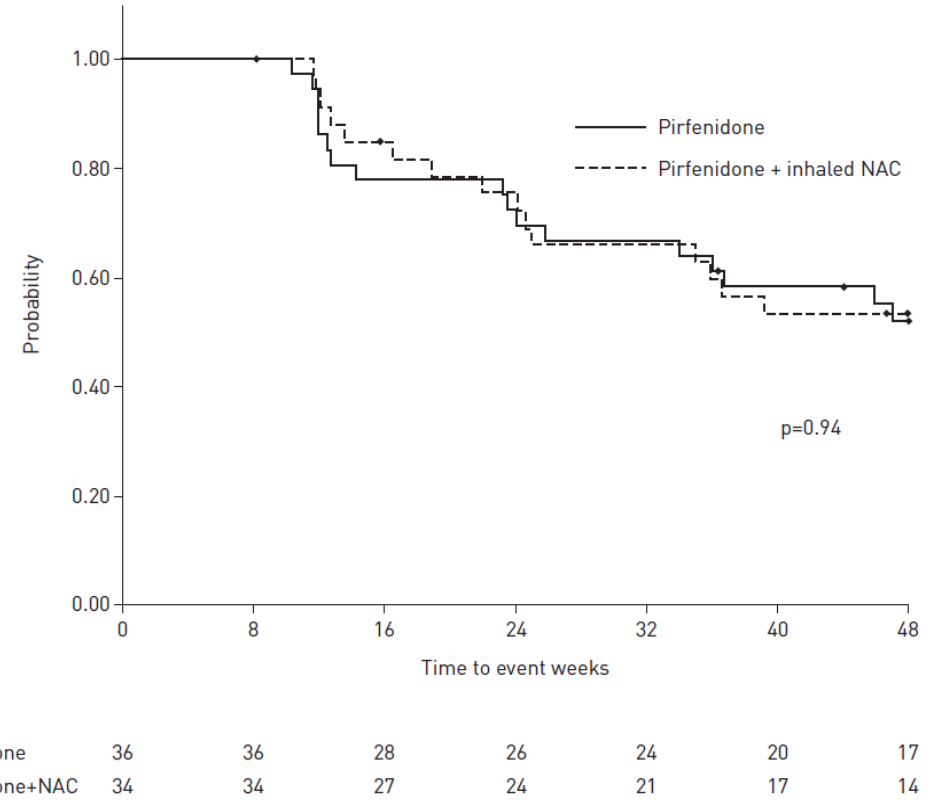
TABLE 2 Secondary lung function end-points at week 48

	Pirfenidone	Pirfenidone +inhaled NAC	Difference between pirfenidone and pirfenidone +inhaled NAC (95% CI)	p-value
Absolute mean change from baseline in FVC % predicted	−4.35	−8.38	−4.2 (−8.4–0.04)	0.05
Absolute mean change from baseline in VC mL	−139	−316	−182 (−332–−4)	0.012*
Absolute mean change from baseline in VC % predicted	−4.4	−9.5	−5.3 (−9.5–−1.1)	0.015*
FVC response at week 48 FVC decline ⩽5%	19 (52.8)	12 (35.3)		0.072
Absolute mean change from baseline in D_{LCO} % predicted	−10.1	−7.4	2.3 (−4.7–9.2)	0.517
Absolute mean change from baseline in 6MWD m	−24.2	−78.1	−36.4 (−69.9–21.6)	0.253

Data are presented as n or n (%), unless otherwise stated. NAC: N-acetylcysteine; FVC: forced vital capacity; VC: vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance. *: p<0.05.



Inhaled N-acetylcysteine combined with pirfenidone may result in worse outcomes for patients with IPF.

The present results indicate that inhaled N-acetylcysteine, as administered in this trial, should not be used to treat IPF

JAMA | Original Investigation

Effect of Antimicrobial Therapy on Respiratory Hospitalization or Death in Adults With Idiopathic Pulmonary Fibrosis

The CleanUP-IPF Randomized Clinical Trial

Fernando J. Martinez, MD, MS; Eric Yow, MS; Kevin R. Flaherty, MD; Laurie D. Snyder, MD; Michael T. Durheim, MD; Stephen R. Wisniewski, PhD; Frank C. Sciurba, MD; Ganesh Raghu, MD; Maria M. Brooks, PhD; Dong-Yun Kim, PhD; Daniel F. Dilling, MD; Gerard J. Criner, MD; Hyun Kim, MD; Elizabeth A. Belloli, MD; Anoop M. Nambiar, MD; Mary Beth Scholand, MD; Kevin J. Anstrom, PhD; Imre Noth, MD; for the CleanUP-IPF Investigators of the Pulmonary Trials Cooperative

- The addition of co-trimoxazole therapy to standard treatment had no effect on lung function but resulted in improved quality of life and a reduction in mortality

Thorax. 2013;68(2):155-162

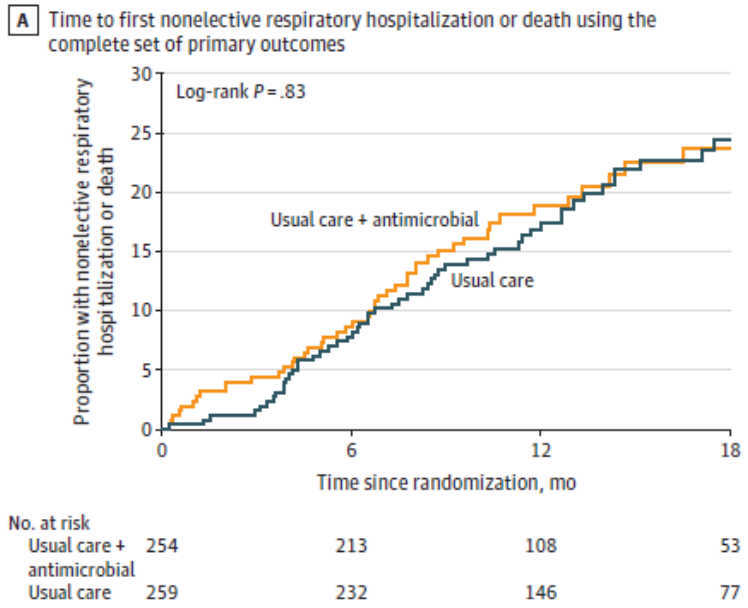
- Randomized, unblinded clinical trial across 35 US sites
- Antimicrobials (n=254) vs. usual care alone (n=259)
- Trimethoprim 160mg/sulfamethoxazole 800mg twice plus folate 5mg daily (n=128), doxycycline 100mg once or twice daily (n=126)

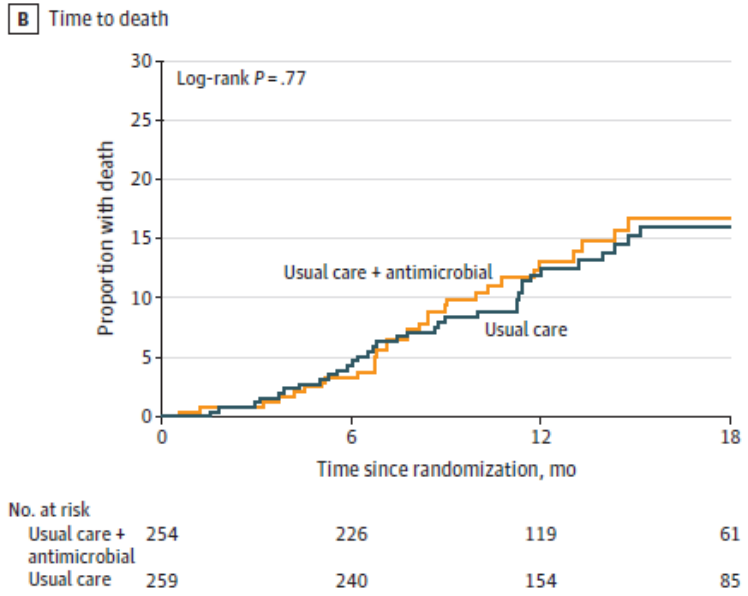
JAMA. 2021;325(18):1841-1851.

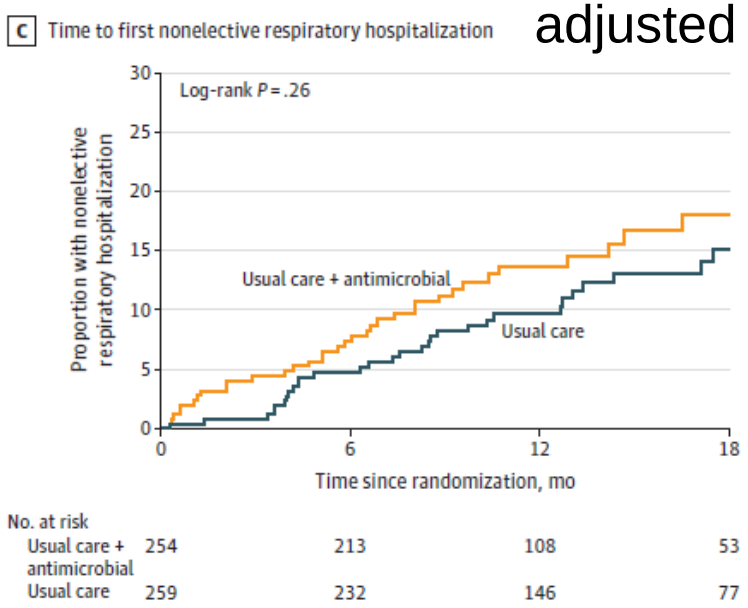
Parameter	No. (%) of patients	
	Usual care + antimicrobial therapy (n = 254)	Usual care (n = 259)
Prior medications, No.[d]	253	259
Proton pump inhibitors	158 (62.5)	158 (61.0)
Prednisone (>1 mo)	43 (17.0)	53 (20.5)
Azathioprine	1 (0.4)	39 (1.22)
H_2 blocker	49 (19.4)	42 (16.2)
N-acetylcysteine	14 (5.5)	13 (5.0)
IPF-specific medication prior to randomization, No.	253	259
Pirfenidone	158 (62.5)	160 (61.8)
Nintedanib	101 (39.9)	97 (37.5)
FVC, No.	247	255
Median (IQR), L	2.68 (2.14-3.23)	2.73 (2.20-3.32)
Percent predicted, No.	237	254
Median (IQR)	68.9 (56.7-81.8)	71.17 (57.4-83.8)
DLCO, No.[a]	240	252
Median (IQR), $mL \cdot min^{-1} \cdot mm\ Hg^{-1}$	10.74 (8.27-14.42)	11.56 (8.74-14.73)
% Predicted, No.	233	251
Median (IQR)	39.50 (29.32-48.61)	38.37 (30.97-49.01)
GAP stage, No.[b]	233	251
I	60 (25.8)	54 (21.5)
II	124 (53.2)	133 (53.0)
III	49 (21.0)	64 (25.5)

JAMA. 2021;325(18):1841-1851.

Figure 2. Time to the Primary Composite End Point and Its Components







There were no statistically significant differences between the antimicrobial therapy plus usual care group and usual care–only group based on the log-rank test for this end point nor for the components.

A. Time to first nonelective respiratory hospitalization or death
event 20.4 vs. 18.4 per 100 patients-years
adjusted HR 1.04 (0.71 to 1.53)
co-trimoxazole HR 1.15 (0.68-1.95)
doxycycline HR 0.82 (0.46-1.47)

B. Time to death
adjusted HR 1.11 (0.70 to 1.78)

C. Time to first nonelective respiratory hospitalization
adjusted HR 1.29 (0.82 to 2.02)

JAMA. 2021;325(18):1841-1851.

Table 4. Patients With Serious Adverse Events and Adverse Events of Special Interest

Event	No. (%) of patients	
	Usual care + antimicrobial therapy (n = 254)	Usual care (n = 259)
Serious adverse events		
Patients with ≥ 1 events[a]	71 (28.0)	65 (25.1)
Respiratory, thoracic and mediastinal	42 (16.5)	26 (10.0)
Idiopathic pulmonary fibrosis	16 (6.3)	5 (1.9)
Respiratory failure	5 (2.0)	4 (1.5)
Dyspnea	5 (2.0)	2 (0.8)
Cardiovascular	11 (4.3)	11 (4.2)
Infections	7 (2.8)	17 (6.6)
Pneumonia	5 (2.0)	7 (2.7)
Nervous system	8 (3.1)	3 (1.2)
Gastrointestinal	3 (1.2)	4 (1.5)
Metabolism and nutrition	2 (0.8)	4 (1.5)
Adverse events of special interest[b]		
Diarrhea	26 (10.2)	8 (3.1)
Rash	17 (6.7)	0
Vomiting	12 (4.7)	2 (0.8)
Hyperkalemia	10 (3.9)	2 (0.8)
Arrhythmia	2 (0.8)	5 (1.9)

JAMA. 2021;325(18):1841-1851.

Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomised, double-blind, placebo-controlled, phase 3 trial

*Jean-Marc Naccache, Stéphane Jouneau, Morgane Didier, Raphaël Borie, Marine Cachanado, Arnaud Bourdin, Martine Reynaud-Gaubert, Philippe Bonniaud, Dominique Israël-Biet, Grégoire Prévot, Sandrine Hirschi, François Lebargy, Sylvain Marchand-Adam, Nathalie Bautin, Julie Traclet, Emmanuel Gomez, Sylvie Leroy, Frédéric Gagnadoux, Frédéric Rivière, Emmanuel Bergot, Anne Gondouin, Elodie Blanchard, Antoine Parrot, François-Xavier Blanc, Alexandre Chabrol, Stéphane Dominique, Aude Gibelin, Abdellatif Tazi, Laurence Berard, Pierre Yves Brillet, Marie-Pierre Debray, Alexandra Rousseau, Mallorie Kerjouan, Olivia Freynet, Marie-Christine Dombret, Anne-Sophie Gamez, Ana Nieves, Guillaume Beltramo, Jean Pastré, Aurélie Le Borgne-Krams, Tristan Dégot, Claire Launois, Laurent Plantier, Lidwine Wémeau-Stervinou, Jacques Cadranel, Cécile Chenivesse, Dominique Valeyre, Bruno Crestani, Vincent Cottin, Tabassome Simon, Hilario Nunes, on behalf of the EXAFIP investigators and the OrphaLung network**

Lancet Respir Med 2022; 10: 26–34

- Double blind, placebo-controlled trial in France
- Adults patients (≥18 years) with acute exacerbation of IPF and those with suspected acute exacerbation of IPF
- High dose glucocorticoids therapy (methylprednisolone 10mg/kg day for 3 days) followed by a progressive tapering to 10 mg (≥ 65kg) or 7.5mg (< 65kg) per day at month 6
- PJP prophylaxis with co-trimoxazole or atovaquone. Pirfenidone or nintedanib was authorized at any point throughout the study.
- IV pulses of cyclophosphamide (600mg/m^2) plus IV uromitexan as hemorrhagic cystitis prophylaxis (200mg/m^2 and 4 hr later) vs. placebo

	Cyclophosphamide (n=60)	Placebo (n=59)
Age, year	71·0 (9·0)	73·2 (7·0)
Sex		
Male	49 (82%)	45 (76%)
Female	11 (18%)	14 (24%)
Severe IPF*	31 (52%)	31 (53%)
Previously known IPF	56 (93%)	53 (90%)
Surgical lung biopsy	9 (15%)	7 (12%)
Median time since diagnosis of IPF, years	1·99 (0·73–3·36)	1·93 (0·59–3·62)
Antifibrotic therapy		
Nintedanib	13 (22%)	8 (14%)
Pirfenidone	9 (15%)	14 (24%)
Pulmonary function tests before acute exacerbation of IPF		
Median time since last pulmonary function tests, months	4·0 (2·0–7·0)	3·0 (1·5–6·0)
Median FVC, % predicted value	68·5 (54·0–85·5)	67·0 (58·0–86·0)
Median DLCO, % predicted value	35·0 (24·0–46·0)	32·0 (27·0–42·0)
Missing data	0	1 (2%)

FVC <50% or
DLCO <35%

	Cyclophosphamide (n=60)	Placebo (n=59)
(Continued from previous column)		
Partial pressure of oxygen to fraction of inspired oxygen ratio at acute exacerbation of IPF diagnosis	272·7 (175·5–344·3)	252·7 (171·4–320·8)
Missing data	11 (18%)	9 (15%)
Blood leukocytes, µL	12 352 (3596·7)	12 103 (4266·2)
Missing data	4 (7%)	0
C-reactive protein, mg/L	22·7 (8·1–66·3)	11·5 (5·0–41·0)
Missing data	4 (7%)	4 (7%)
Bronchoalveolar lavage or tracheal aspirate	18 (30%)	18 (31%)
Time between first signs and symptoms and administration of treatment of acute exacerbation of IPF, days	12·0 (5·0–22·0)	13·0 (5·0–25·0)
Missing data	5 (8%)	4 (7%)

Lancet Respir Med 2022;10:26-34

Death at 3 months
45% vs. 31%

	Cyclophosphamide (n=60)	Placebo (n=59)	Difference (95% CI)	p value
Death at 3 months in the ITT population*	27/60 (45%)	18/59 (31%)	14·5 (−3·1 to 31·6)	0·10
Death at 3 months in the ITT population with available data	26/59 (44%)	18/59 (31%)	13·6 (−4·1 to 30·7)	0·13
Death at 3 months in the per-protocol population	17/42 (40%)	15/50 (30%)	10·5 (−9·6 to 30·1)	0·29

Data are n/N (%), unless otherwise specified. ITT=intention-to-treat. *The missing data for one patient have been replaced by death.

Table 2: **Primary outcomes**

Death at 12 months
59.5% vs. 50.5%

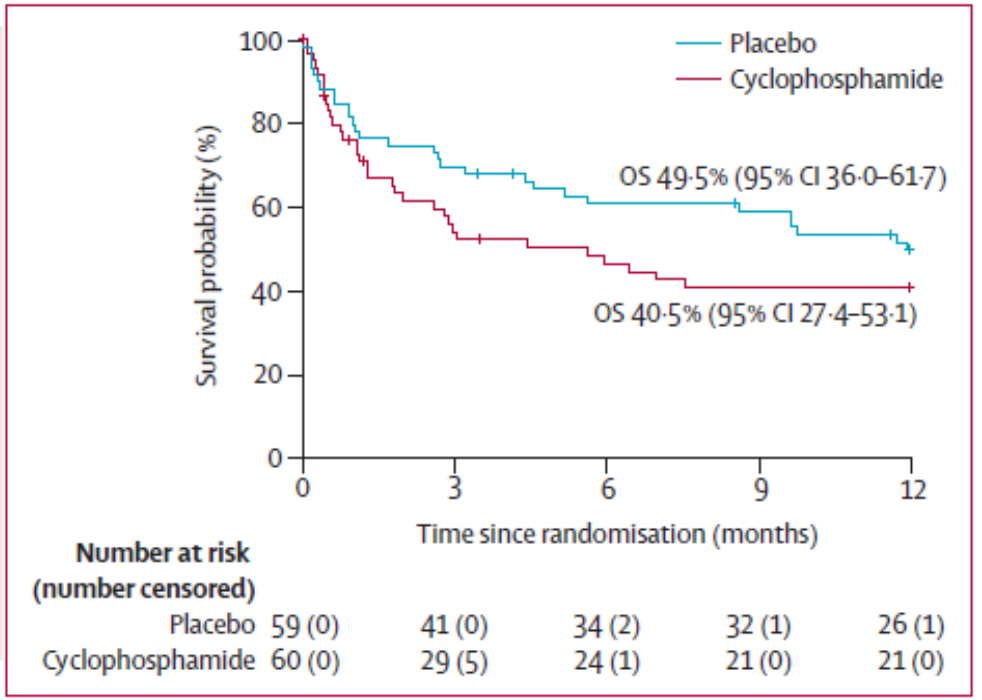


Figure 2: **Survival probability over 12 months**

Lancet Respir Med 2022;10:26-34

Risk factors associated with 3 month mortality

- Severity of IPF

  2.62 [1.12-6.12], p=0.03
- Antifibrotic therapy

  0.33 [0.13-0.82], p=0.02

	Cyclophosphamide (n=60)	Placebo (n=59)	Difference (95% CI)
Death at 3 months	26 (43%)	18 (31%)	..
Death related to respiratory cause at 3 months	25 (96%)	17 (94%)	1·7 (–14·8 to 23·7)
Death at 6 months	30 (50%)	23 (39%)	..
Death related to respiratory cause at 6 months	29 (97%)	22 (96%)	1·0 (–14·3 to 18·8)
Morbidity at 6 months			
Patients who are alive and have not undergone a transplantation	24 (40%)	34 (58%)	..
At least one respiratory morbidity at 6 months of the available data	15/16 (94%)	27/29 (93%)	0·6 (–23·4 to 18·7)
Missing data	8 (33%)	5 (15%)	..
Worsening in gas exchanges at 6 months of the available data*	12/20 (60%)	19/29 (66%)	–5·5 (–33·7 to 21·9)
Missing data	4 (17%)	5 (15%)	..
Decrease in FVC ≥10% of the predicted value at 6 months of the available data†	4/17 (24%)	8/27 (30%)	–6·1 (–32·0 to 23·4)
Missing data	7 (29%)	7 (21%)	..
Decrease in DLCO ≥15% of the predicted value at 6 months of the available data†	3/12 (25)	7/23 (30)	–5·4 (–34·7 to 29·4)
Missing data	12 (50%)	11 (32%)	..
Median variation of global extent of interstitial fibrosing features†‡	10·0% (5·0 to 15·0)	15·0% (7·0 to 19·0)	–5 (–10·0 to 5·0)

Lancet Respir Med 2022;10:26-34

Side effects

	Cyclophosphamide (n=60)	Placebo (n=59)
Any adverse event between month 0 and month 6	25 (42%)	30 (51%)
Haemorrhagic cystitis	0	0
Leukopenia	1 (2%)	0
Neutropenia	3 (5%)	0
Lymphopenia	0	1 (2%)
Anaemia	1 (2%)	0
Thrombopenia	0	2 (3%)
Nausea or vomiting	4 (7%)	3 (5%)
Diarrhoea	7 (12%)	4 (7%)
Newly developed diabetes	0 (0%)	1 (2%)
Newly developed hypertension	2 (3%)	2 (3%)
Infectious disease	20 (33%)	21 (36%)
Any serious adverse event between 0 and 12 months	53 (88%)	50 (85%)
Serious adverse event excluding progression of IPF between 0 and 12 months	26 (43%)	29 (49%)
Serious infectious disease	9 (15%)	15 (25%)
Cardiac disorder	6 (10%)	10 (17%)

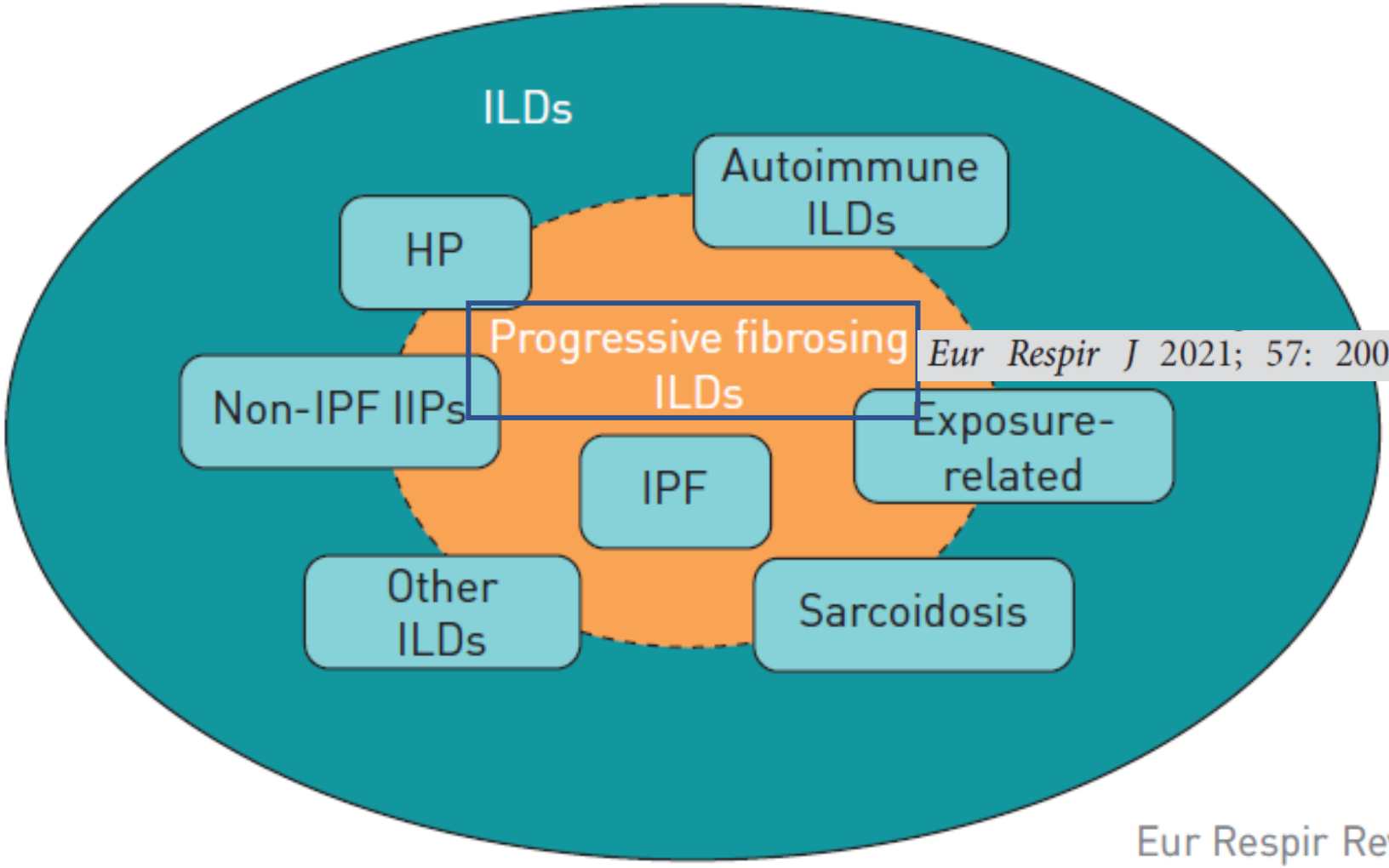
IPF=idiopathic pulmonary fibrosis.

Table 4: **Adverse events and serious adverse events**

In patients with acute exacerbation of IPF, adding intravenous cyclophosphamide pulses to glucocorticoids increased 3-month mortality.

These findings provide evidence against the use of intravenous cyclophosphamide in such patients.

Fibrosing ILD



Eur Respir J 2021; 57: 2002718

Eur Respir Rev 2019; 28: 180100

Clinical characteristics of selected broad categories of pulmonary fibrosis

Condition	Progressive fibrosing phenotype	Relative prevalence (among all patients with ILD)	prognosis
IPF	90-100%	12%	Median survival, 3–4 yr; potential for slowing progression
SSc-ILD	40%	9%	10-Yr mortality, 40%; 35% of SSc-related deaths due to ILD; possible stabilization with treatment
RA-ILD	32%	8%	Median survival, 3yr (UIP pattern) or longer (other patterns); effect of treatment on lung disease Unknown
Sarcoidosis, fibrotic	13%	45%	10-Yr mortality, about 10%; 75% of sarcoidosis-related deaths due to lung disease; generally responsive to Immunomodulation
Chronic HP	21%	3%	5-Yr survival, 50–80%; potential for improvement or stabilization with Treatment
Unclassifiable fibrotic ILD	53%	8%	5-Yr survival, 45–70%; variable disease course

N Engl J Med 2020;383:958-68.

Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study)

Mouhamad Nasser[1,2], Sophie Larrieu[3], Salim Si-Mohamed[4], Kaïs Ahmad[1,2], Loic Boussel[4], Marie Brevet[5,6], Lara Chalabreysse[5], Céline Fabre[3], Sébastien Marque[3], Didier Revel[4], Françoise Thivolet-Bejui[5], Julie Traclet[1,2], Sabrina Zeghmar[1,2], Delphine Maucort-Boulch[7] and Vincent Cottin[1,2]

- Real world, single center clinical cohort in Franc between January 1, 2010 and December 31, 2017
- Patients had ≥10% fibrosis at baseline HRCT

  (any one within 24 months)

  - Relative decline of ≥10% in FVC
  - Relative decline of ≥15% in DLCO
  - worsening symptoms or worsening radiological appearance (≥5-<10% relative decreased in FVC)
- Patients who received antifibrotics treatment at baseline were excluded

Eur Respir J 2021; 57: 2002718

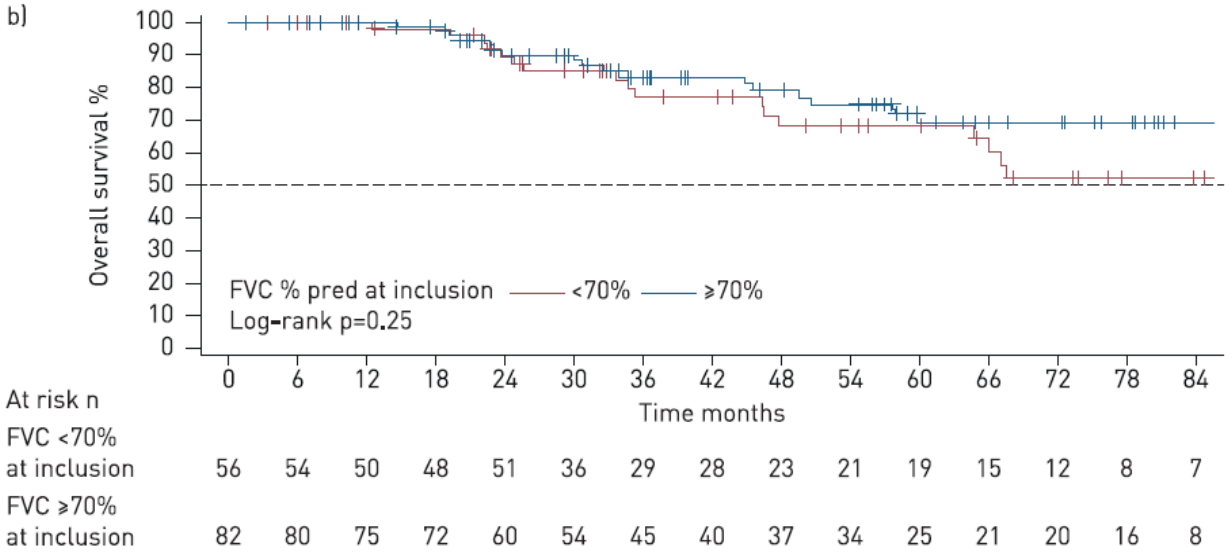
Patients	165
Female	94 (57.0)
Age years median (range)	61 (18–83)
Former or current smoker	69 (41.8)
GAP index[+]	
Stage I	81 (64.3)
Stage II	39 (31.0)
Stage III	6 (4.8)
UIP-like fibrotic pattern on HRCT	46 (27.9)
Criteria for disease progression in previous 24 months	
Relative FVC decline of ⩾10% pred	109 (66.1)
Relative FVC decline of 5–<10% pred plus worsening of respiratory symptoms or increased extent of fibrosis on HRCT	41 (24.8)
Worsening of respiratory symptoms and increased extent of fibrosis on HRCT	15 (9.1)
FVC	
Volume mL[#]	2333±935
% predicted[¶]	74±22
D_{LCO}[#] % predicted	44±18
Time from diagnosis to first meeting criteria for progression[#] years mean (IQR)	2.0 (0–3.3)
Chronic fibrosing hypersensitivity pneumonitis	14 (8.5)
Idiopathic interstitial pneumonia	12 (7.3)
Unclassifiable ILD	52 (31.5)
Interstitial pneumonitis with autoimmune features	2 (1.2)
Autoimmune ILD	77 (46.7)
Rheumatoid arthritis-ILD	7 (4.2)
Systemic sclerosis-ILD	43 (26.1)
Dermatomyositis-ILD	12 (7.3)
Mixed connective tissue disease-ILD	10 (6.1)
Other autoimmune ILD[#]	5 (3.0)
Other ILDs[¶]	10 (6.1)

IPF and CPFE excluded

Total n=165

Overall survival at 12, 48 and 84 months

99.3% (95% CI 95.4-99.9%), 77.1% (68.6-83.6%) and 65% (54.7-73.5%)



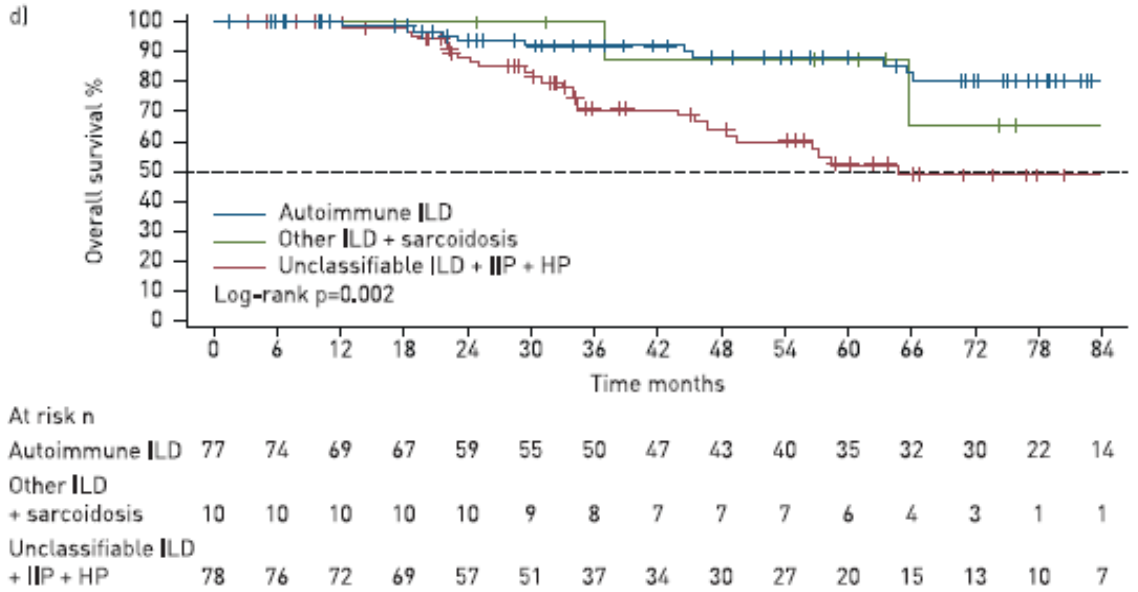


TABLE 4 Factors associated with mortality (multivariate Cox model)

Parameter	Reference	Observations n	HR (95% CI)	p-value
FVC % at inclusion	<70%	131	1.90 (0.96–3.77)	0.065
Decline in FVC of ⩾10% at baseline within 24 months	Yes	131	2.43 (1.06–5.61)	0.04
Diagnosis	Unclassifiable ILD or IIP or HP *versus* autoimmune ILD	131	3.45 (1.59–7.50)	0.002
Categorised age	⩾50 years	131	5.03 (1.53–16.54)	0.008

HR: hazard ratio; FVC: forced vital capacity; ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; HP: hypersensitivity pneumonitis.

Effects of nintedanib by inclusion criteria for progression of interstitial lung disease

Toby M. Maher[1,2,3], Kevin K. Brown[4], Michael Kreuter[5], Anand Devaraj[1,6], Simon L.F. Walsh[1], Lisa H. Lancaster[7], Elizabeth A. Belloli[8], Maria Padilla[9], Juergen Behr[10], Rainer-Georg Goeldner[11], Kay Tetzlaff[12,13], Rozsa Schlenker-Herceg[14] and Kevin R. Flaherty[15], on behalf of the INBUILD trial investigators

- In INBUILD trial, nintedanib slowed the rate of decline in FVC over 52 weeks by 57% compared with placebo

N Engl J Med 2019;381:1718-27.

- Group A, relative decline in FVC ⩾10% predicted

  Group B, relative decline in FVC ⩾5–<10% predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT

  Group C, worsened respiratory symptoms and increased extent of fibrosis on HRCT only

Eur Respir J 2022; 59: 2004587

TABLE 1 Baseline characteristics in subgroups in the overall population by inclusion criteria for ILD progression

	Group A[#]		Group B[¶]		Group C[+]	
	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Placebo
Subjects, n	160	172	110	97	62	61
Male	81 (50.6)	85 (49.4)	66 (60.0)	53 (54.6)	32 (51.6)	38 (62.3)
Age, years	66.5±9.0	67.2±9.1	64.8±9.6	66.0±9.3	62.8±11.2	64.1±12.1
Body mass index, $kg \cdot m^{-2}$	27.9±5.2	28.0±5.5	28.1±4.8	28.9±5.8	28.8±5.1	28.8±5.1
ILD diagnosis						
Hypersensitivity pneumonitis	44 (27.5)	51 (29.7)	24 (21.8)	27 (27.8)	16 (25.8)	11 (18.0)
Autoimmune ILDs[§]	43 (26.9)	42 (24.4)	26 (23.6)	31 (32.0)	13 (21.0)	15 (24.6)
Idiopathic NSIP	30 (18.8)	32 (18.6)	16 (14.5)	16 (16.5)	18 (29.0)	13 (21.3)
Unclassifiable IIP	30 (18.8)	25 (14.5)	26 (23.6)	14 (14.4)	8 (12.9)	11 (18.0)
Other ILDs[f]	13 (8.1)	22 (12.8)	18 (16.4)	9 (9.3)	7 (11.3)	11 (18.0)
UIP-like fibrotic pattern on HRCT	100 (62.5)	98 (57.0)	76 (69.1)	68 (70.1)	30 (48.4)	39 (63.9)
FVC, mL	2210±706	2121±633	2452±705	2487±752	2477±837	2601±772
FVC % predicted	66.5±14.8	65.6±12.7	70.0±16.3	73.4±16.8	72.1±17.9	73.0±16.8
D_{LCO} % predicted	44.8±12.3	45.1±13.2	43.5±11.7	51.8±15.4	44.7±11.6	49.5±17.4

TABLE 2 Rate of decline in FVC (mL per year) over 52 weeks with nintedanib *versus* placebo by inclusion criteria for ILD progression

	Group A[#]		Group B[¶]		Group C[+]	
	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Placebo
Overall population						
Subjects analysed, n	160	172	110	97	62	61
Adjusted mean±SE rate of decline in FVC, mL per year	−72.±21.8	−235.0±20.8	−109.5±26.0	−145.3±27.5	−49.7±34.3	−127.5±33.8
Difference *versus* placebo (95% CI)	162.5 (103.5 to 221.4)		35.8 (−38.4 to 109.9)		77.8 (−16.5 to 172.0)	
Treatment-by-subgroup-by-time interaction			p=0.026			
Subjects with a UIP-like fibrotic pattern on HRCT						
Subjects analysed, n	100	98	76	68	30	39
Adjusted mean±SE rate of decline in FVC, mL per year	−68.7±29.7	−279.4±30.0	−117.3±34.0	−172.7±35.9	−40.9±54.4	−114.4±46.0
Difference *versus* placebo (95% CI)	210.7 (128.0 to 293.4)		55.4 (−41.7 to 152.5)		73.6 (−65.5 to 212.7)	
Treatment-by-subgroup-by-time interaction			p=0.039			
Subjects with other fibrotic patterns on HRCT						
Subjects analysed, n	60	74	34	29	32	22
Adjusted mean±SE rate of decline in FVC, mL per year	−79.4±31.9	−182.7±28.2	−99.2±41.4	−91.3±43.8	−55.6±42.3	−145.9±49.7
Difference *versus* placebo (95% CI)	103.3 (19.7 to 186.9)		−8.0 (−126.1 to 110.2)		90.3 (−38.3 to 218.9)	
Treatment-by-subgroup-by-time interaction			p=0.30			

FVC: forced vital capacity; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography. [#]: decline in FVC ⩾10% predicted; [¶]: decline in FVC ⩾5–<10% predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; [+]: worsened respiratory symptoms and increased extent of fibrosis on HRCT only.

Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial

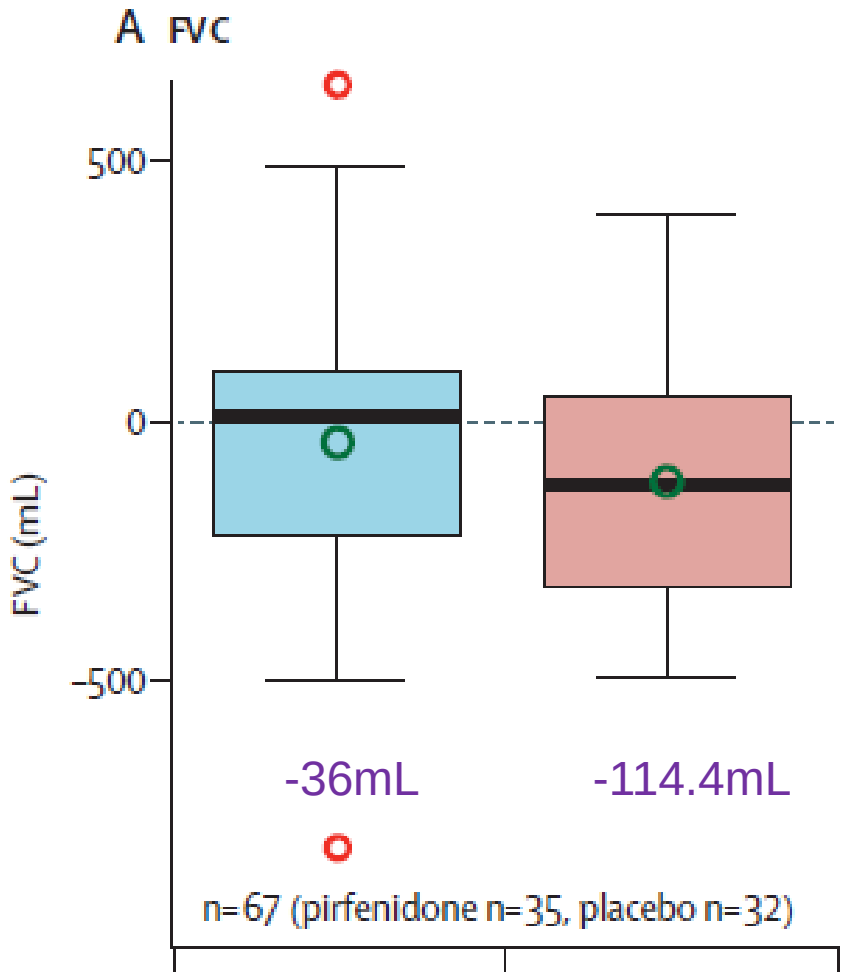
Lancet Respir Med 2021; 9: 476–86

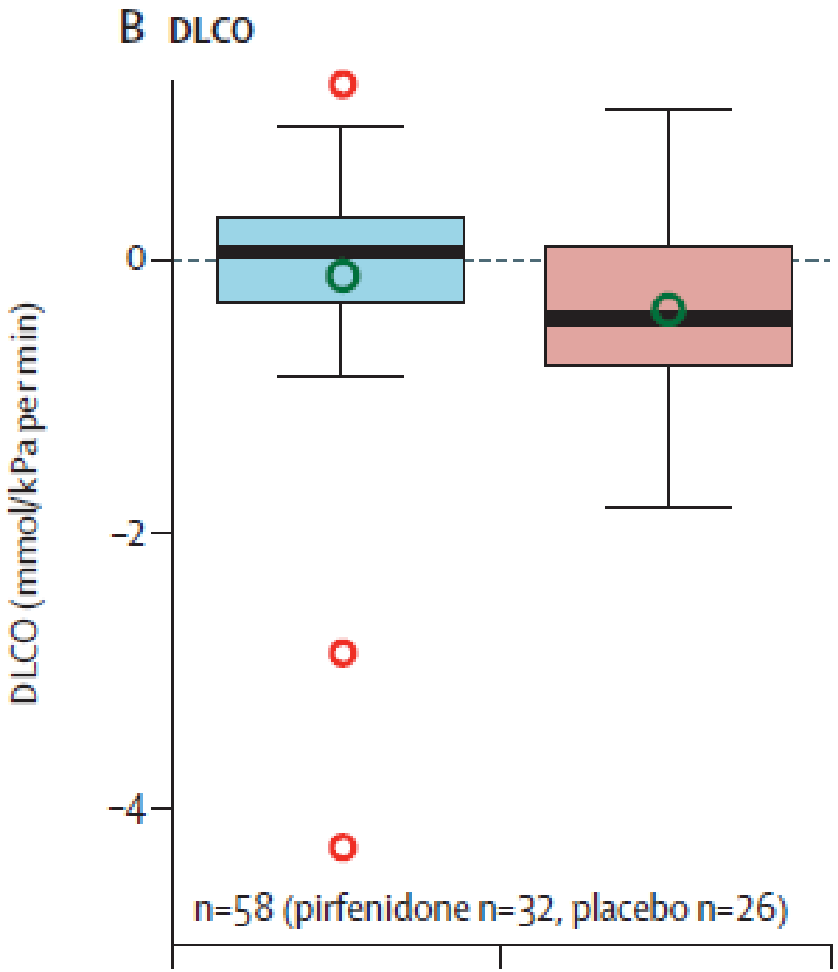
Patients

- FVC 40-90%, DLCO 25-75% (10-90%), 6MWT ≥150m
- Progression FVC ≥ 5% decline (at least 3 FVC measurements within 6-24months)

Diagnosis of ILD

- Chronic HP 57 (45%)
- CTD-ILD 37 (29%)
- Fibrotic NSIP 27 (21%)
- Asbestos induced lung fibrosis 6 (5%)





From baseline to week 48

Lancet Respir Med 2021; 9: 476–86

Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society

Lancet Respir Med 2020; 8: 726–37

Hiroto Hatabu*, Gary M Hunninghake, Luca Richeldi, Kevin K Brown, Athol U Wells, Martine Remy-Jardin, Johny Verschakelen, Andrew G Nicholson, Mary B Beasley, David C Christiani, Raúl San José Estépar, Joon Beom Seo, Takeshi Johkoh, Nicola Sverzellati, Christopher J Ryerson, R Graham Barr, Jin Mo Goo, John H M Austin, Charles A Powell, Kyung Soo Lee, Yoshikazu Inoue, David A Lynch†

- What are ILAs?

 - **Incidental** identification of non-dependent abnormalities, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts

 - Involving at least 5% of a lung zone (upper, middle, and lower lung zone)

 - In individuals in whom interstitial disease is not suspected

Risk factors associated with the development of interstitial lung abnormalities

The Mexican National Institute of Respiratory Disease

Ivette Buendía-Roldán[1,3], Rosario Fernandez[1], Mayra Mejía[1], Fortunato Juarez[1], Gustavo Ramirez-Martinez[1], Eduardo Montes[1], Ana Karem S. Pruneda[1], Karen Martinez-Espinosa[1], Aime Alarcon-Dionet[1], Iliana Herrera[1], Carina Becerril[1], Leslie Chavez-Galan[1], Mario Preciado[1], Annie Pardo[2] and Moisés Selman[1,3]

	ILA		Non-ILA control	p-value
Subjects	80	9.7%	564	
Age years	72±8		69±8	<0.0001
Male	34 (43)		149 (26)	0.005
Smoking status				
Never-smoker	31 (39)		302 (54)	0.01
Ex-smoker	40 (50)		161 (29)	0.3
Current smoker	9 (11)		101 (18)	0.08
FVC % pred	93±17		95±15	0.19
D_{LCO} % pred#	87±18		102±19	<0.0001
D_{LCO}/V_A index	95±29		109±20	<0.0001
S_{pO_2} at rest %	94±2		95±2	0.0003
S_{pO_2} post-exercise %	87±9		91±5	<0.0001
6MWD m	407±144		460±112	0.0001

Gene polymorphisms and biomarkers

MUC5B promoter polymorphism was found to be significantly associated with ILAs (OR 3.5, 95% CI 1.3-9.4; p=0.01)

Eur Respir J 2021; 58: 2003005

TABLE 3 Basal serum concentrations of biomarkers between groups

	ILA	Non-ILA control	p-value	Corrected p-value[#]
Subjects	80	80		
MMP-1 $ng \cdot mL^{-1}$	7±4	6±3	0.02	0.2
MMP-2 $ng \cdot mL^{-1}$	38±4	37±2	0.53	1.0
MMP-3 $ng \cdot mL^{-1}$	19±11	17±10	0.28	1.0
MMP-7 $\mu g \cdot mL^{-1}$	6±4	4±2	0.008	0.09
MMP-8 $ng \cdot mL^{-1}$	4±4	3±3	0.28	1.0
MMP-9 $ng \cdot mL^{-1}$	14±9	12±8	0.32	1.0
MMP-12 $pg \cdot mL^{-1}$	30±12	27±10	0.16	1.0
MMP-13 $pg \cdot mL^{-1}$	357±143	298±116	0.004	0.04
IL-6 $ng \cdot mL^{-1}$	16±21	11±15	0.04	0.4
SP-D $ng \cdot mL^{-1}$	10±11	8±6	0.04	0.4
α-Klotho $pg \cdot mL^{-1}$	735±462	519±133	0.99	1.0
Resistin $ng \cdot mL^{-1}$	12±5	9±4	0.0005	0.006

Data are presented as n or mean±SD, unless otherwise stated. ILA: interstitial lung abnormality; MMP: matrix metalloproteinase; IL: interleukin; SP: surfactant protein. [#]: corrected by Bonferroni adjustment.

- **Progression** was determined when the individual presented two of the following conditions

- decline of FVC >10%, DLCO >15% or reduction of 50m in 6MWT
- initiation or worsening of respiratory symptoms
- an increase of >30% of lesions compared with the previous HRCT or the appearance of new lesions such as honeycombing or traction bronchiectasis

- On follow-up (24±18months), **18 (23%) showed progression**

None of the biomarkers, MUC5B polymorphism or demographic data showed an association with progression

GERD(OR 4.1, 95% CI 1.2–12.9; p=0.02)

Females with diabetes mellitus (OR 5.3, 95% CI 1.0–27.4; p=0.01)

Eur Respir J 2021; 58: 2003005

Original research

Prospective nationwide multicentre cohort study of the clinical significance of autoimmune features in idiopathic interstitial pneumonias

Multicenter prospective study 376 patients in 28 hospitals in Japan

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and,
2. Exclusion of alternative etiologies and,
3. Does not meet criteria of a defined CTD and,
4. At least one feature from at least two of these domains:
    - A. Clinical domain
    - B. Serologic domain
    - C. Morphologic domain

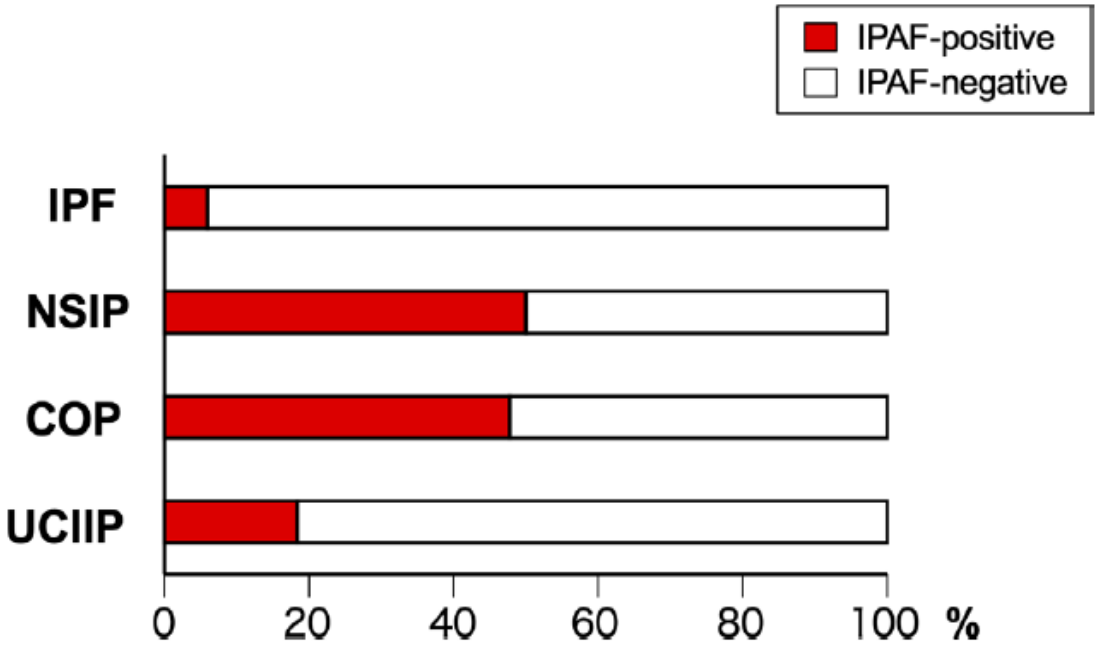
Eur Respir J 2015; 46: 976–987

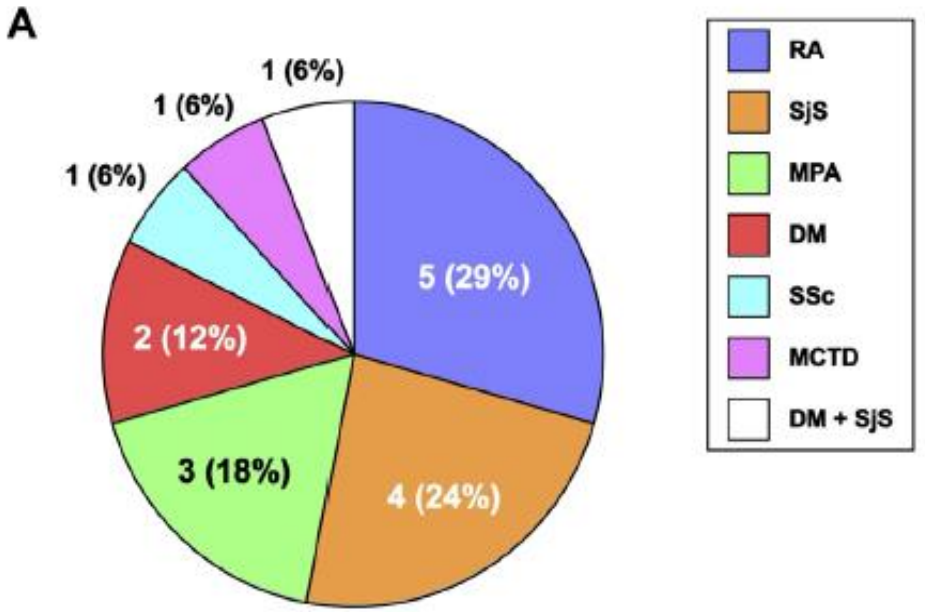
IPAF 70 patients (18.6%)

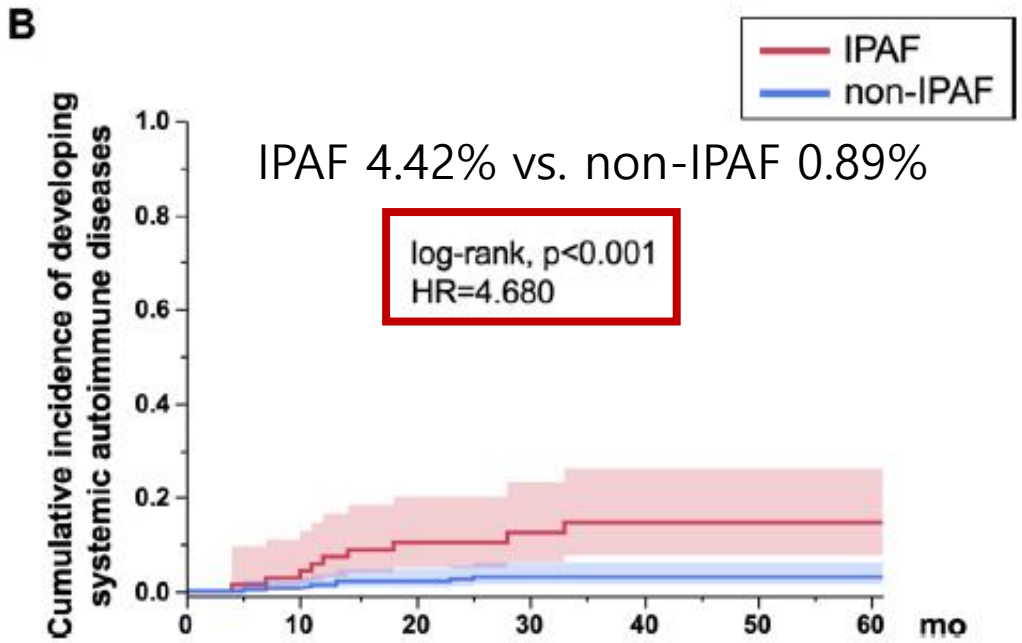
- B+C: 41 patients
- A+B: 30 patients
- C+A: 21 patients
- A+B+C: 11 patients

Enomoto N, *et al*. *Thorax* 2022;**77**:143–153.

During 35 months, defined systemic autoimmune disease were developed in 17 patients (4.5%)

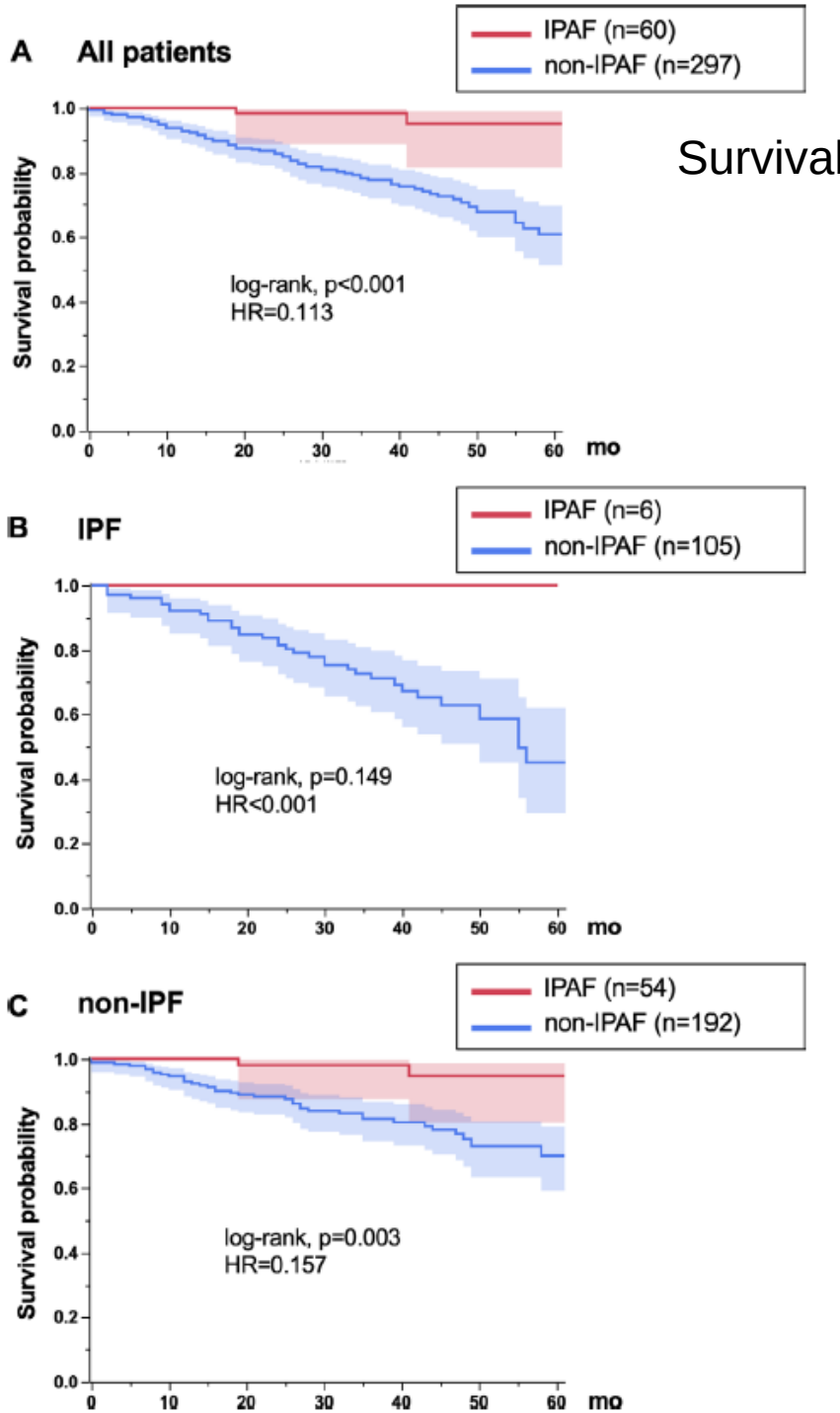




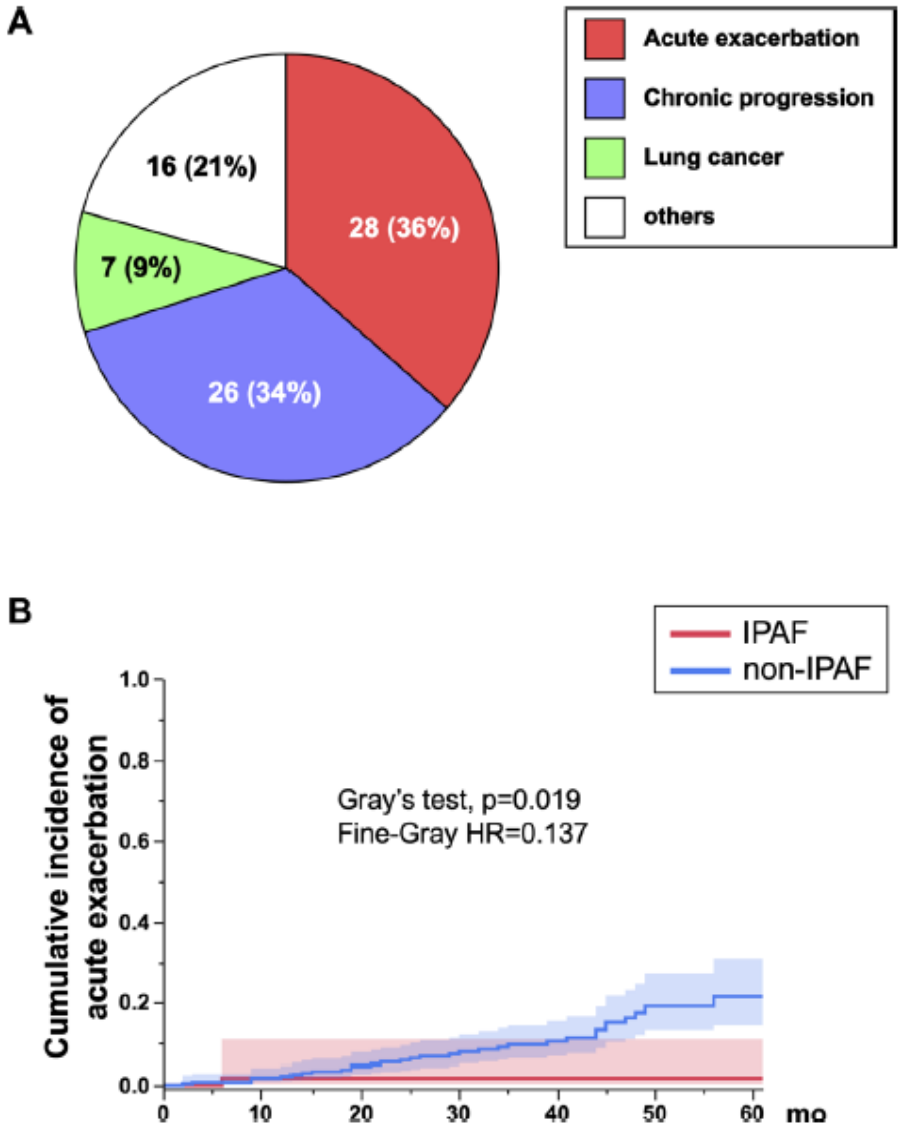


Enomoto N, *et al*. *Thorax* 2022;**77**:143–153.

Survival



Causes of death and occurrence of acute exacerbation



Enomoto N, *et al*. *Thorax* 2022;**77**:143–153.

Methotrexate and rheumatoid arthritis associated interstitial lung disease

- Whether MTX exposure increases the risk of ILD in patients with RA
- Case-control study

RA with ILD (RA-ILD) (n = 410) vs. RA without ILD (n=673)

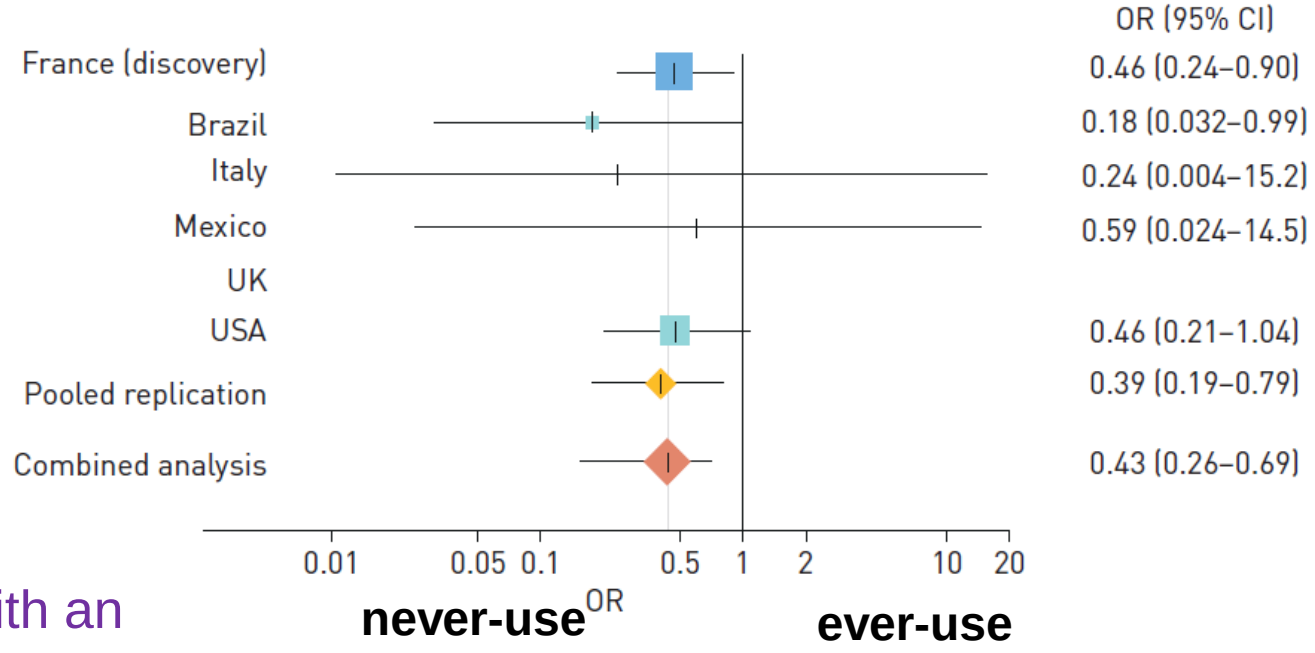
MTX ever-use
307(74.9%) vs. 622 (92.4%), p=0.0006

MTX cumulative dose
1.3g vs 3.9g, p<0.0001

ILD detection was significantly delayed in MTX ever-users compared to never-users (111.4±10.4 years and 4.0±7.4 years; p<0.001)

MTX use is not associated with an increased risk of RA ILD

MTX ever-use and risk of RA ILD



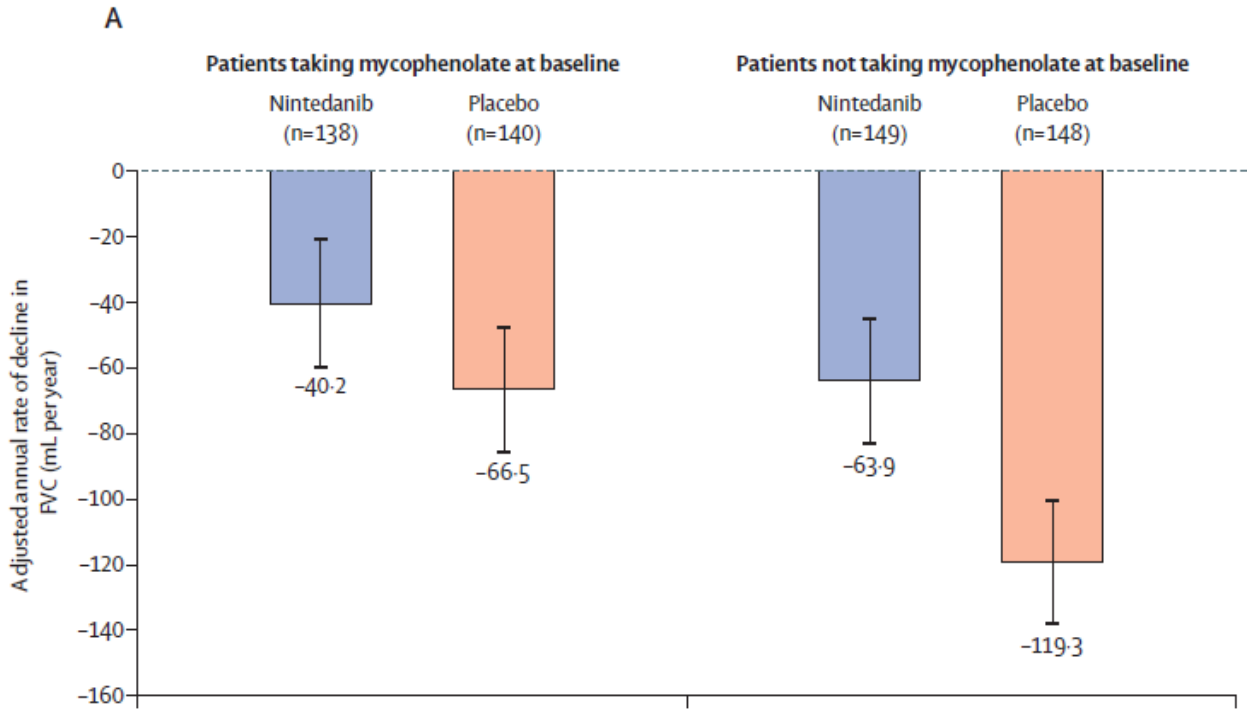
Pierre-Antoine Jude et al. Eur Respir J 2021;57:2000337

Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial

Kristin B Highland, Oliver Distler*, Masataka Kuwana, Yannick Allanore, Shervin Assassi, Arata Azuma, Arnaud Bourdin, Christopher P Denton, Jörg H W Distler, Anna Maria Hoffmann-Vold, Dinesh Khanna, Maureen D Mayes, Ganesh Raghu, Madelon C Vonk, Martina Gahlemann, Emmanuelle Clerisme-Beaty, Mannaig Girard, Susanne Stowasser, Donald Zoz, Toby M Maher, on behalf of the SENSCIS trial investigators†*

- In SENCIS trail, Nintedanib reduced the rate of decline in FVC in patients with SSc-ILD

NEJM 2019;380:2518-28



Total 576 patients

Patients taking MMF at baseline
Nintedanib (n=138) vs. placebo (n=140)
Patients not taking MMF at baseline
Nintedanib (n=149) vs. placebo (n=148)

Lancet Respir Med 2021;9:96-106

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Any adverse event*	136 (98%)	135 (96%)	147 (99%)	141 (95%)
Most frequent adverse events†				
Diarrhoea	106 (76%)	48 (34%)	112 (75%)	43 (29%)
Nausea	43 (31%)	23 (16%)	48 (32%)	16 (11%)
Skin ulcer	22 (16%)	23 (16%)	31 (21%)	27 (18%)
Vomiting	32 (23%)	17 (12%)	39 (26%)	13 (9%)
Cough	20 (14%)	33 (24%)	14 (9%)	19 (13%)
Nasopharyngitis	10 (7%)	22 (16%)	26 (17%)	27 (18%)
Upper respiratory tract infection	19 (14%)	25 (18%)	14 (9%)	10 (7%)
Abdominal pain	14 (10%)	6 (4%)	19 (13%)	15 (10%)
Fatigue	19 (14%)	14 (10%)	12 (8%)	6 (4%)
Headache	16 (12%)	15 (11%)	11 (7%)	9 (6%)
Urinary tract infection	16 (12%)	11 (8%)	8 (5%)	12 (8%)
Weight decreased	10 (7%)	4 (3%)	24 (16%)	8 (5%)
Decreased appetite	14 (10%)	10 (7%)	13 (9%)	2 (1%)
Severe adverse event	28 (20%)	18 (13%)	24 (16%)	18 (12%)
Serious adverse event	36 (26%)	22 (16%)	33 (22%)	40 (27%)
Fatal adverse event	3 (2%)	2 (1%)	2 (1%)	2 (1%)
Adverse event leading to treatment discontinuation	15 (11%)	9 (6%)	31 (21%)	16 (11%)

Nintedanib reduced the progression of ILD both in patients with SSc-ILD who were and were not using MMF at baseline. The adverse event profile of nintedanib was similar in the subgroups

Lancet Respir Med 2021;9:96-106

Original research

Risk of drug-induced interstitial lung disease in hospitalised patients: a nested case–control study

Taisuke Jo,[1,2] Nobuaki Michihata,[2] Hayato Yamana,[2] Kojiro Morita,[3,4] Miho Ishimaru,[3,4] Yasuhiro Yamauchi,[1] Wakae Hasegawa,[1] Hirokazu Urushiyama,[1] Kazuaki Uda,[4] Hiroki Matsui,[4] Kiyohide Fushimi,[5] Hideo Yasunaga,[4] Takahide Nagase[1]

- Japanese national inpatient database
- Patients without interstitial pneumonia on admission who developed DILD and required corticosteroid therapy during hospitalization
- 1541 case patients vs. 5677 control (one to four case control matching)
- 42 classified categories of drugs with 216 generic names as drugs with potential risk of DILD

Jo T, *et al*. *Thorax* 2021;**76**:1193–1199. doi:10.1136/thoraxjnl-2020-215824

Table 4 Multivariable conditional logistic regression analysis for the occurrence of drug-induced interstitial lung disease

Characteristics	OR	95% CI	P value
Barthel index			
95–100	Reference		
0–90	0.93	0.78 to 1.09	0.352
Brinkman index			
0–199	Reference		
200–599	1.64	1.31 to 2.05	<0.001
≥600	2.54	2.17 to 2.98	<0.001
Body mass index			
<18.50	1.65	1.38 to 1.96	<0.001
18.50–24.99	Reference		
≥25.00	1.18	0.93 to 1.48	0.169
Charlson Comorbidity Index			
0–2	Reference		
3–5	1.01	0.77 to 1.32	0.955
≥6	2.39	2.00 to 2.86	<0.001
Lung cancer	2.38	1.81 to 3.12	<0.001
Other cancer (other than lung cancer)	1.77	1.43 to 2.20	<0.001
ICU admission within 2 days of hospitalisation	0.68	0.46 to 1.02	0.063
Mechanical ventilation within 2 days of hospitalisation	1.77	1.22 to 2.47	0.002
Drug category with potential risk			
Anticoagulants	2.58	0.76 to 8.81	0.130
Statins	0.53	0.37 to 0.75	<0.001
Class III antiarrhythmic drugs	7.01	3.86 to 12.73	<0.001
NSAIDs	1.90	1.56 to 2.31	<0.001
Sulfamethoxazole/trimethoprim	2.54	1.04 to 6.24	0.042
Quinolones	3.10	2.41 to 3.99	<0.001
Tetracyclines	1.60	0.97 to 2.66	0.067
Beta-lactams	1.54	1.29 to 1.84	<0.001
EGFR inhibitors	16.84	9.32 to 30.41	<0.001
Anthracyclines	1.89	0.68 to 5.23	0.223

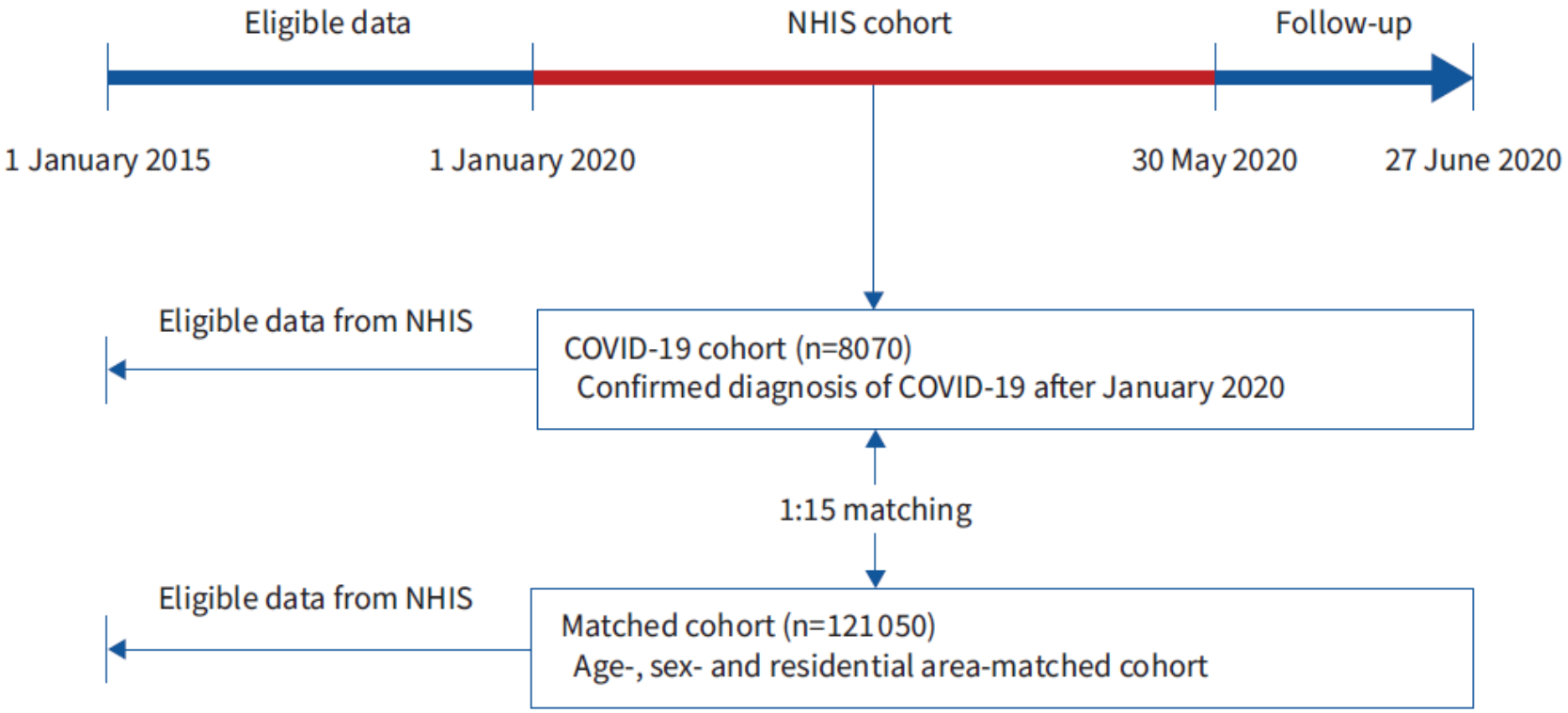
Smoking

Jo T, *et al*. *Thorax* 2021;**76**:1193–1199. doi:10.1136/thoraxjnl-2020-215824

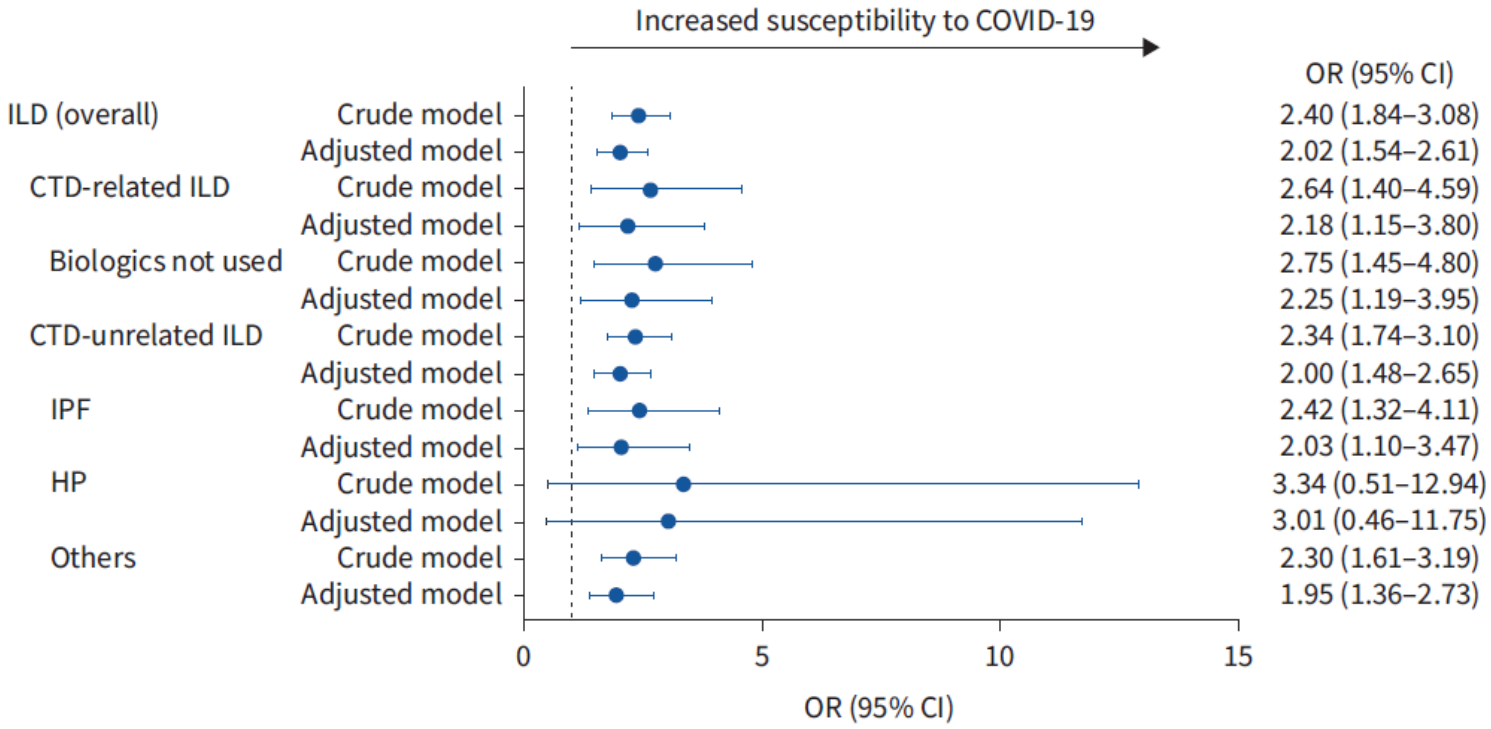
Interstitial lung disease increases susceptibility to and severity of COVID-19

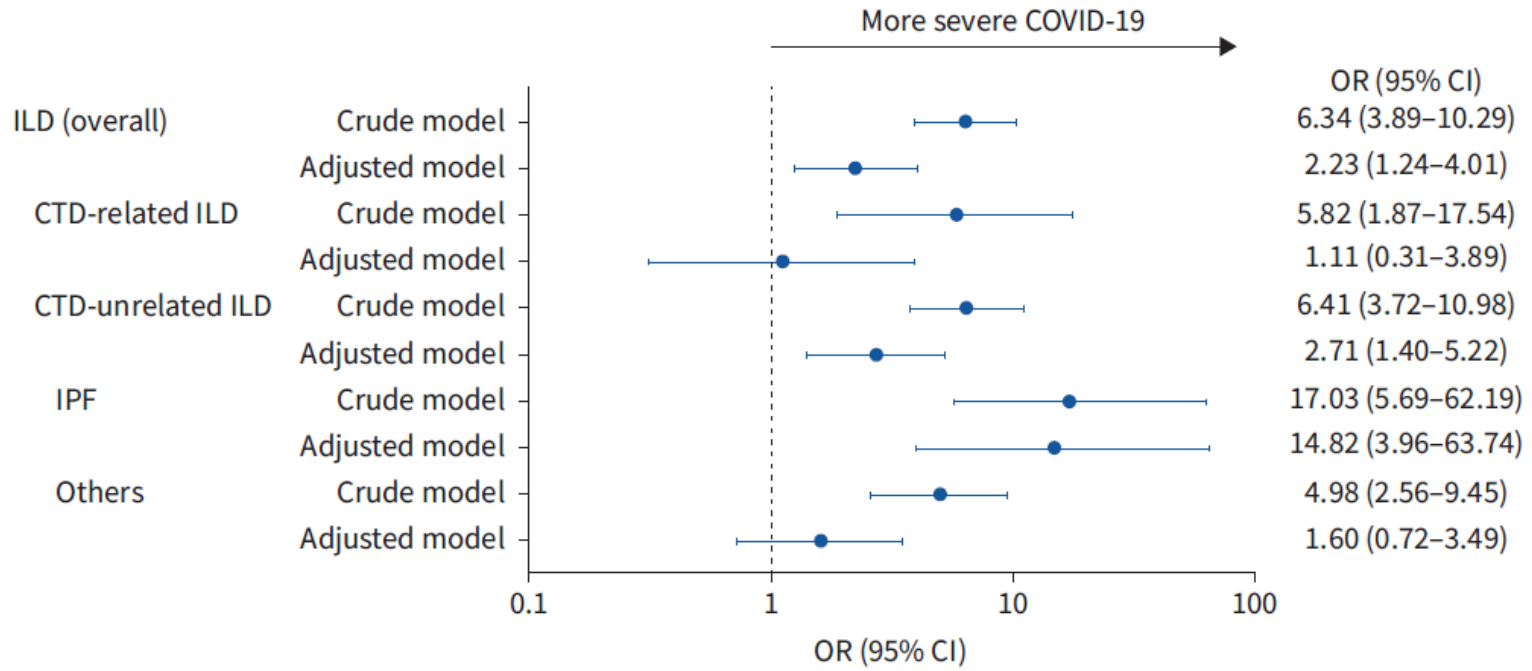
Hyun Lee[1,5], Hayoung Choi [2,5], Bumhee Yang[3,5], Sun-Kyung Lee[1,4], Tai Sun Park[1], Dong Won Park [1], Ji-Yong Moon[1], Tae-Hyung Kim [1], Jang Won Sohn[1], Ho Joo Yoon[1] and Sang-Heon Kim [1]

Nationwide cohort of patients who had confirmed diagnoses of COVID-19 (n=8070)



Eur Respir J 2021; 58: 2004125





Patients with ILD are more susceptible to COVID-19 and experience more severe COVID-19 compared with those without ILD.

Eur Respir J 2021; 58: 2004125

Take home message

- Active and maternal tobacco smoking have an independent detrimental effect on risk of IPF
- Subpleural and/or paraseptal fibrosis were not essential for diagnosing UIP in TBLC. The diagnostic accuracy of TBLC was strengthened when increased numbers of samples were taken
- R-scale-PF correlates well with the K-BILD and EQ-5D-5L
- Elevated monocyte count was associated with increased risks of IPF progression, hospitalization, and mortality

- Treatments

  Antifibrotics: all-cause mortality ↓ , acute exacerbation ↓ **Better!!**

  Pirfenidone + inhaled N-acetylcysteine: change in FVC ↑ **Worse!!**

  Antimicrobial therapy: nonelective hospitalization or death **No significance**

Take home message

- In patients with PF-ILD not receiving antifibrotic therapy, the disease followed a course characterized by continued decline in lung function, which predicted mortality
- Nintedanib reduced the rate of decline in FVC across the subgroups based on the inclusion criteria
- Pirfenidone might attenuate disease progression as measured by decline in FVC

- Patients with IPAF showed a significantly better prognosis with less frequent AE than patients with non-IPAF in IIPs
- MTX use is not associated with an increased risk of RA-ILD, and that ILD was detected later in MTX-treated patients.
- Combination of MMF and nintedanib offers a safe treatment option for patients with SSc-ILD