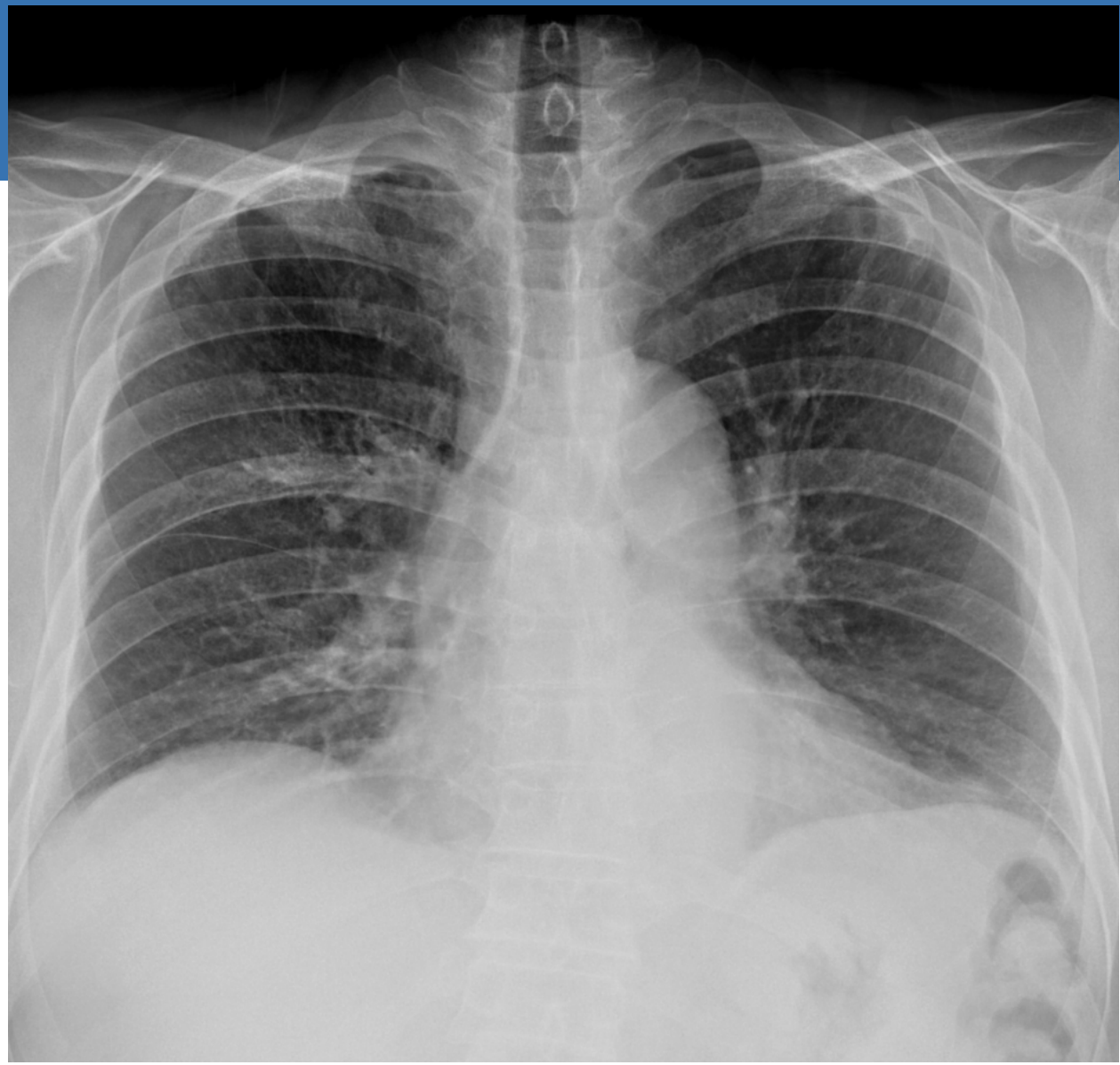
외래에서 폐섬유화증의 진단 및 치료

전남대학교병원
호흡기내과
신홍준

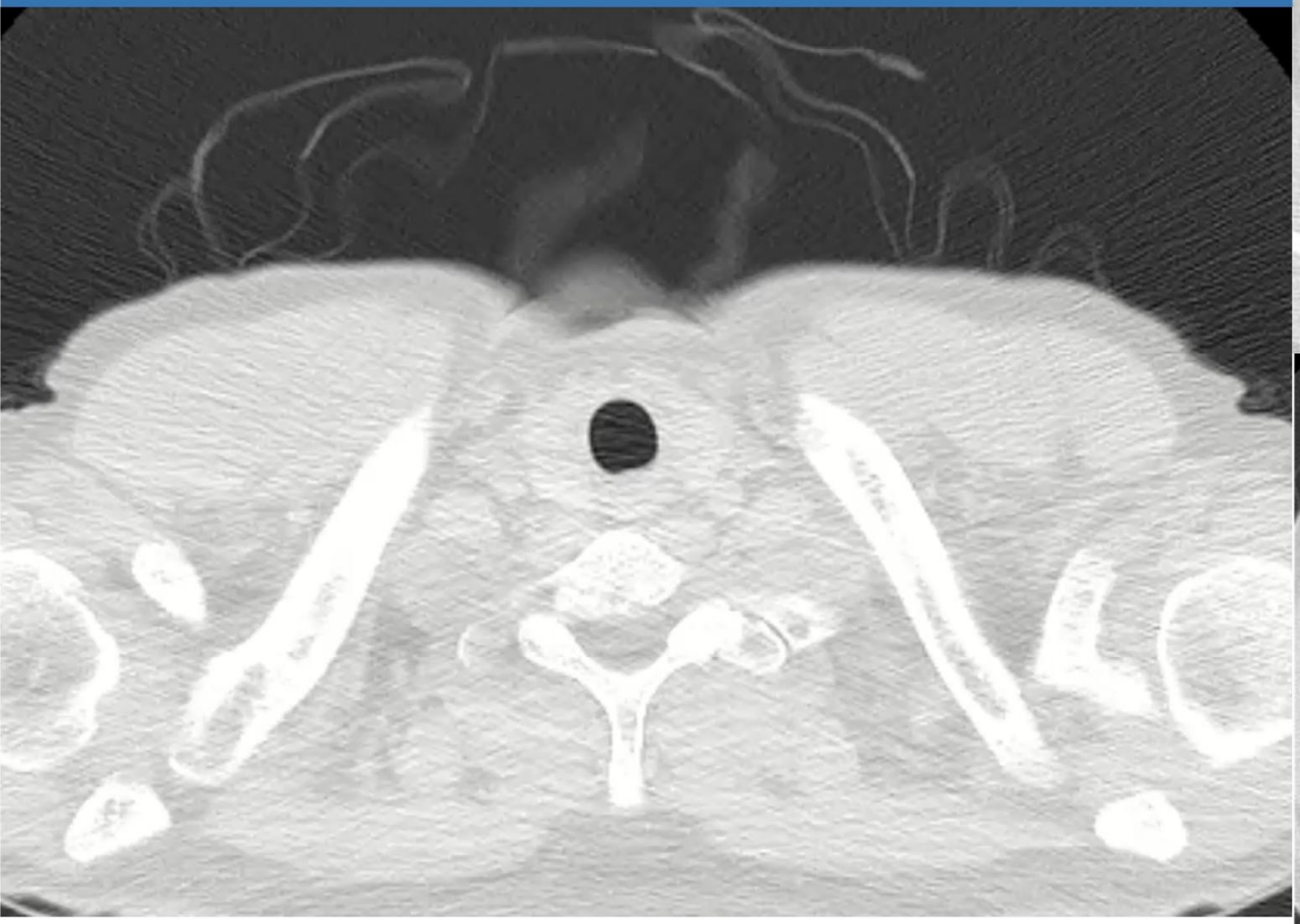
CASE 1. 60/M

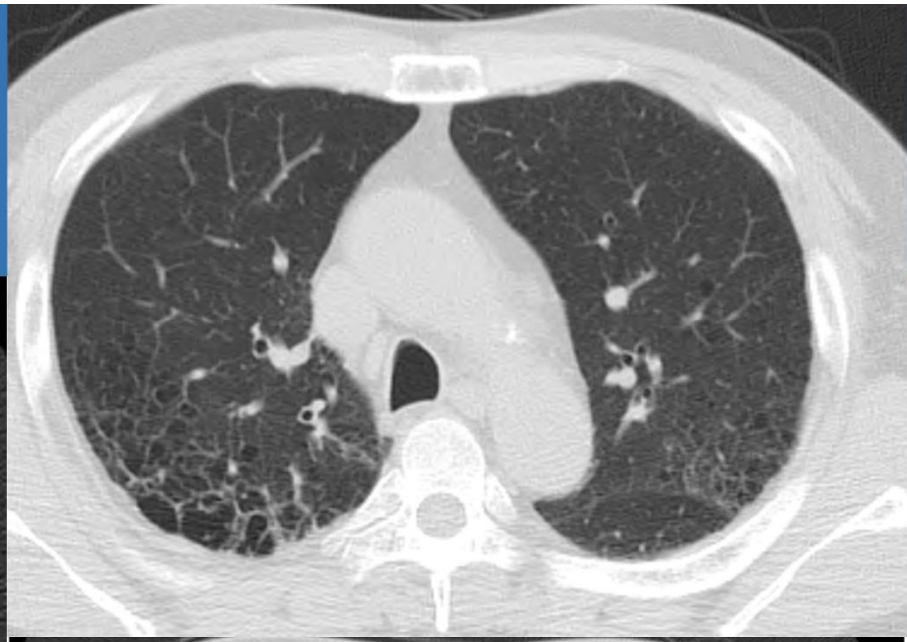
- C/C 검진 chest CT상 ILD 의심되어 의뢰됨
- P/H No underlying disease

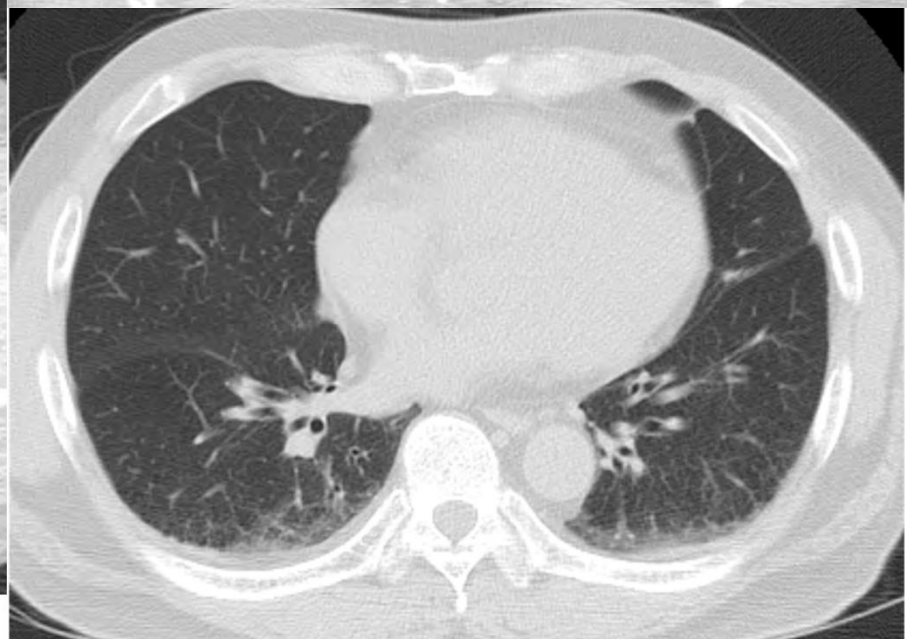
- C-smoker, 80 PYs
- C/S +/- mMRC Gr 0-1



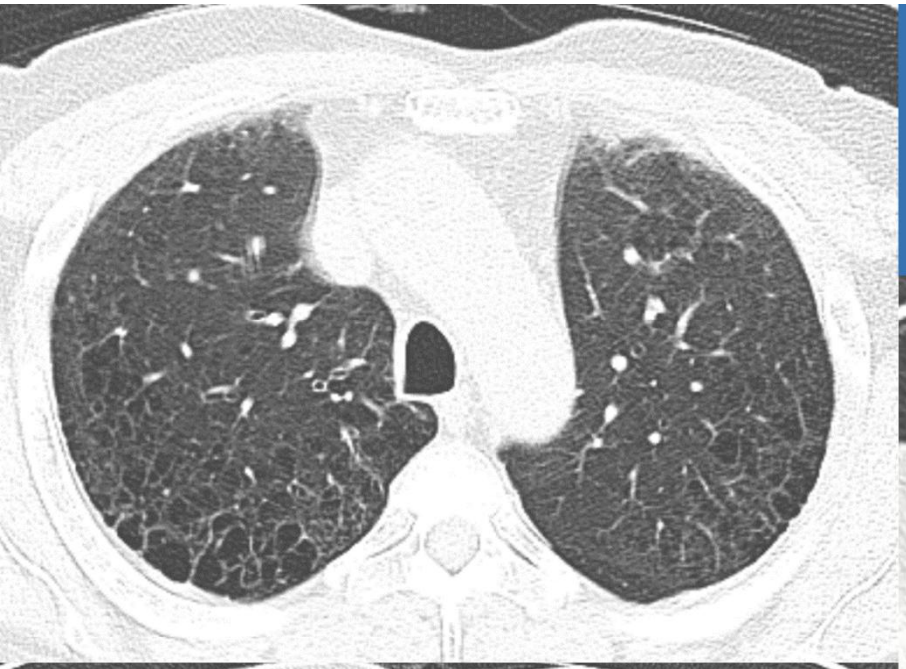
타원 Chest CT

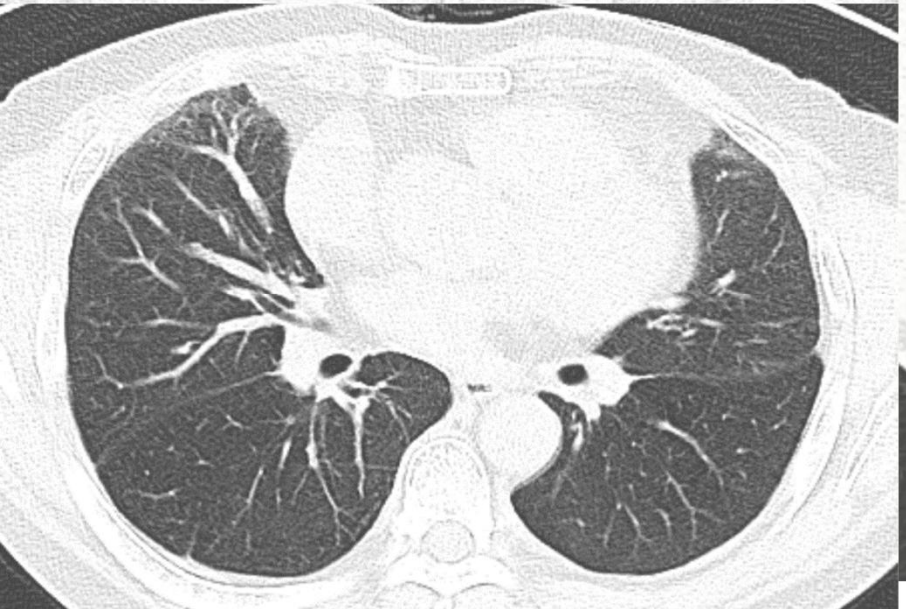


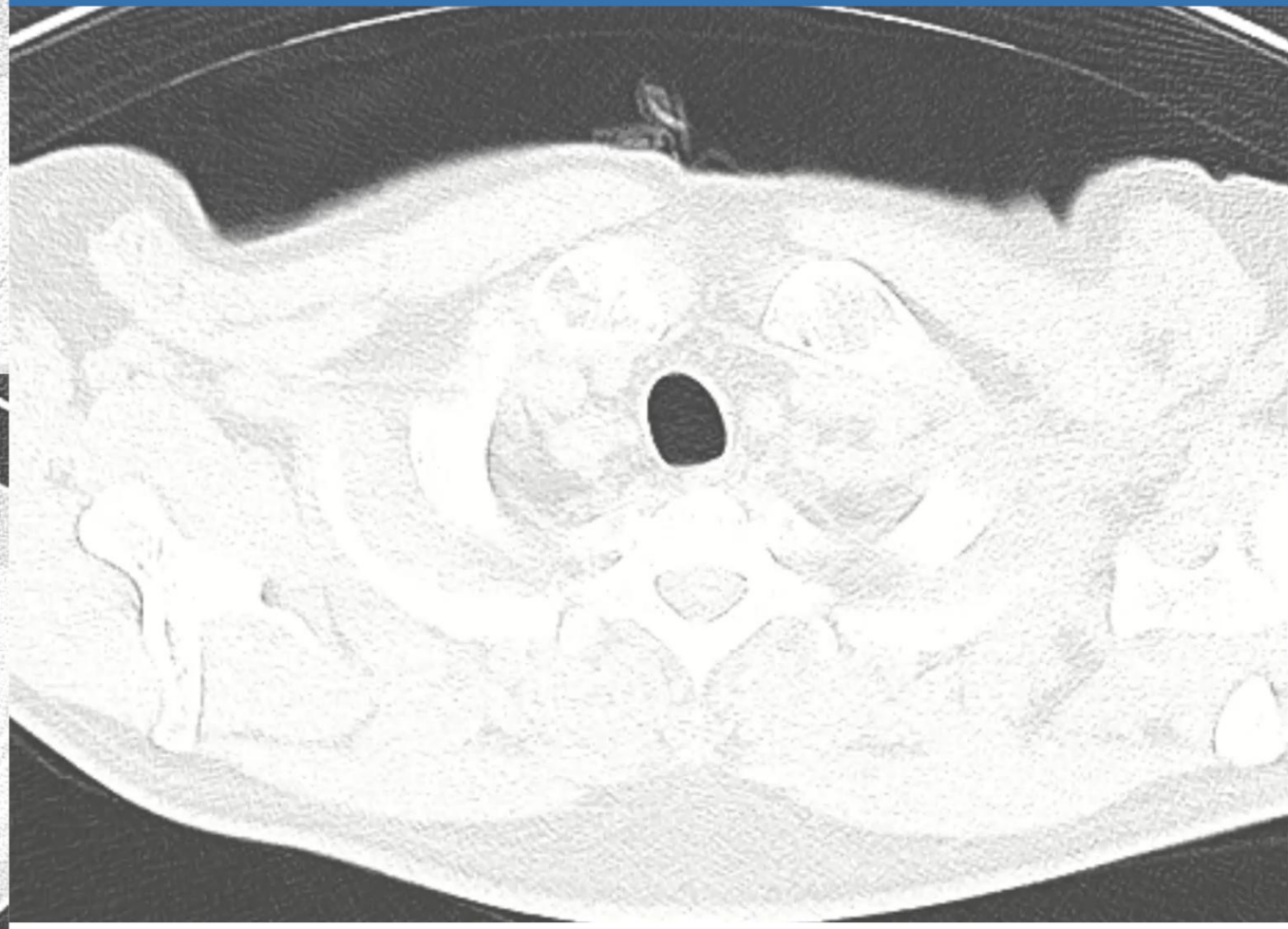




본원 Prone HRCT







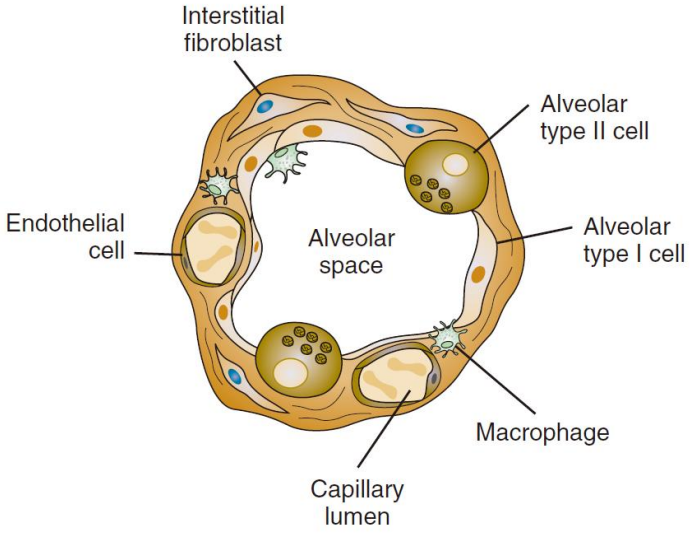
진단

- Emphysema
- Dependent opacities

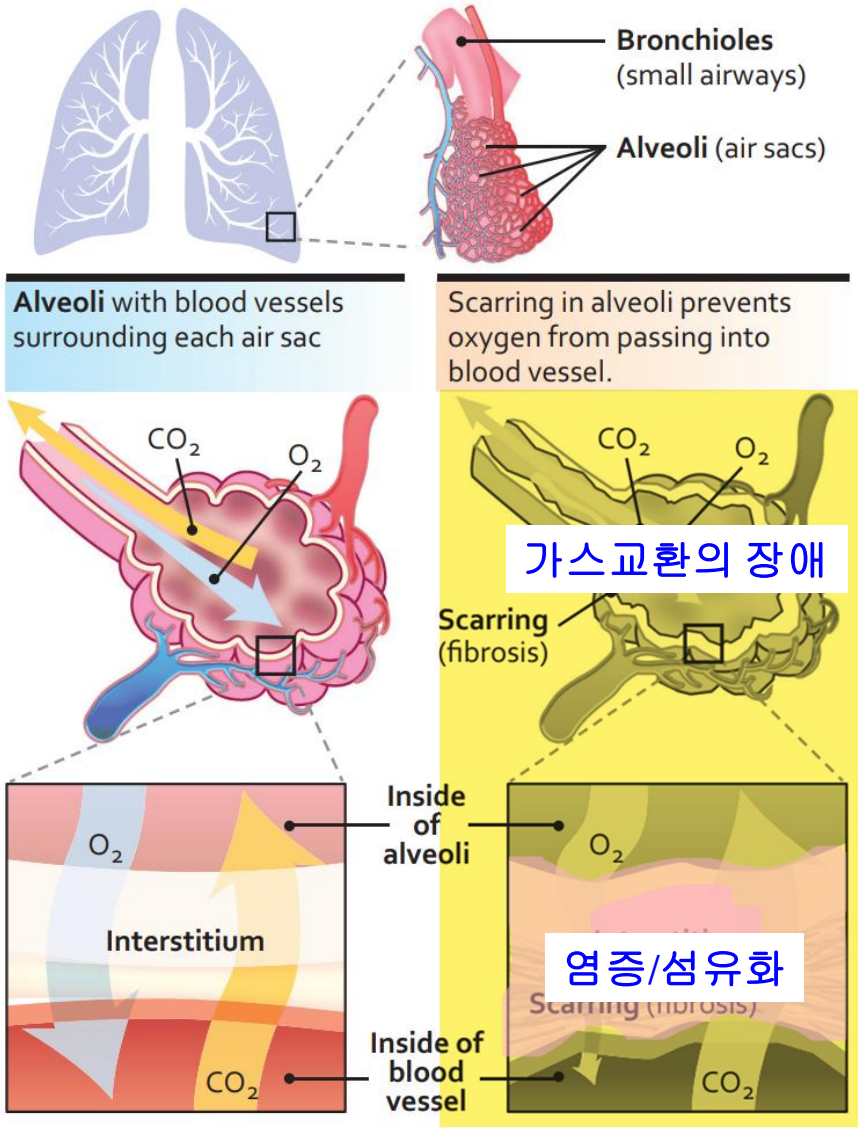
간질성 폐질환 ??

Epilepsy??

간질성폐질환
Interstitial lung diseases (ILD)

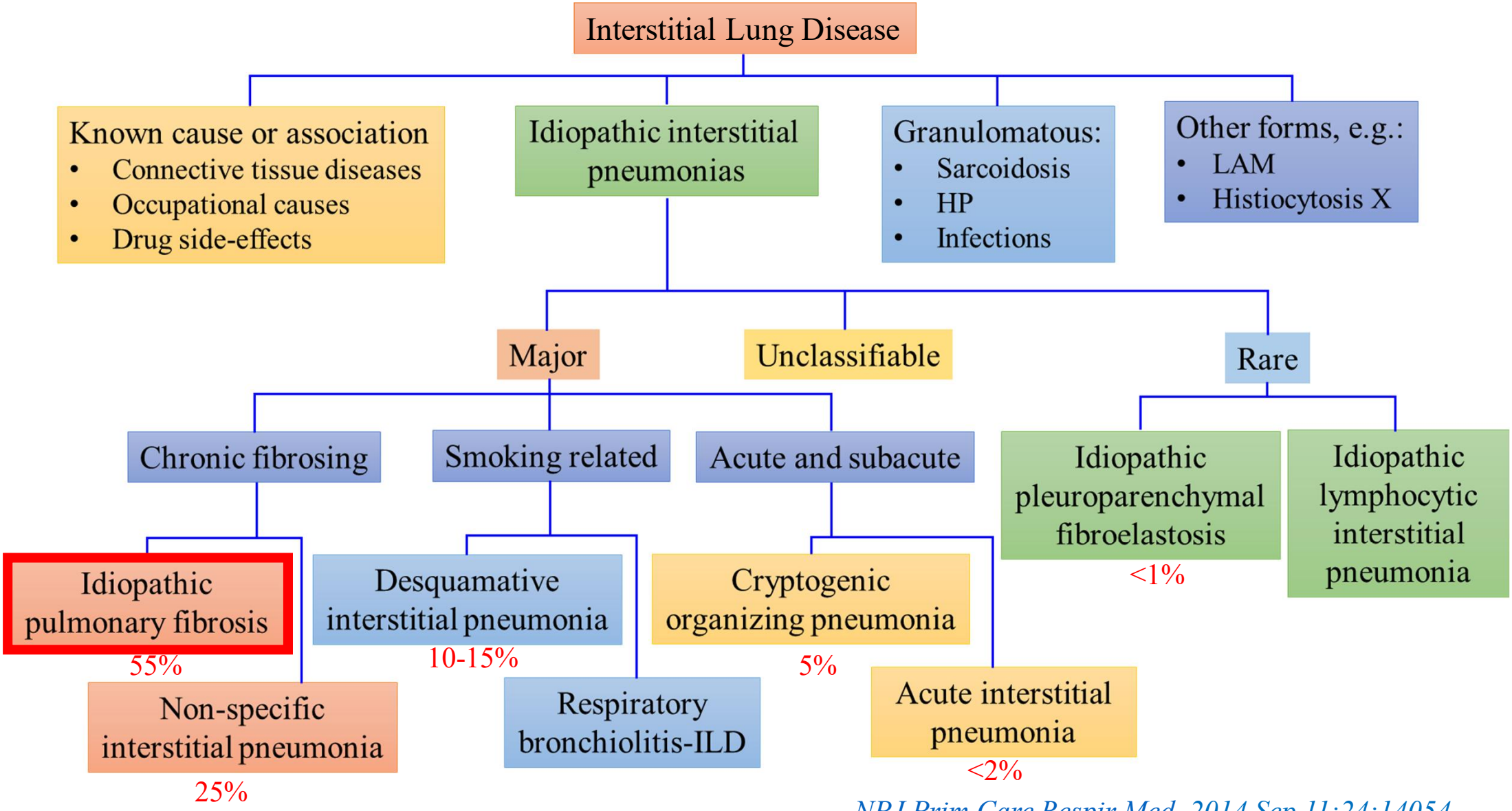


- 폐실질을 침범하는 비감염성, 비종양성 질환
- 폐포 사이 공간인 간질에 세포의 증식과 분화, 만성적인 염증 및 섬유화 등 다양한 병리 기전이 나타는 질환군을 통칭.



Mayo Clin Proc. 2007;82(8):976-986

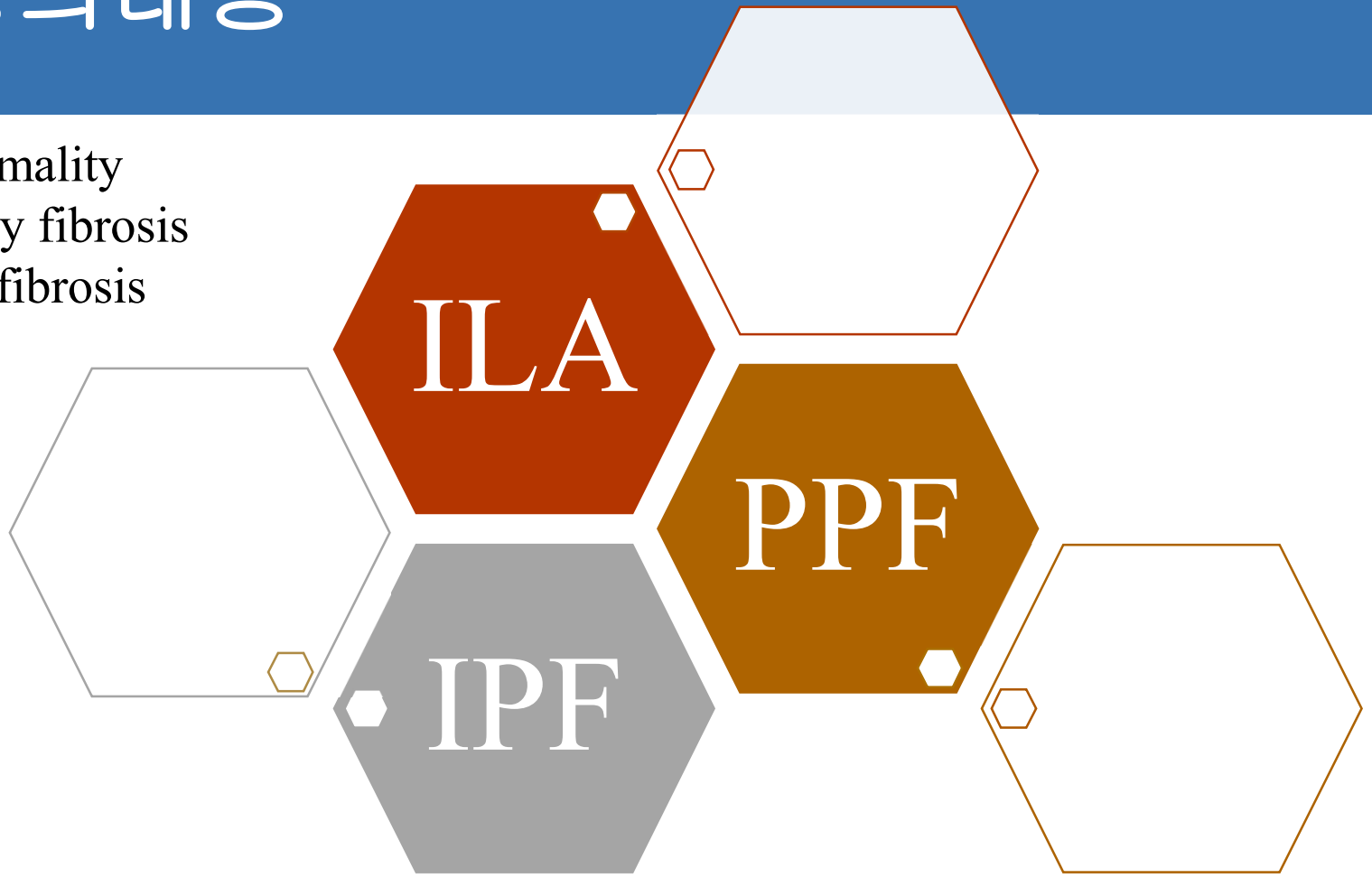
Am J Respir Crit Care Med Vol. 203, P5-P6, 2021



NPJ Prim Care Respir Med. 2014 Sep 11;24:14054.

강의내용

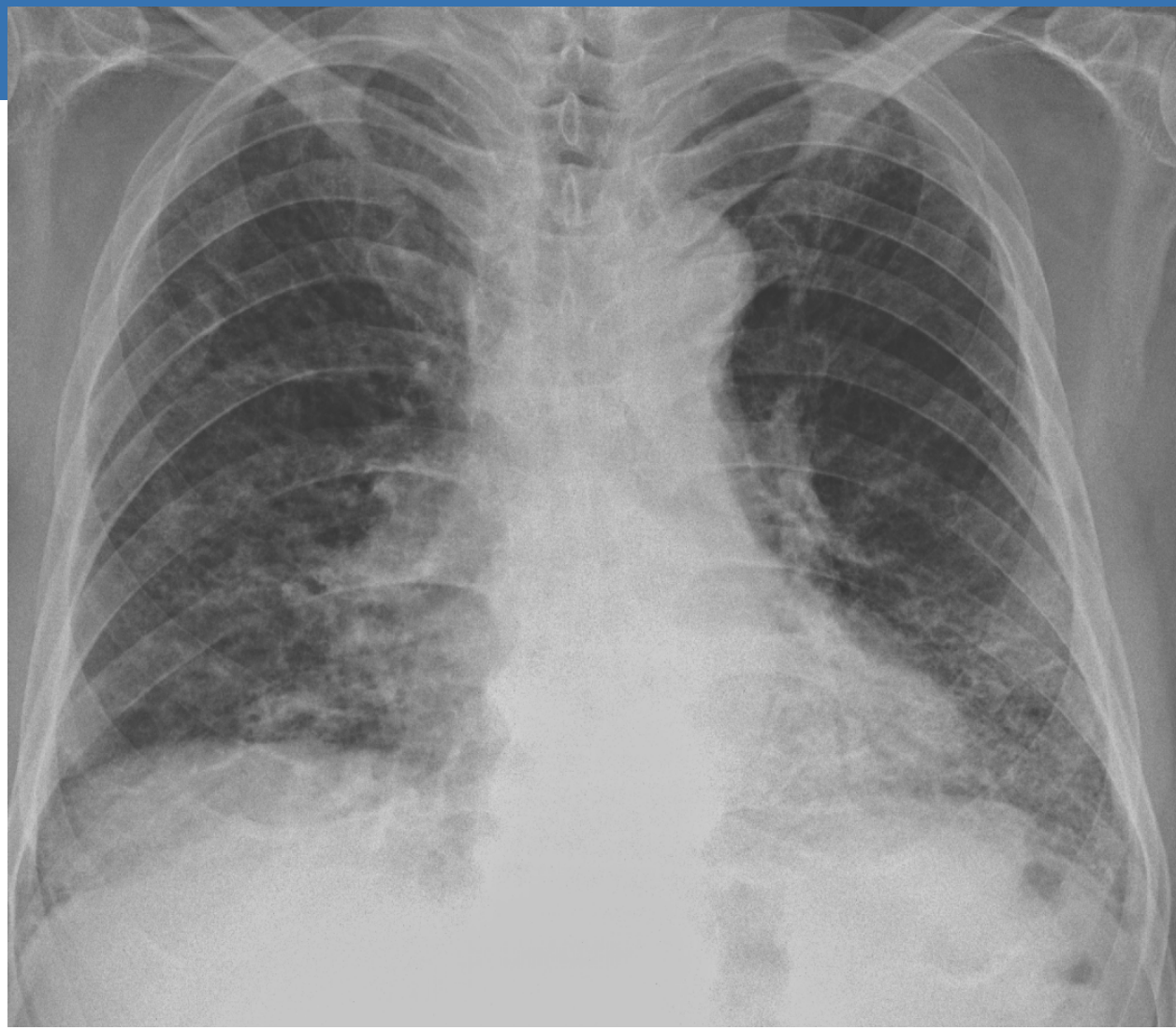
ILA: interstitial lung abnormality
PPF: progressive pulmonary fibrosis
IPF: idiopathic pulmonary fibrosis



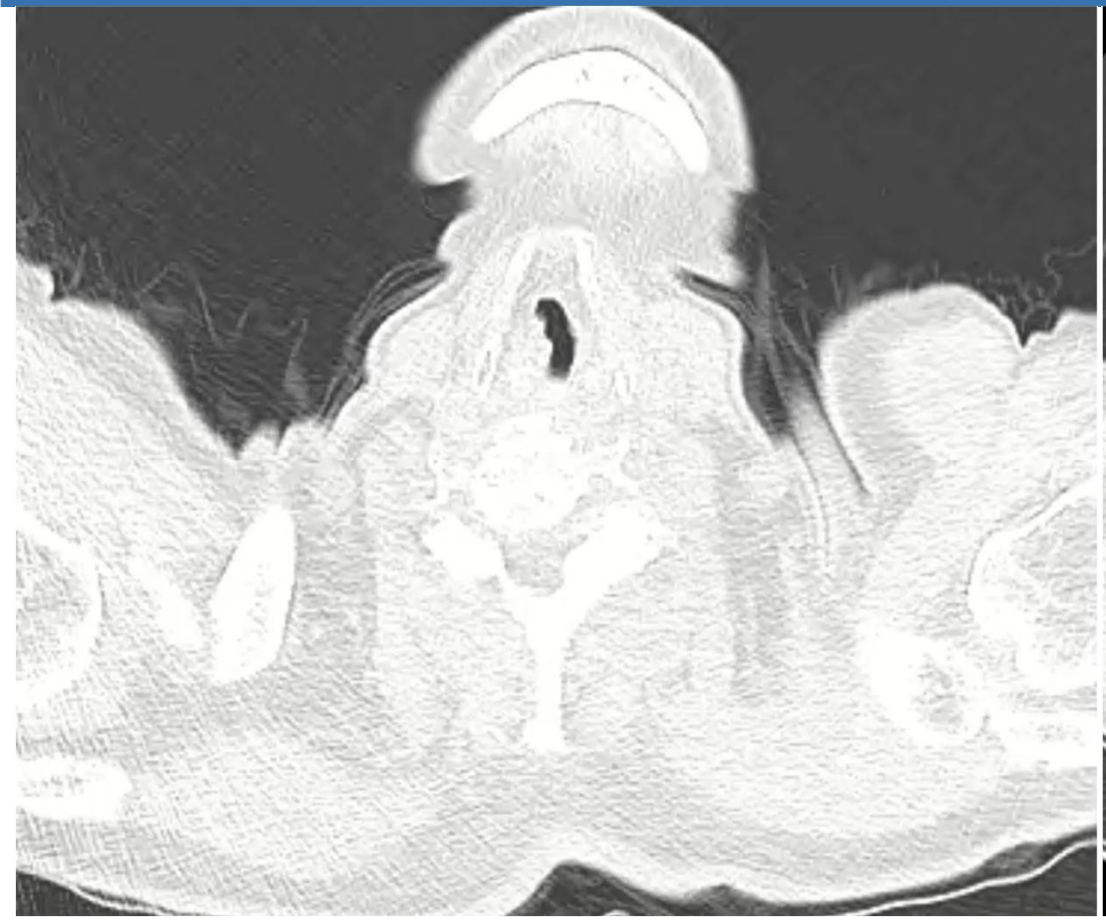
CASE 2. 78/M

- C/C 호흡곤란으로 타원에서 chest CT상 ILD 의심되어 내원
- P/H HTN+, DL+
- Ex, 30년전 quit, 25 PYs

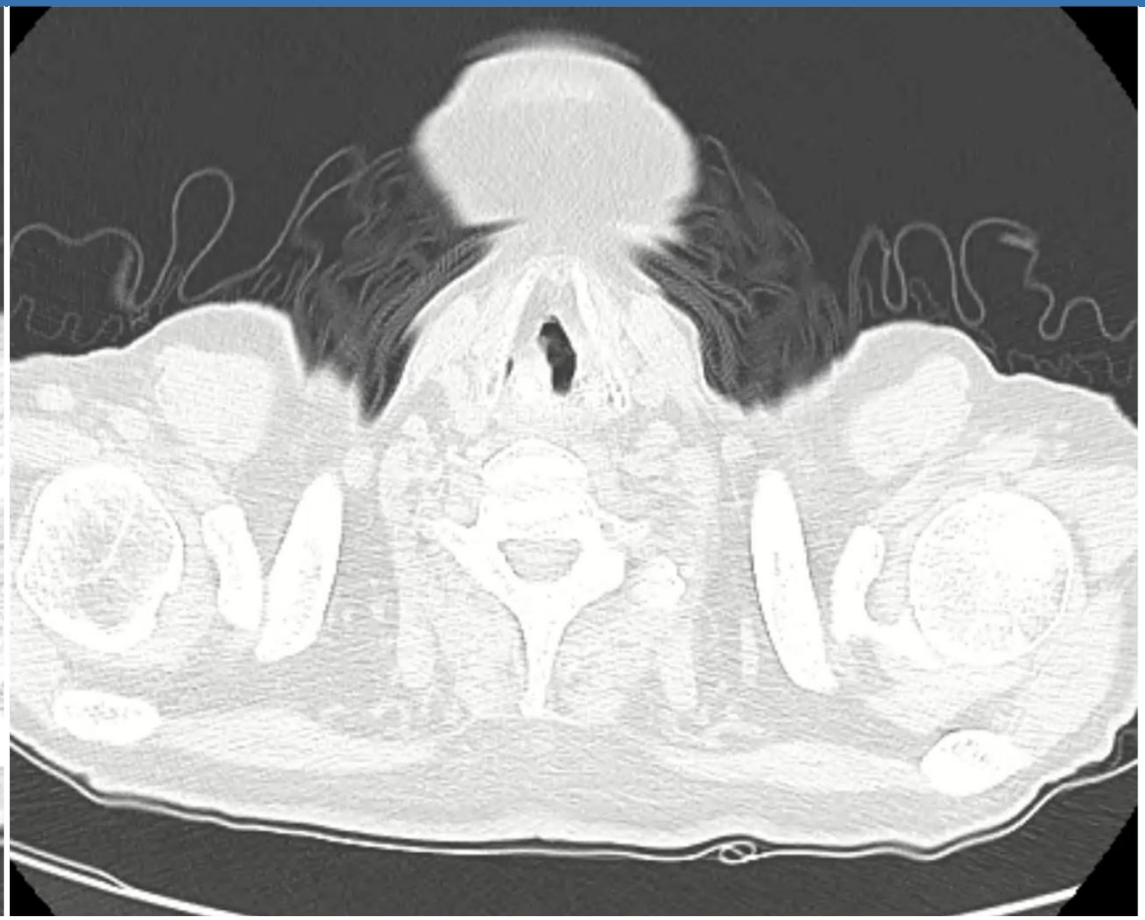
- 어부
- C/S -/- mMRC 2-3



타원 chest CT

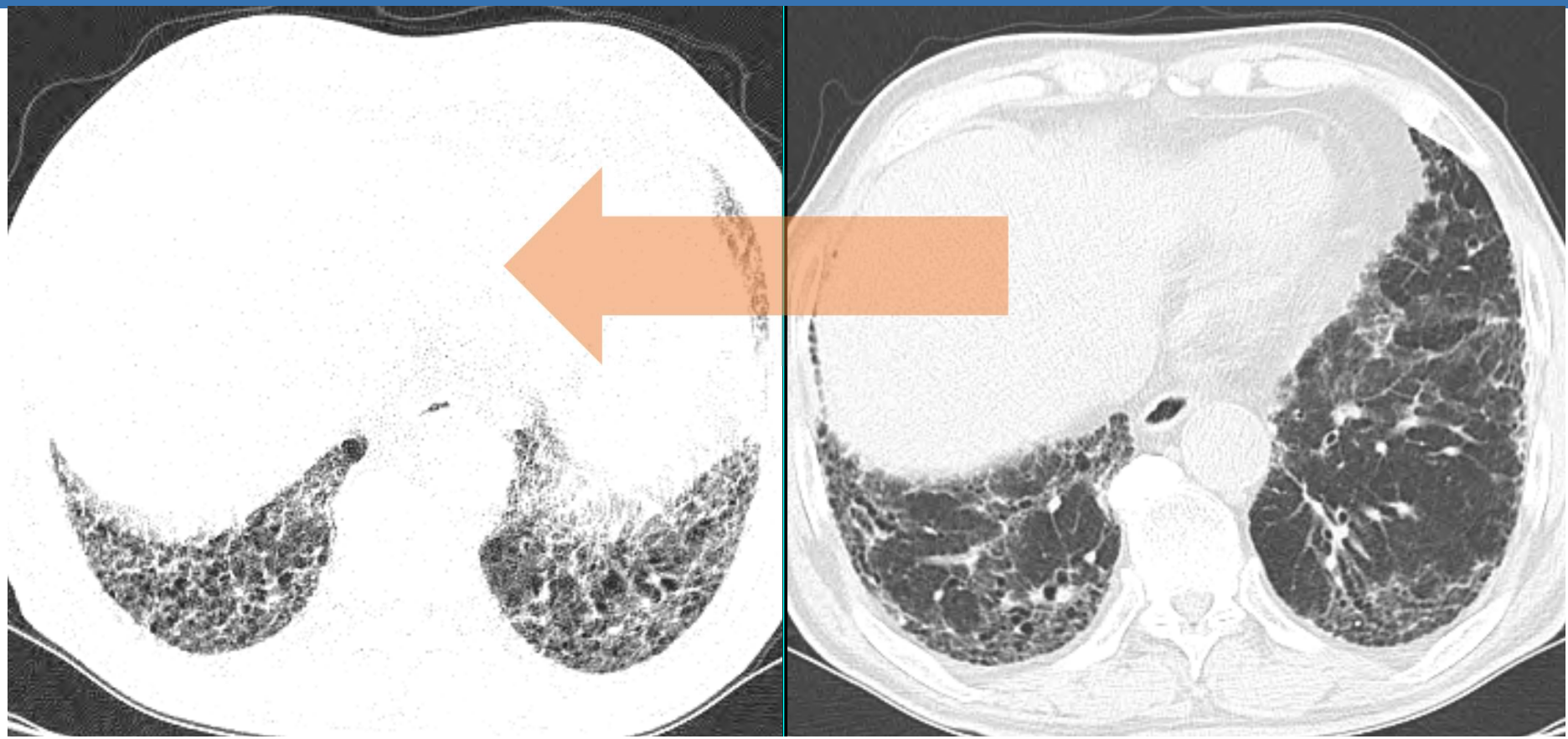


2023년



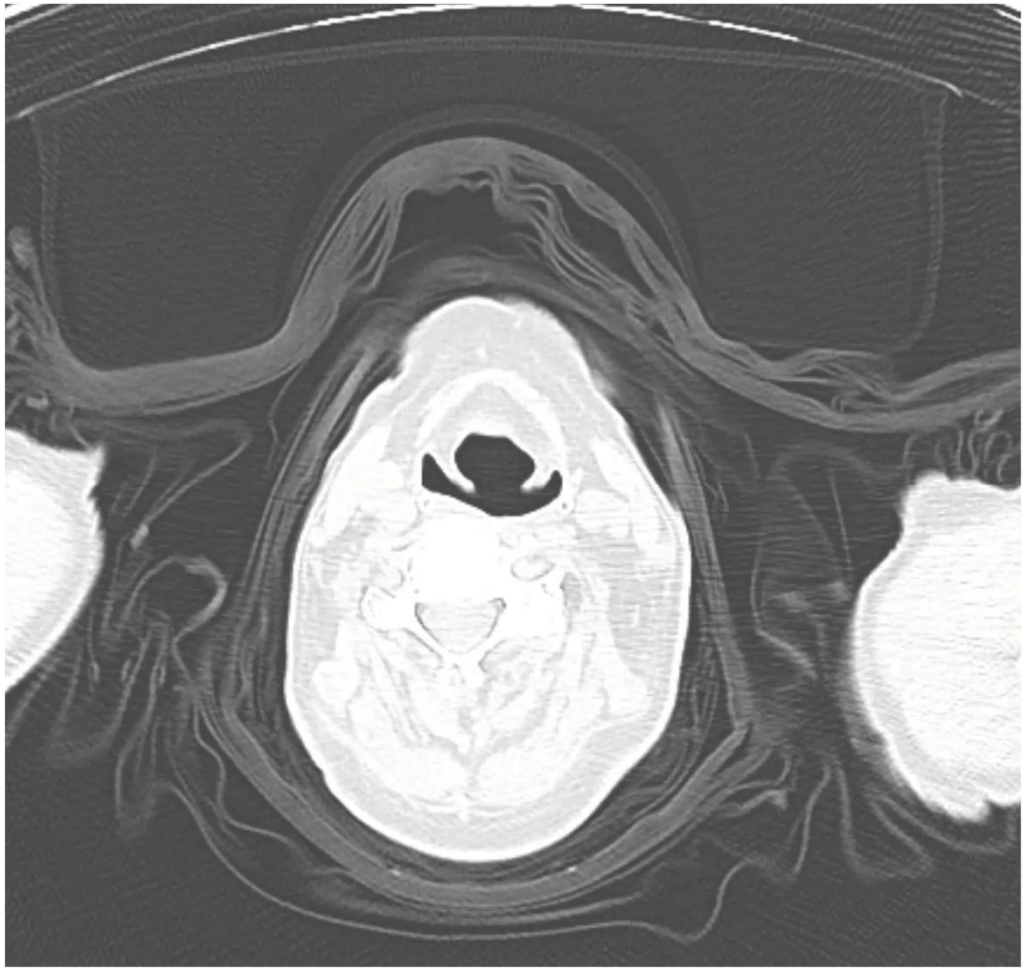
2021년

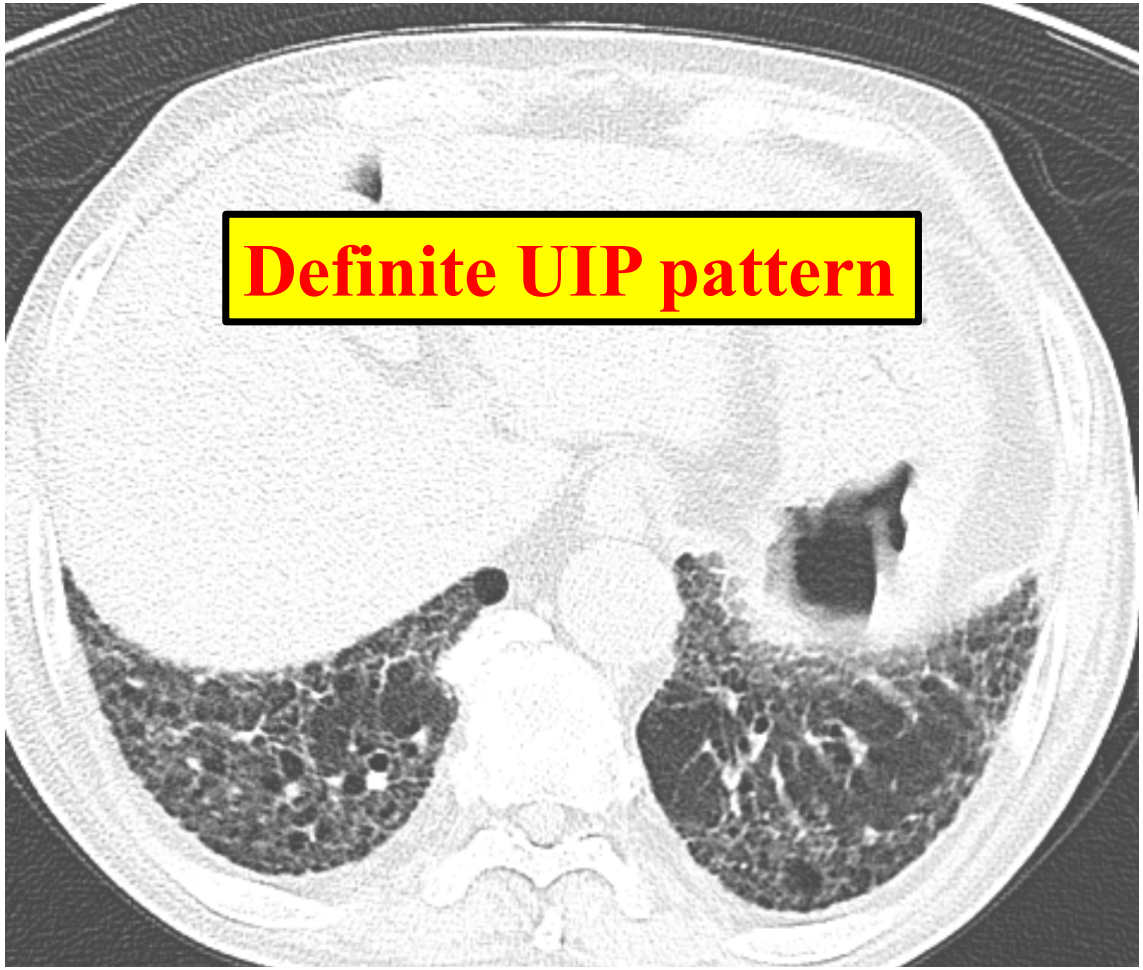
타원 chest CT



2023년 2021년

본원 Prone HRCT

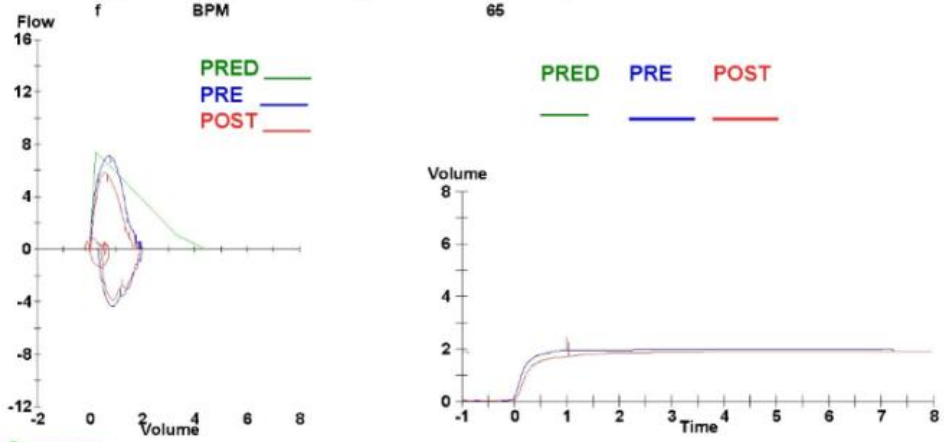




폐기능 검사 및 혈액검사

Spirometry (BTPS)

		PRED	PRE-RX BEST	PRE-RX %PRED	POST-RX BEST	POST-RX %PRED	% CHG
FVC	Liters	4.42	1.99	45	1.89	43	-5
FEV1	Liters	2.95	1.93	65	1.70	58	-12
FEV1/FVC	%	68	97		90		
FEF25-75%	L/sec	2.18	5.11	234	3.61	165	-29
IsoFEF25-75	L/sec	2.18	5.11	234	3.16	145	-38
FEF75-85%	L/sec	0.30	1.60	541	0.80	268	-50
PEF	L/sec	7.44	7.11	96	5.83	78	-18
FET100%	Sec		7.26		8.14		12
FIVC	Liters	3.83	1.67	44	1.44	38	-14
FEV1	Liters	2.95	1.93	65	1.70	58	-12
FIV1	Liters						
FEF/FIF50		<1.00	1.97		1.91		-3
Vol Extrap	Liters		0.11		0.10		-16
FVL ECode			000000		001000		
MVV	L/min	110	81	74			
f	BPM		65				



Comments:

Interpretation:
There is no obstructive lung defect indicated by the FEV1/FVC ratio. Since VC is 45% of predicted, an additional restrictive lung defect cannot be excluded by spirometry alone. On the basis of this study, more detailed pulmonary function testing may be useful if clinically indicated. This is interpreted as an insignificant response to bronchodilator.

- Pre FVC 1.99 L (45%)
- Pre FEV1 1.93 L (65%)
- FEV1/FVC 97%
- DLco NA

Restrictive pattern

***Autoimmune marker (Screening)**

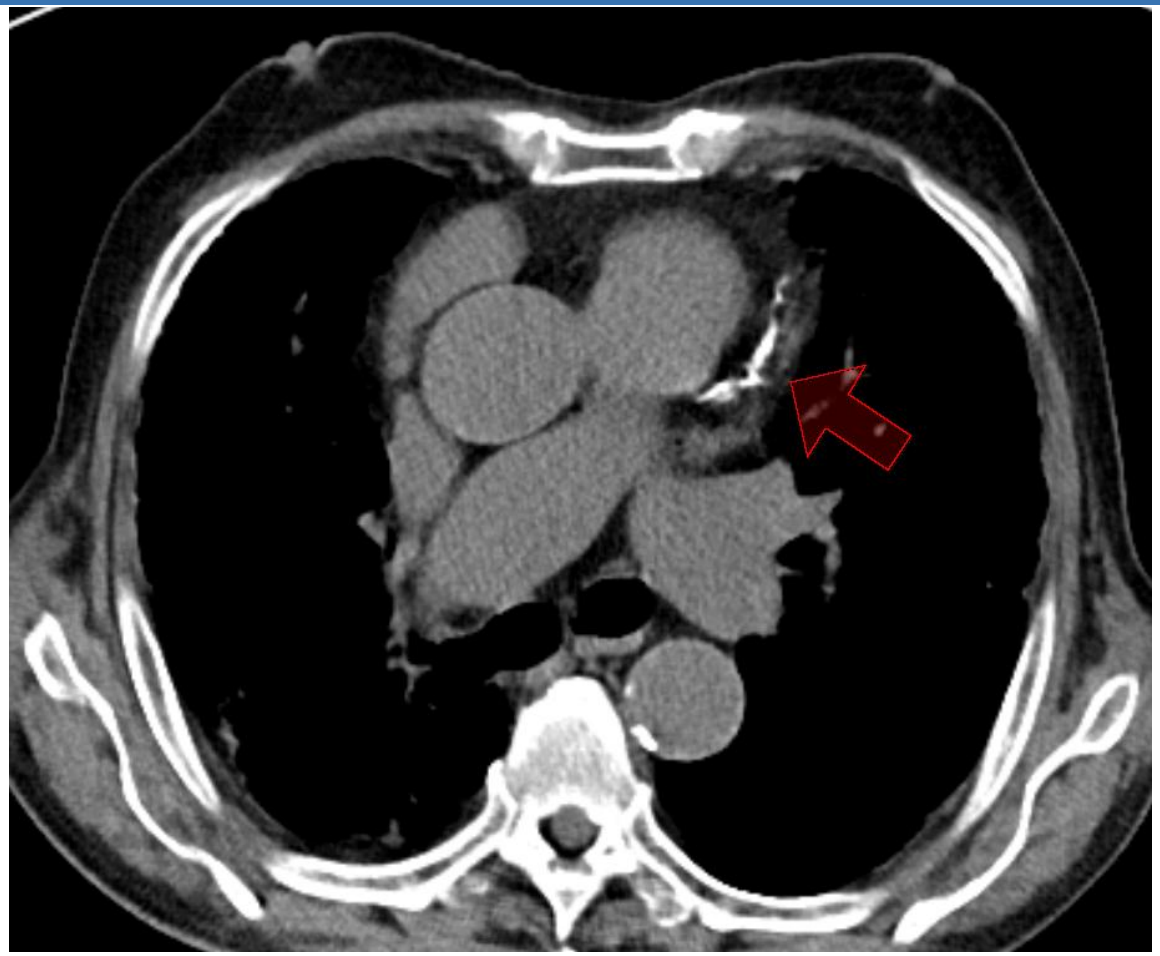
Anti-CCP	<0.5
ANA titer	Negative
ANCA	Negative
Rheumatoid factor titration	9.5
KL-6	526

진단 및 치료

- Idiopathic pulmonary fibrosis [영상학적인 진단]

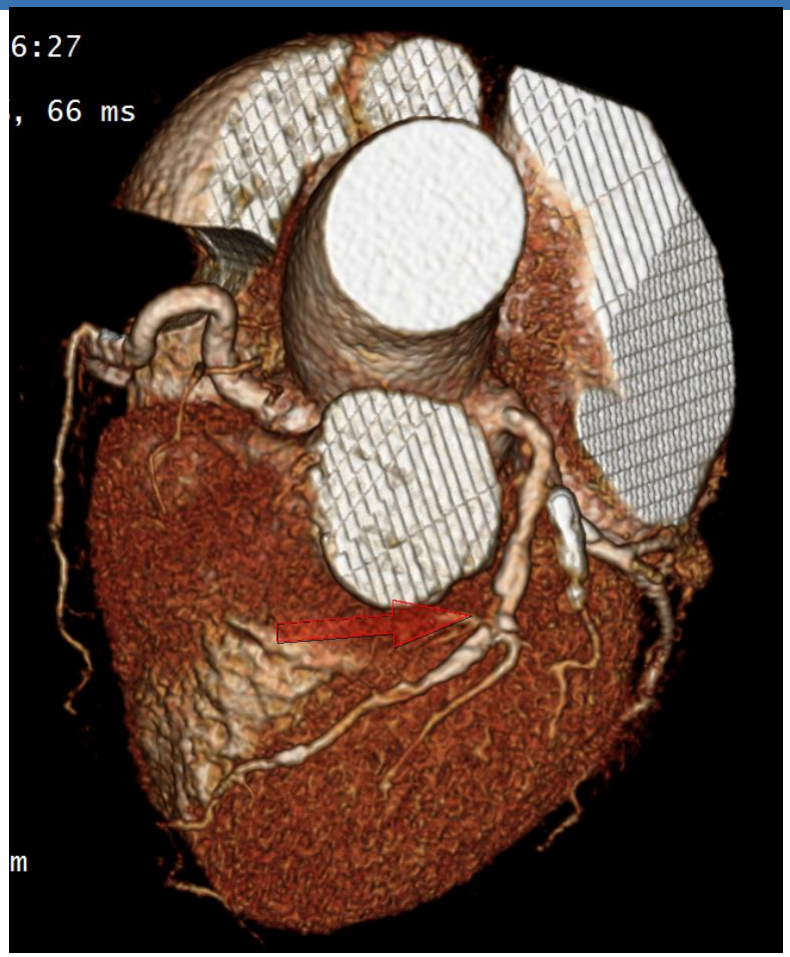
- 희귀질환 등록
- Pirfenidone start

Heavy coronary calcification



순환기내과 **Consult**

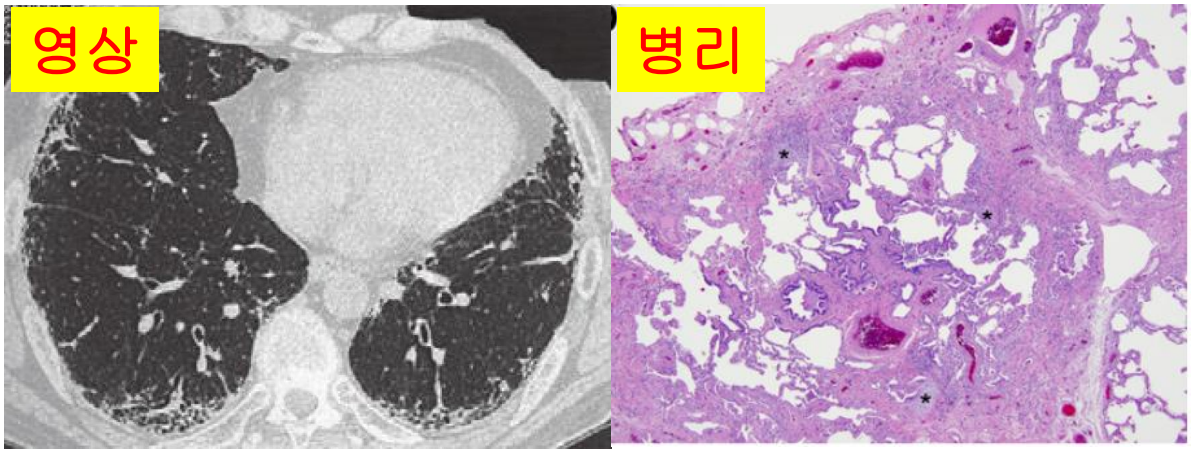
Cardiac CTA



- **Coronary artery CT angiogram.**
- m-LAD : tubular calcified and non-calcified plaque with near total occlusion.
- p-LAD : tubular calcified and non-calcified plaque with moderate stenosis.
- d-RCA : diffuse calcified and non-calcified plaque with mild stenosis.
- m-RCA : discrete calcified plaque with minimal stenosis.
- p-LCX : discrete calcified and non-calcified plaque with mild stenosis.

Idiopathic pulmonary fibrosis (IPF)

- IPF is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause
- Associated with the radiological and histologic features of usual interstitial pneumonia (UIP)
- Occurs primarily in older adults, is characterized by progressive worsening of dyspnea and lung function, and has a poor prognosis



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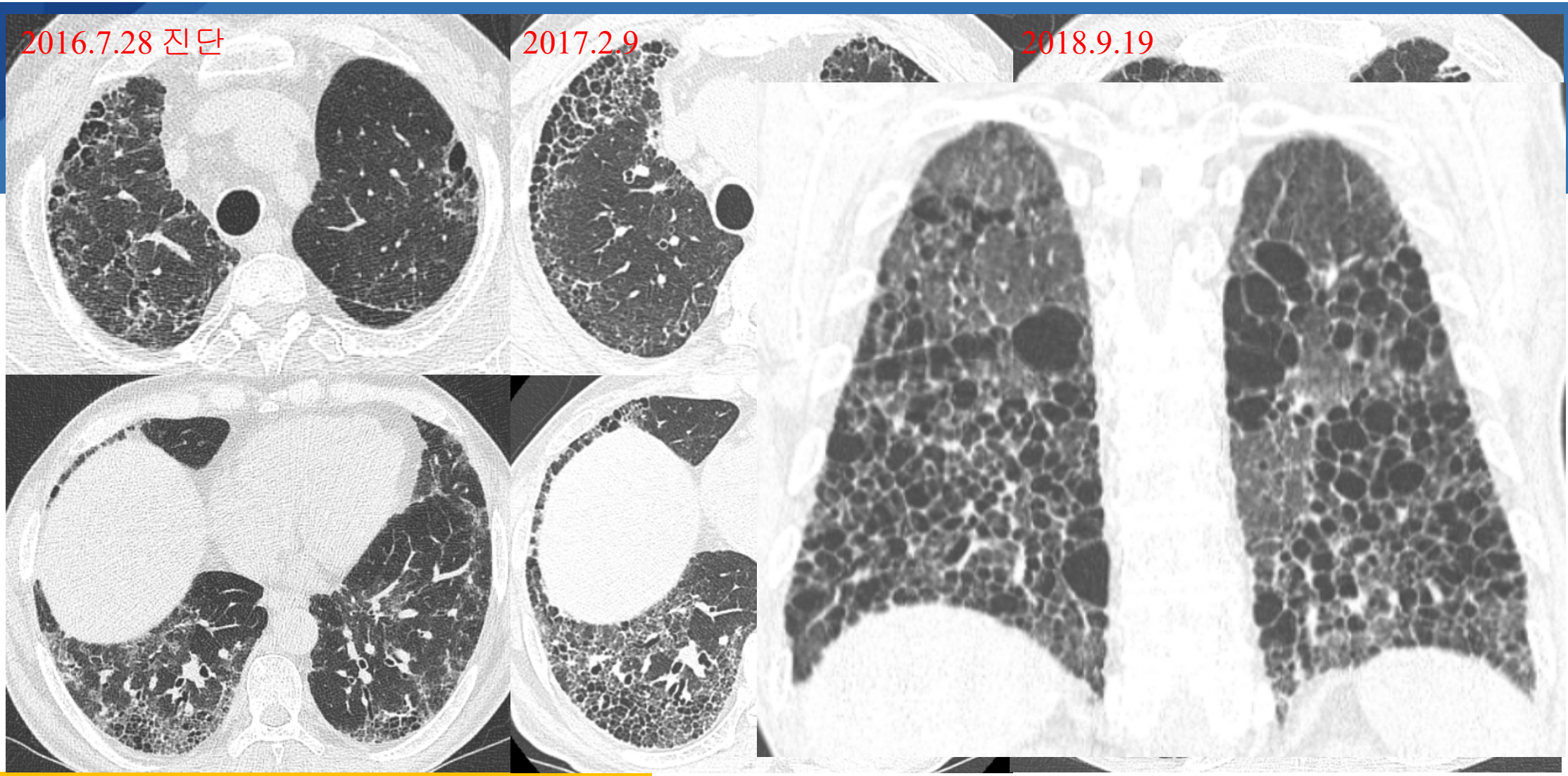
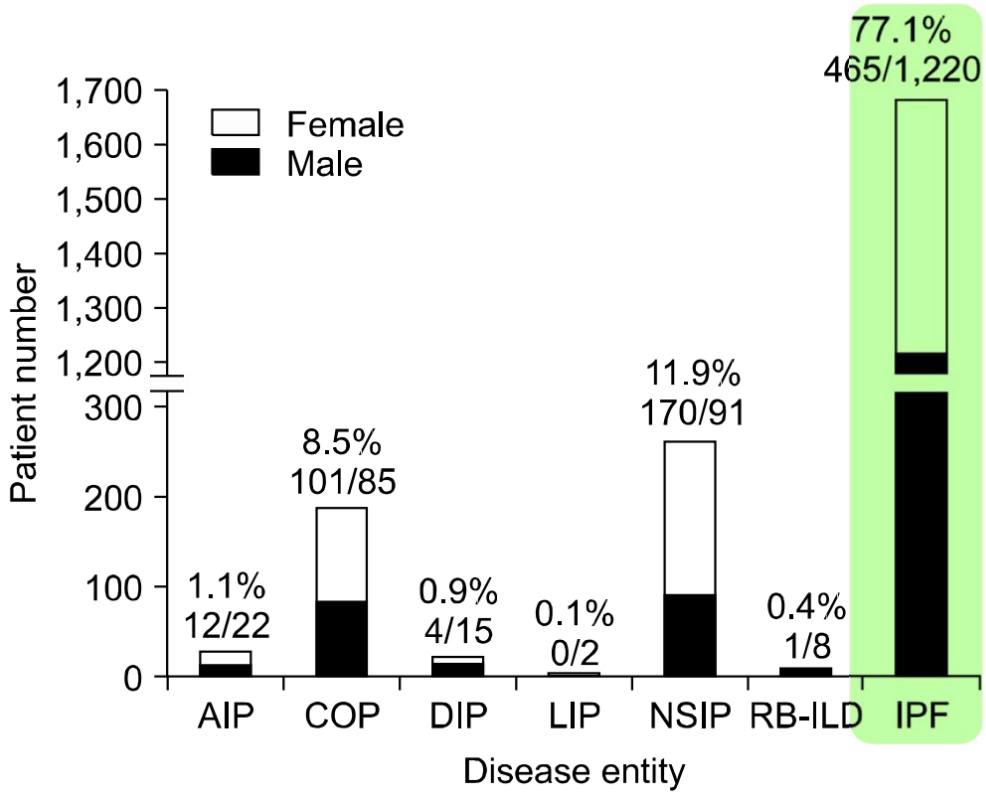


2018.11.17 expired due to respiratory failure

2008 National Survey of Idiopathic Interstitial Pneumonia in Korea



- 2003-2007, South Korea
- IIP + comfirmed by lung biopsy
- Total 2186 cases

희귀질환

Tuberc Respir Dis 2009;66:141-151

Clinical presentation of IPF

History	• Chronic exertional dyspnea (nearly universal) • Chronic cough without purulence • Fatigue
Physical examination	• Bilateral Velcro-like crackles • Clubbing • Acrocyanosis
Physiological findings	• Low FVC, low TLC (restrictive pattern) • Low DLco • Resting hypoxemia or exertional desaturation
Chest radiograph	• Nonspecific changes or bilateral basal reticular abnormalities

N Engl J Med 2018;378:1811-23.

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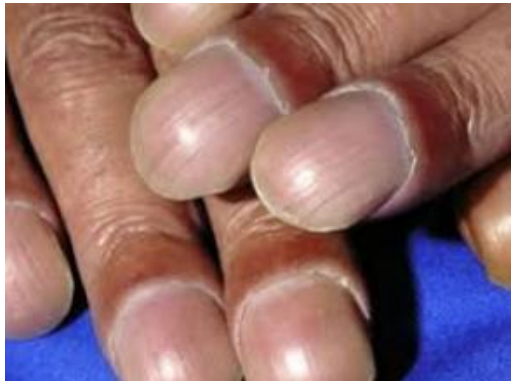

N Engl J Med 2018;378:1811-23.

Organ	Main manifestations to be evaluated
Peripheral circulation	Raynaud's phenomenon
Skin	Sclerodactyly
	Digital ulcerations or scars
	Telangiectasia
	Violaceous erythematous rash over the interphalangeal joints, knuckles, elbows and knees (Gottron's sign)
	Lilaceous rash of the eyelids
	Rash of the neck and upper chest and shoulders (heliotrope rash, e.g. photosensitivity)
	Mechanics' hands
Joints	Joint pain or swelling (arthritis, arthralgia)
	Morning stiffness lasting for more than 60 min
Muscle	Muscle pain, muscle weakness
Mouth and eyes	Dry mouth, dry eyes (sicca syndrome)

CTD를 의심할 수 있는 주요 증상들

- **Rheumatoid factor**
- **Anti-CCP Antibody**
- **ANA (titer)**
- **ANCA**

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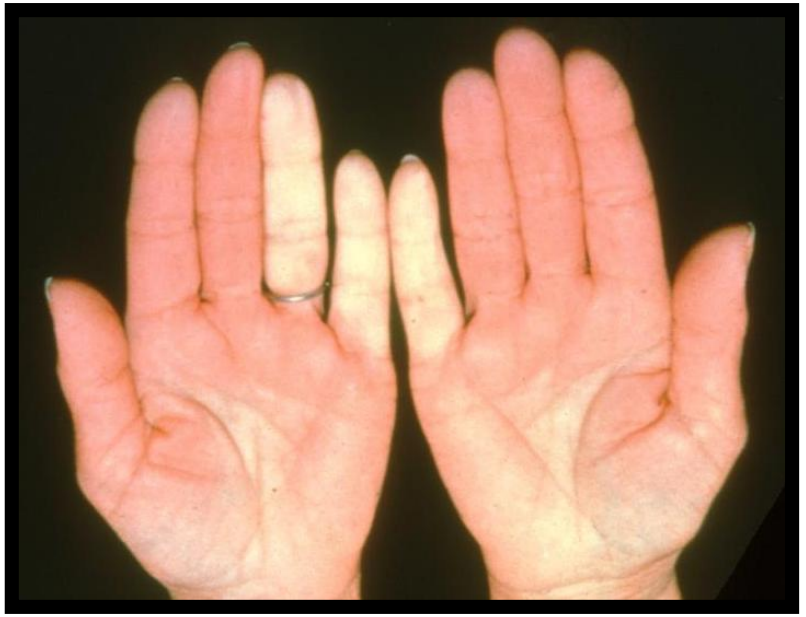

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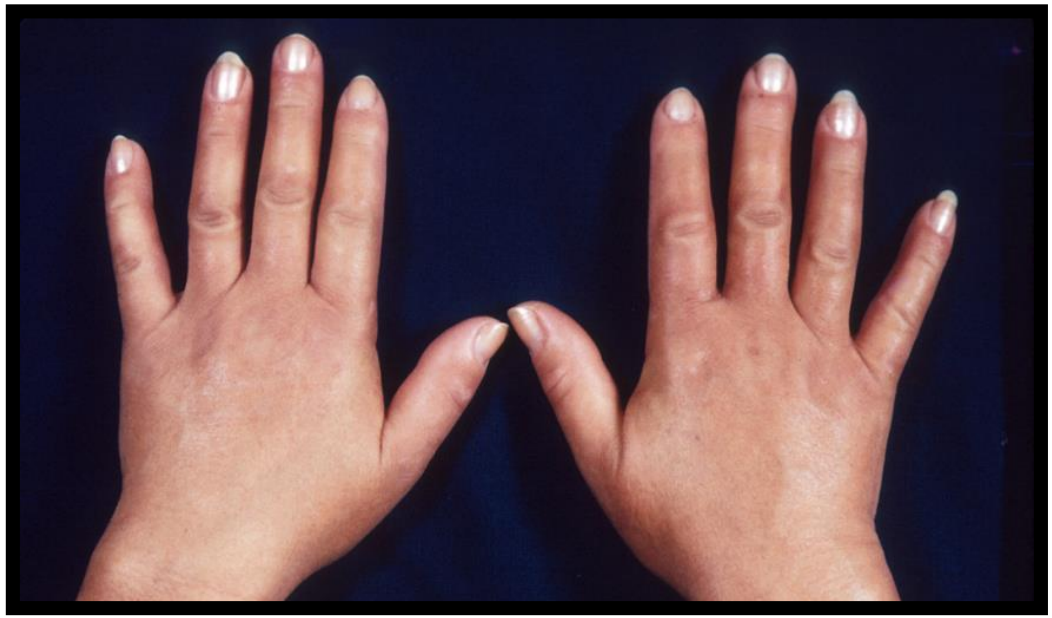

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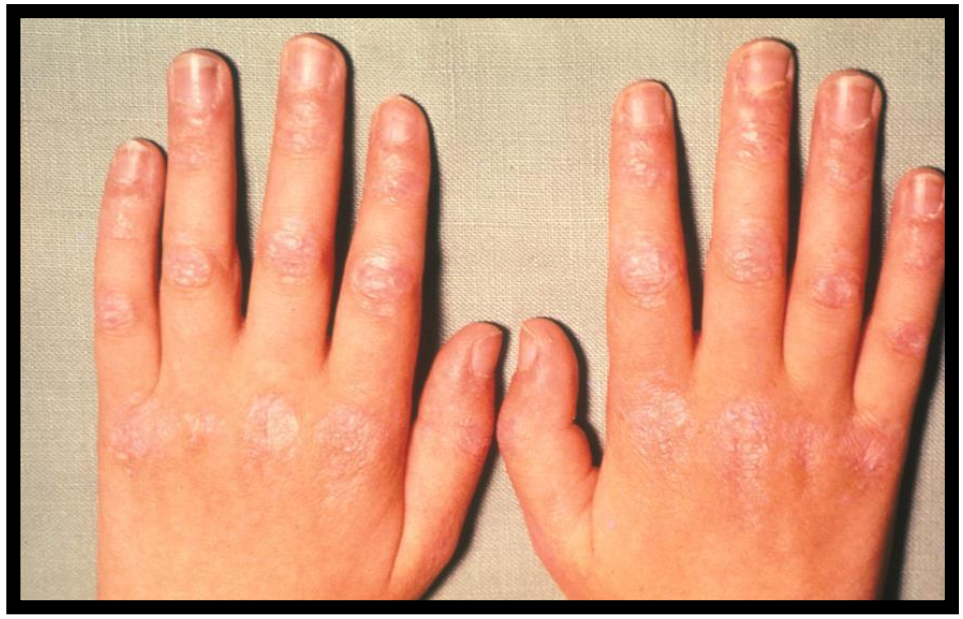

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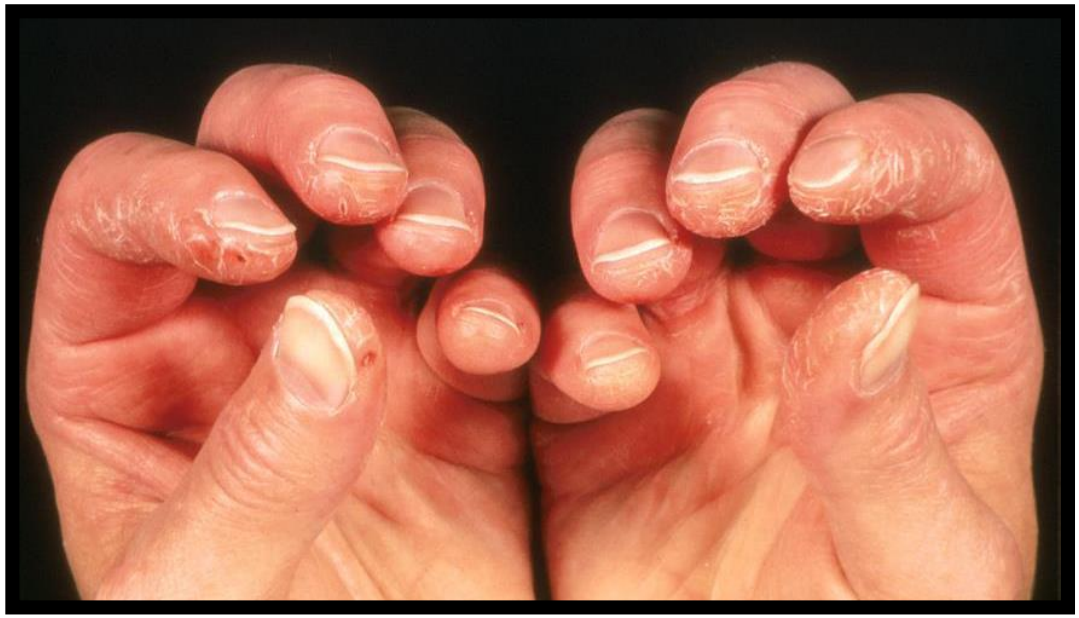

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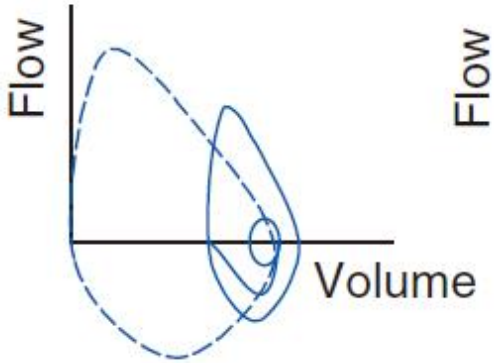

FVC: forced vital capacity
TLC: total lung capacity
DLco: diffusing capacity of the lung for carbon monoxide

N Engl J Med 2018;378:1811-23.

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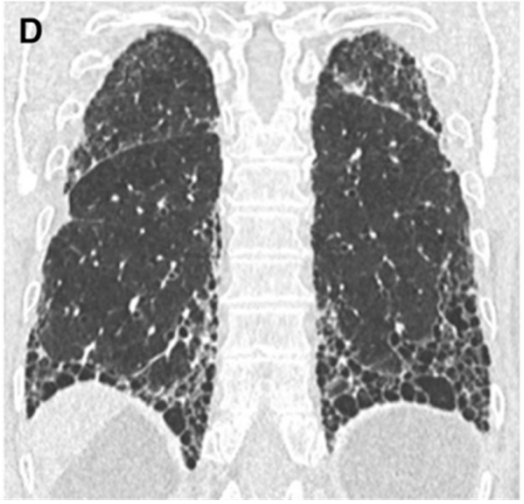


N Engl J Med 2018;378:1811-23.

AMERICAN THORACIC SOCIETY DOCUMENTS

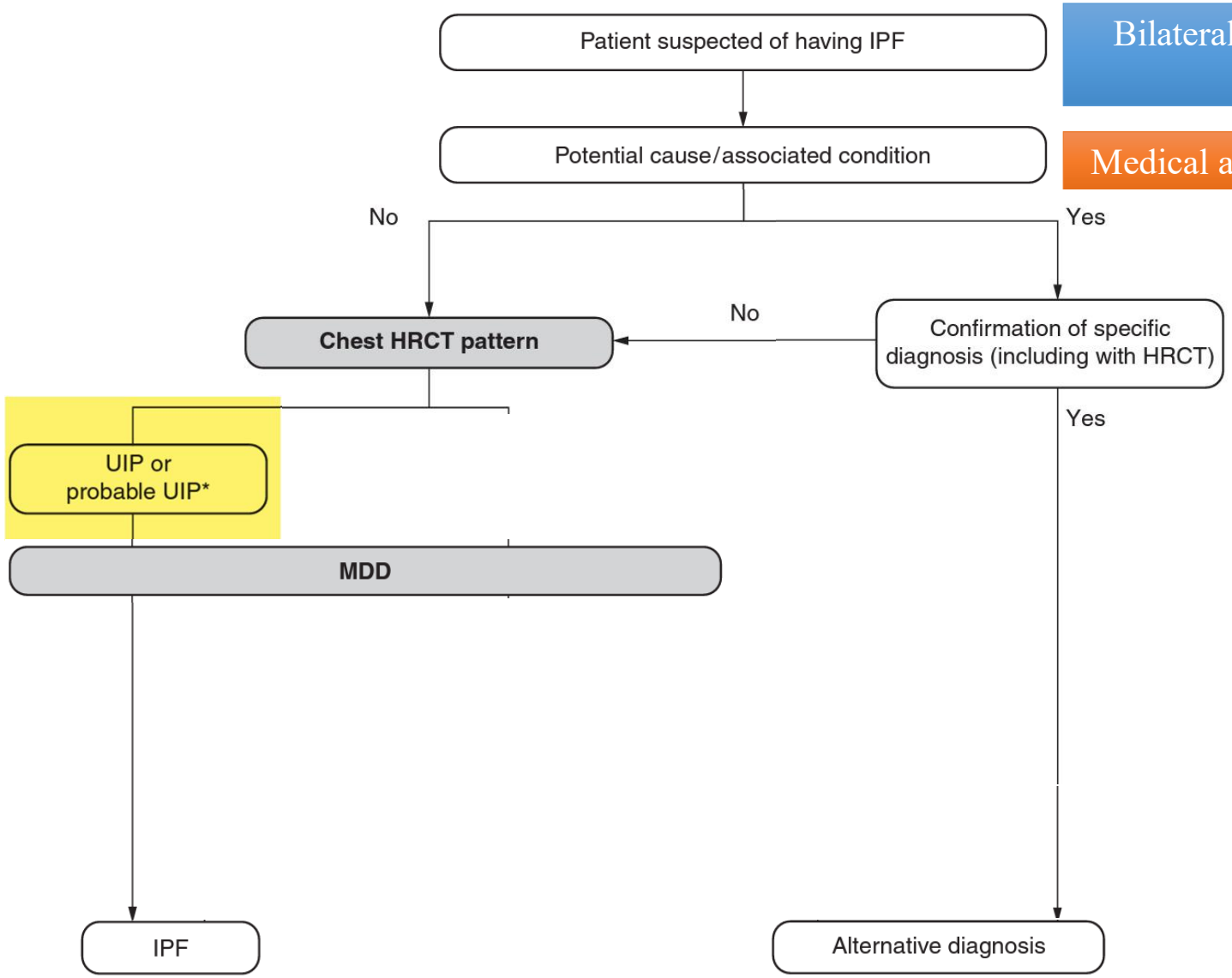
Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY, EUROPEAN RESPIRATORY SOCIETY, JAPANESE RESPIRATORY SOCIETY, AND ASOCIACIÓN LATINOAMERICANA DE TÓRAX FEBRUARY 2022

Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.



Bilateral pulmonary fibrosis + bibasilar inspiratory crackles+ > 60yrs

Medical and environmental exposure, excluding CTD

***MDD: multidisciplinary discussion**

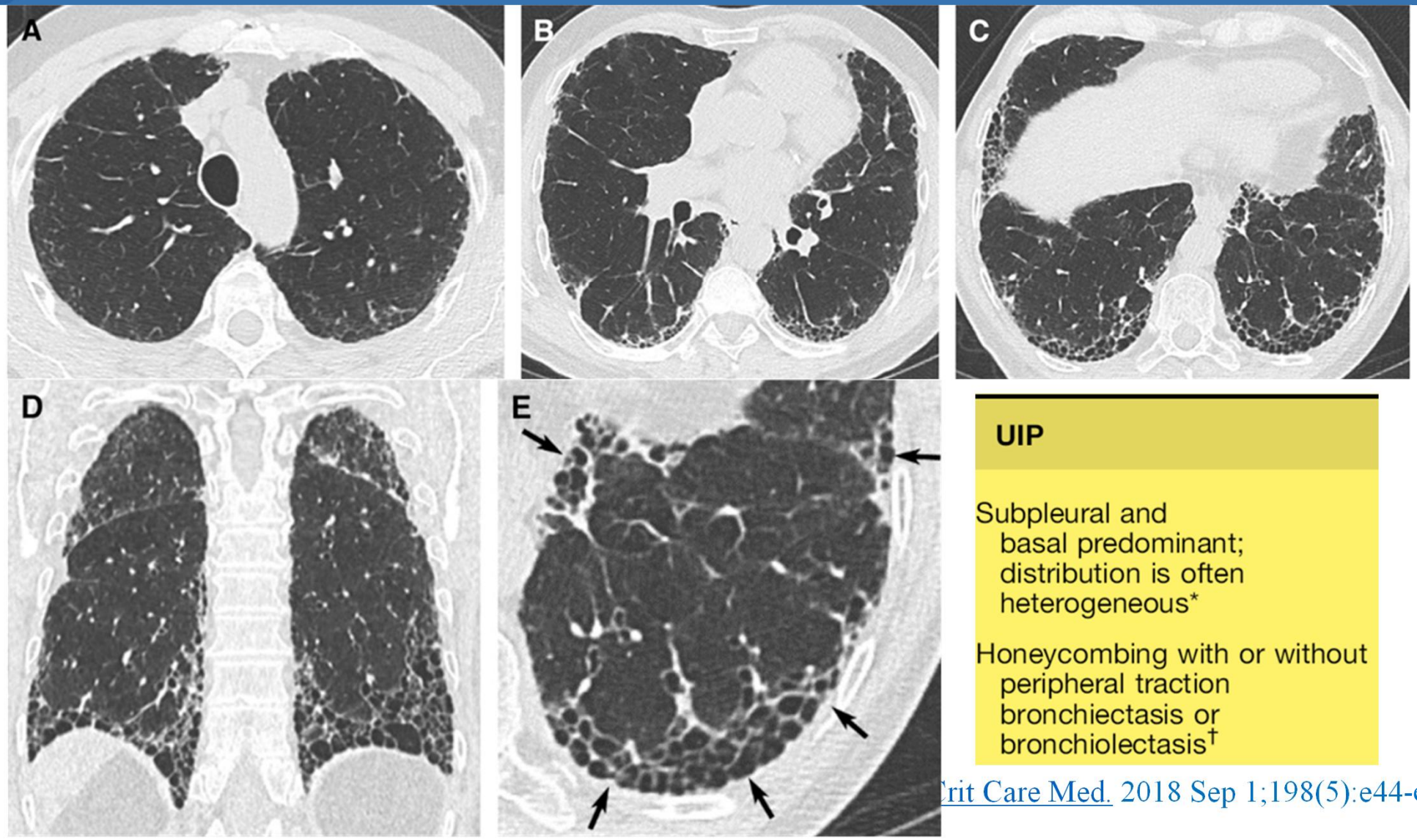
Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

High-Resolution Computed Tomography (HRCT) Patterns

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
Subpleural and basal predominant; distribution is often heterogeneous*	Subpleural and basal predominant; distribution is often heterogeneous	Subpleural and basal predominant	Findings suggestive of another diagnosis, including: • CT features: ◦ Cysts ◦ Marked mosaic attenuation ◦ Predominant GGO ◦ Profuse micronodules ◦ Centrilobular nodules
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis	Subtle reticulation; may have mild GGO or distortion ("early UIP pattern")	
	May have mild GGO	CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate for UIP")	

Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.

High-Resolution Computed Tomography (HRCT) Patterns



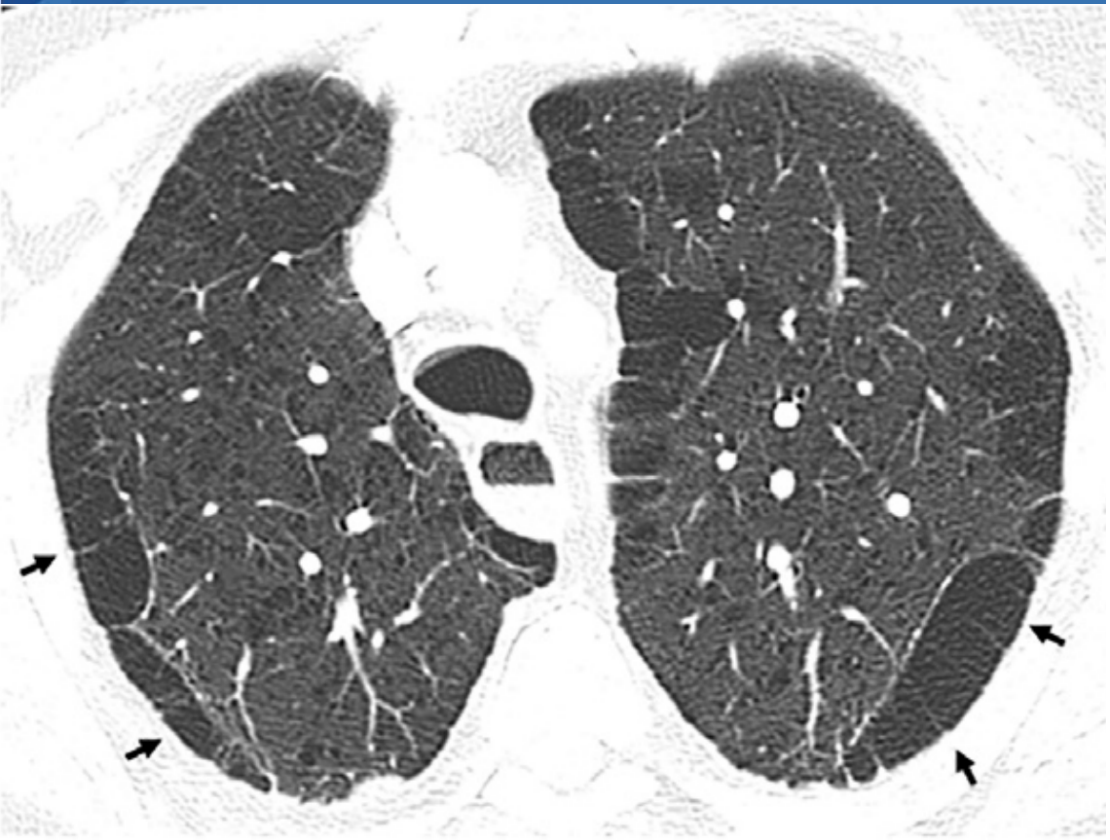
UIP

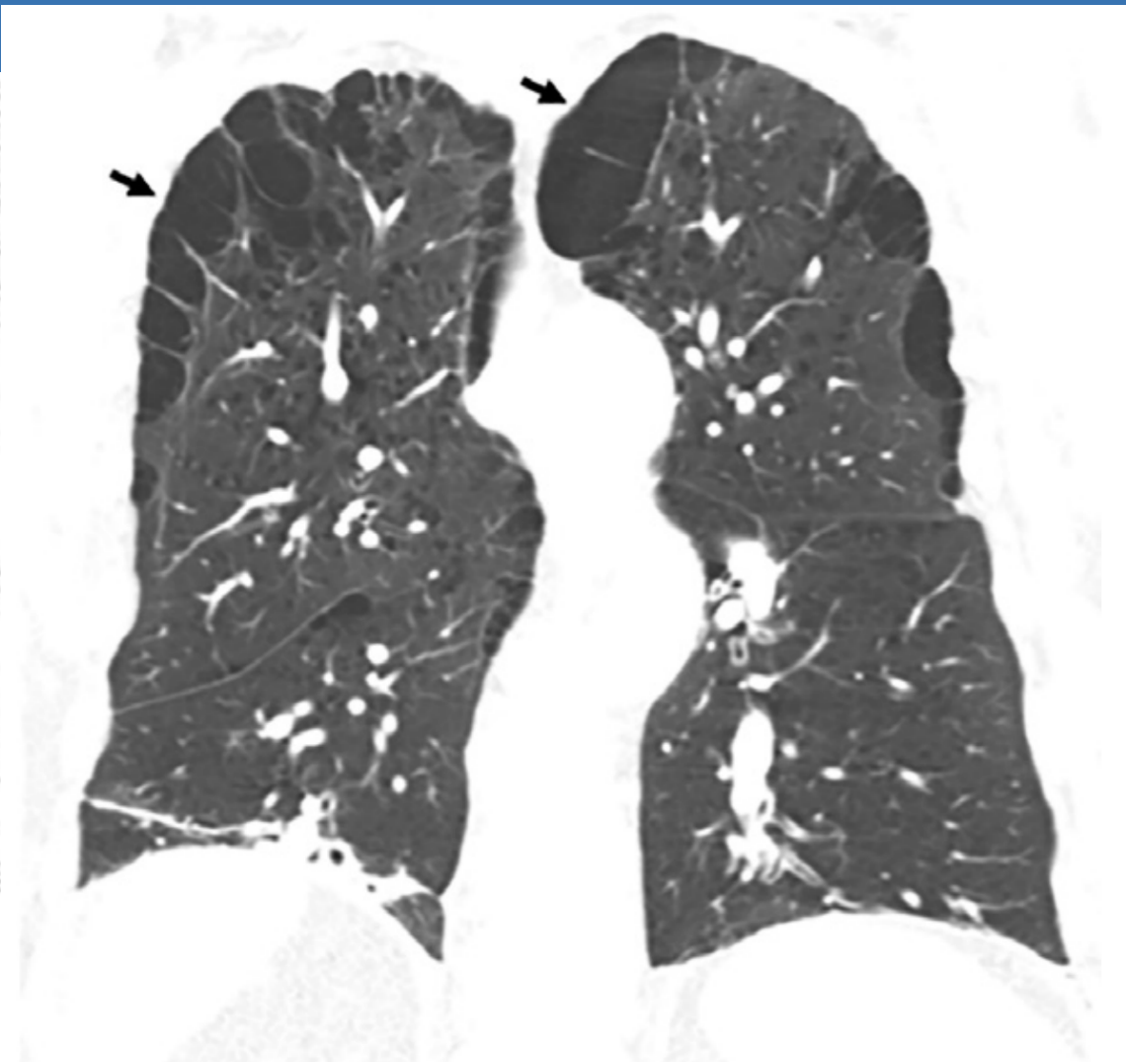
Subpleural and basal predominant; distribution is often heterogeneous*

Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†

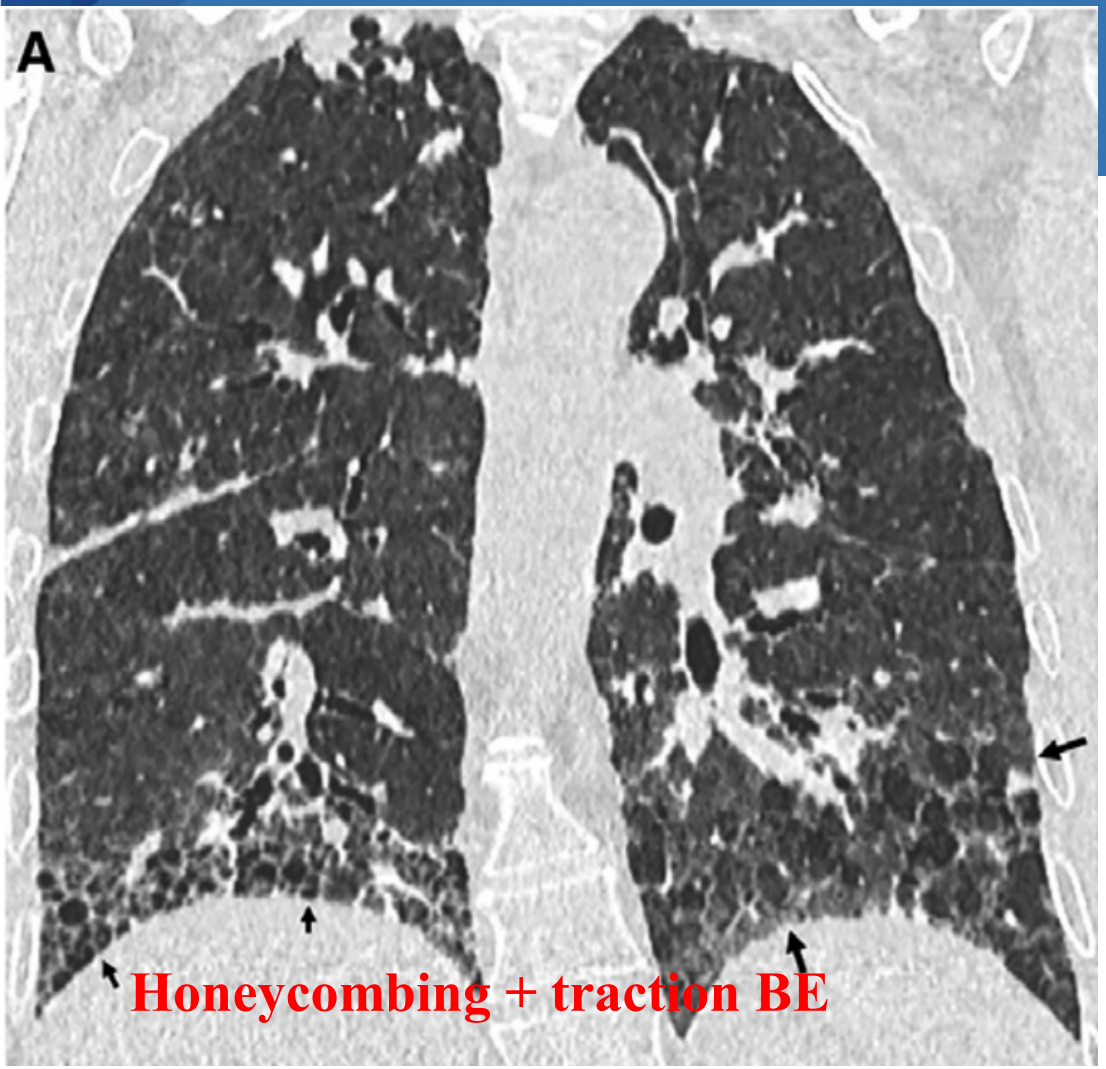
rit Care Med. 2018 Sep 1;198(5):e44-e68.

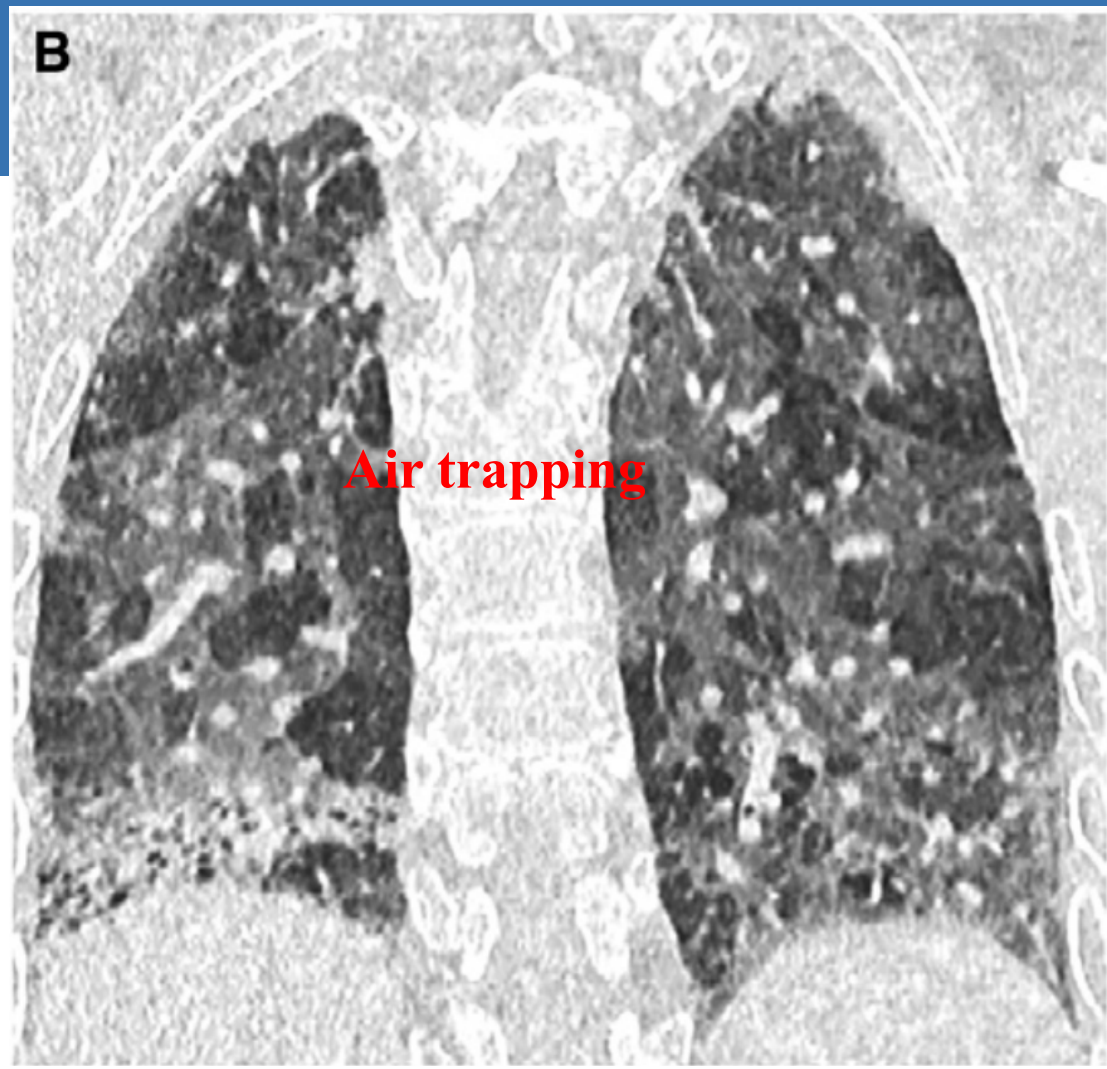
Emphysema



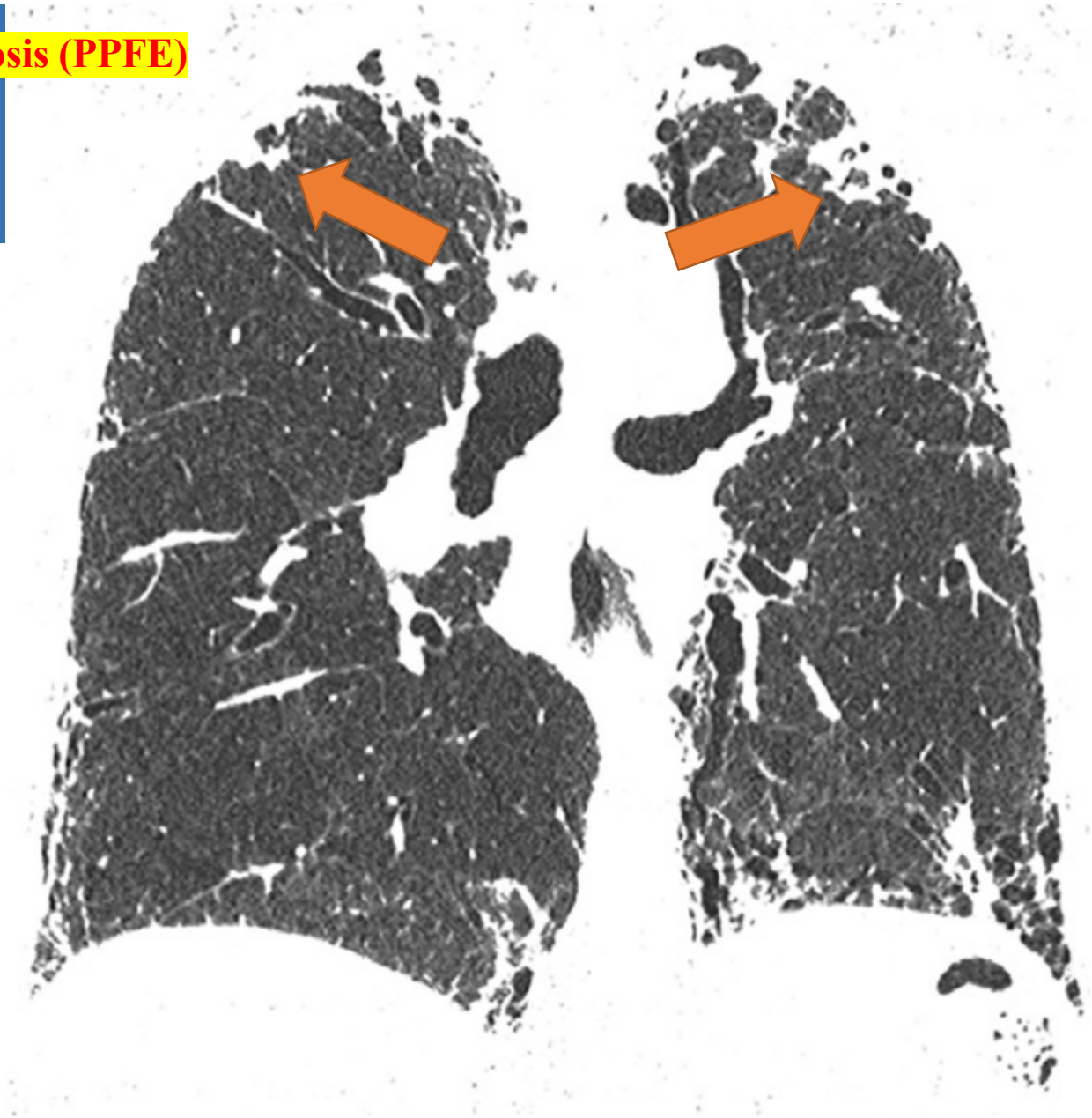


Chronic hypersensitivity pneumonitis



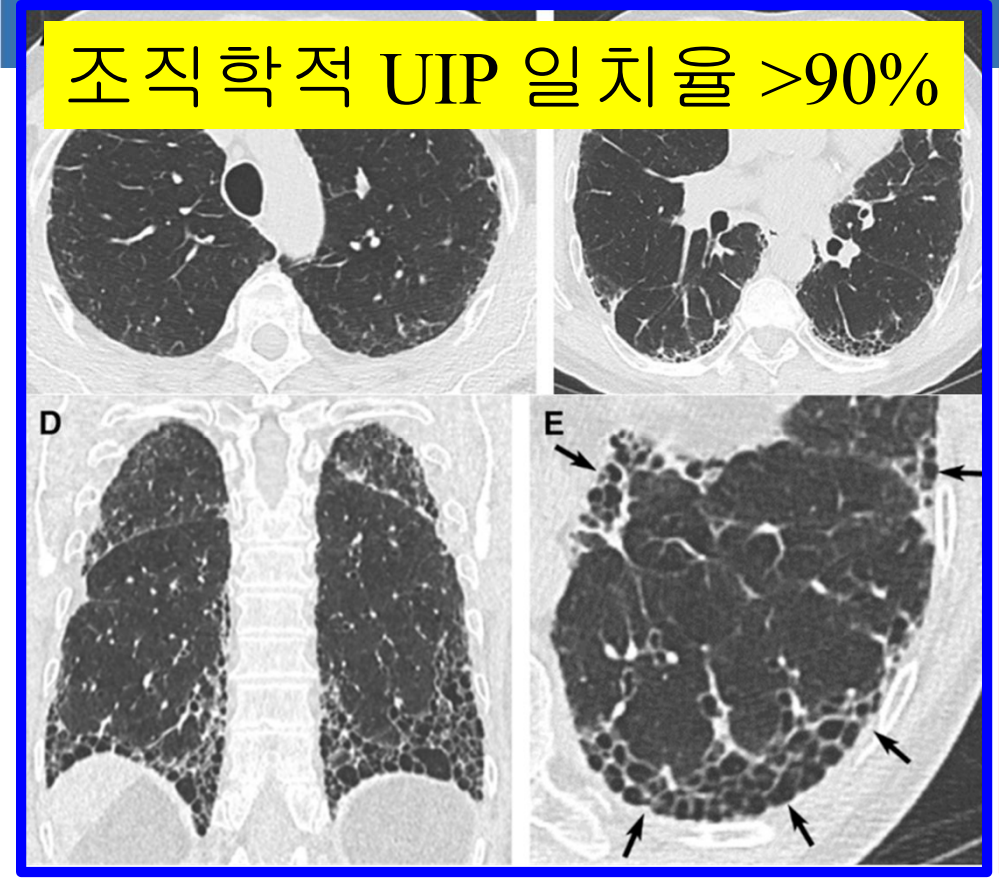


Pleuropharenchymal fibroelastosis (PPFE)



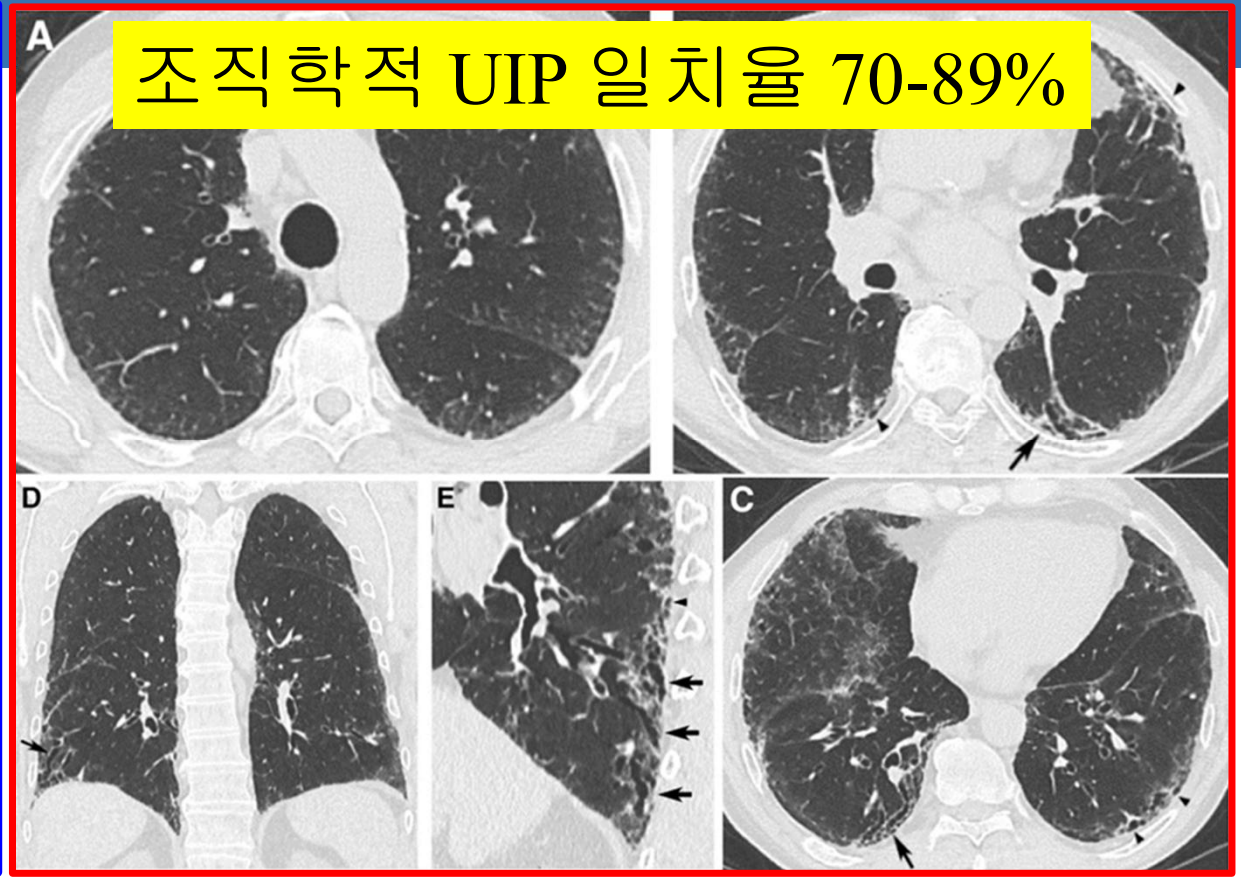
High-Resolution Computed Tomography Scanning Patterns

조직학적 UIP 일치율 >90%



UIP

조직학적 UIP 일치율 70-89%

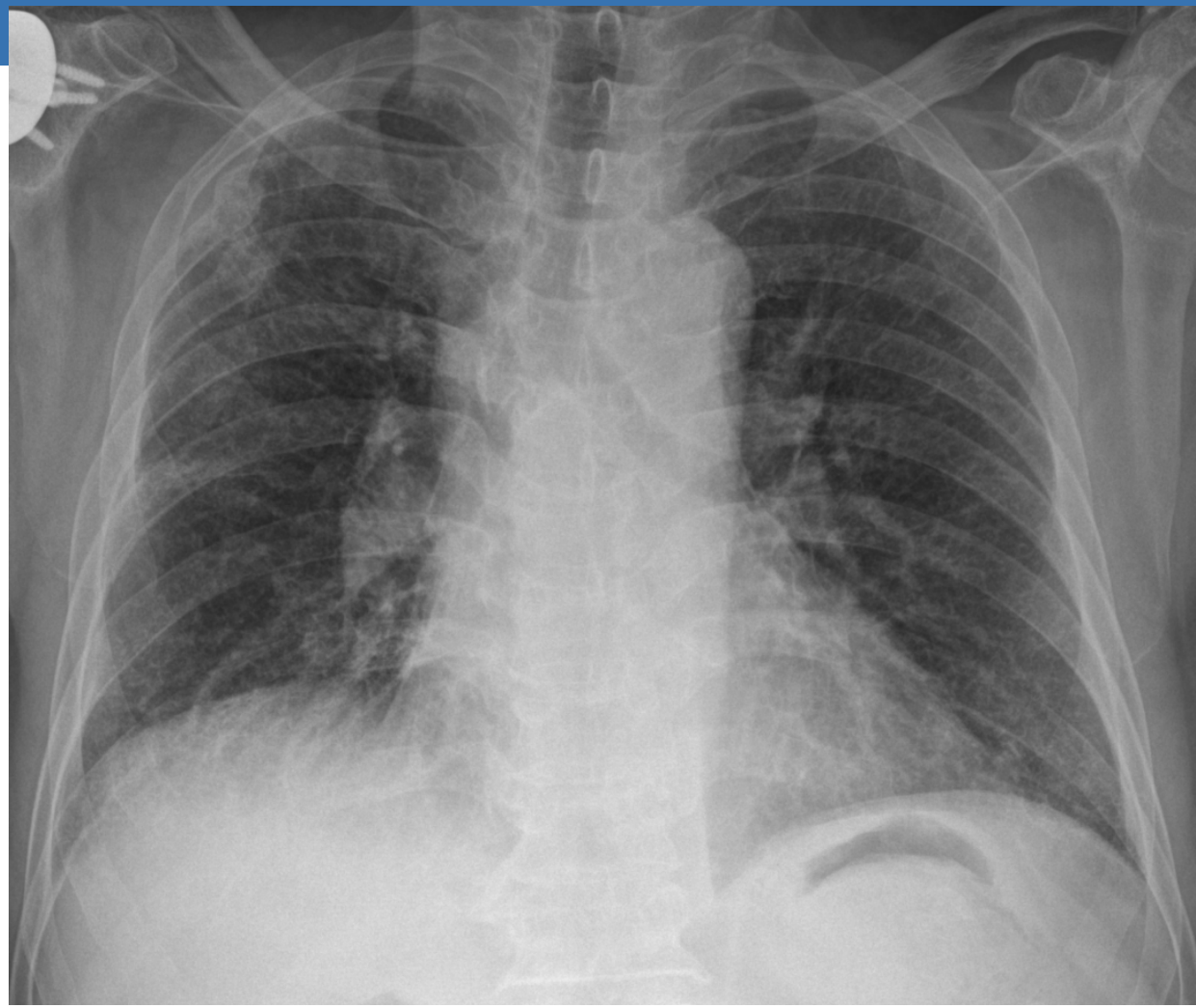


Probable UIP

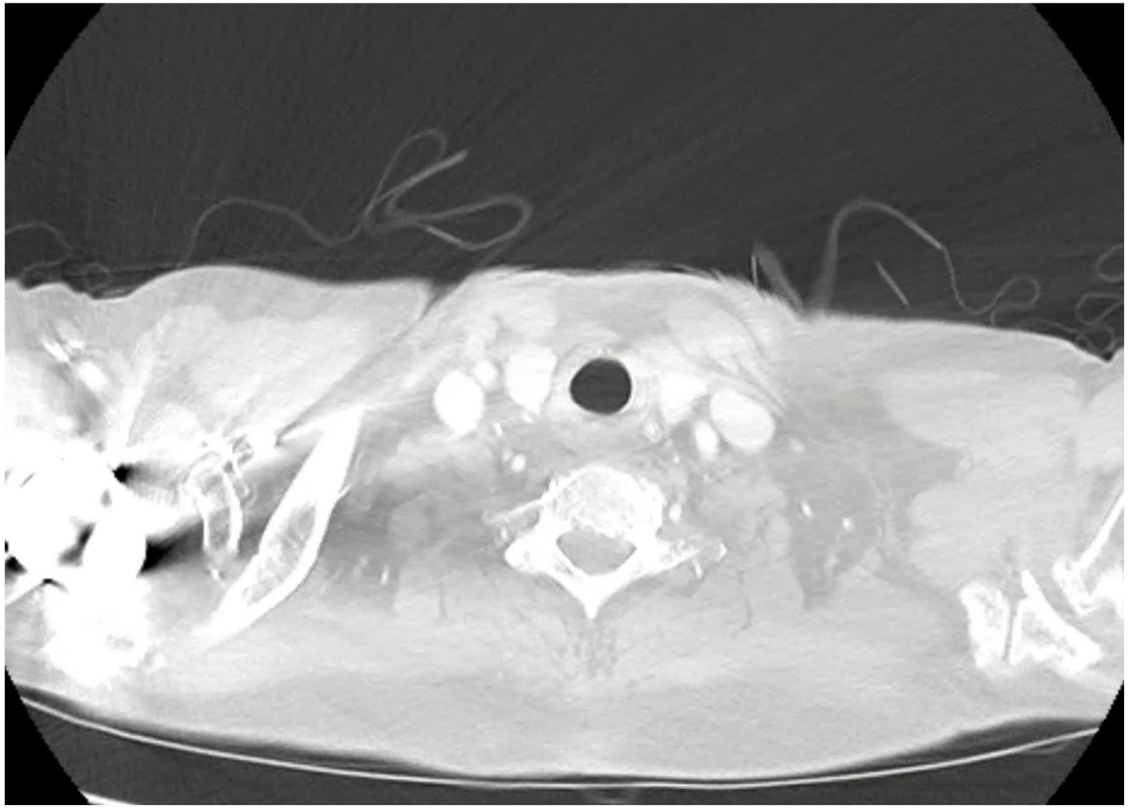
Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.

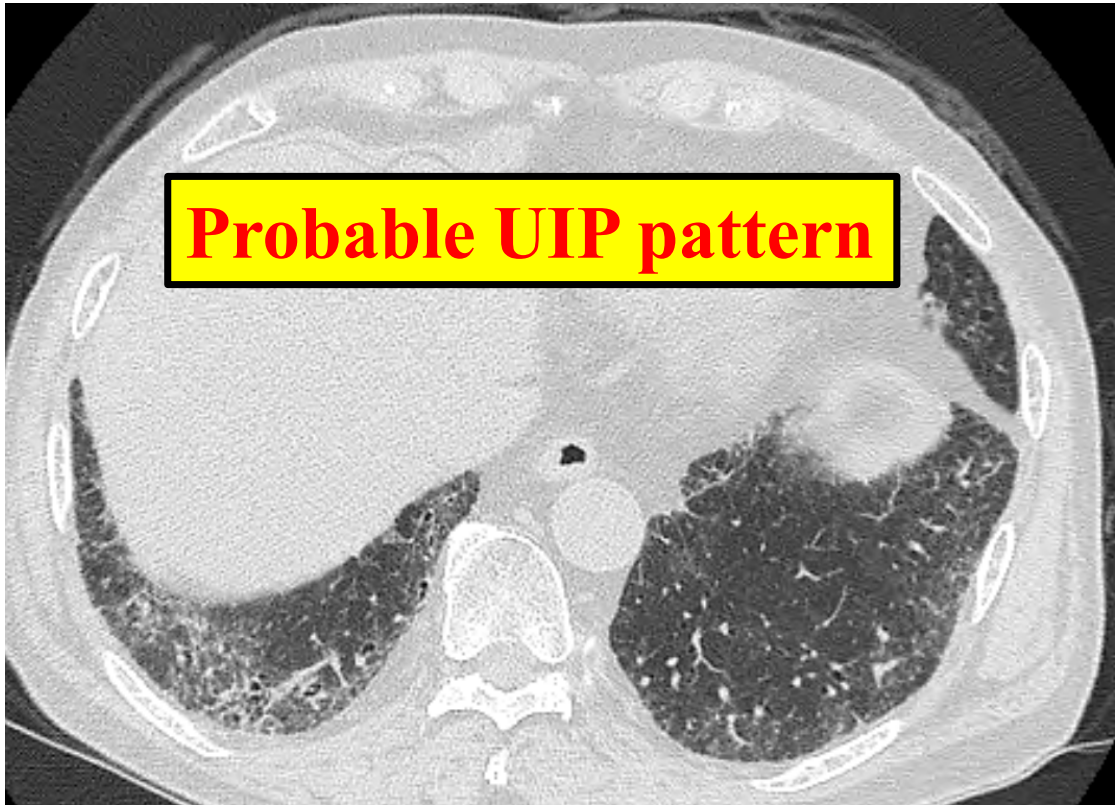
CASE 3. 82/M

- C/C 2년전부터 진행되는 호흡곤란으로 타원에서 시행한 chest CT 상 ILD 의심되어 내원함
- P/H HTN+
- Ex-40년전, 40 PYs
- C/S -/- mMRC Gr 1-2
- SaO2 97% (RA)

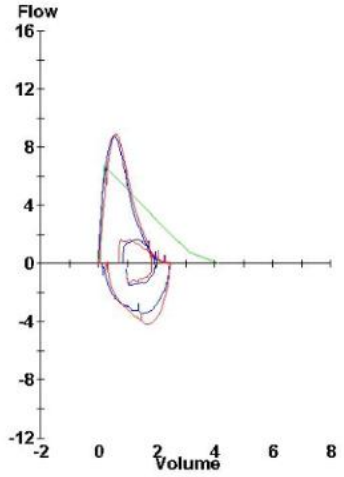


타원 HRCT





폐기능 검사 및 혈액검사

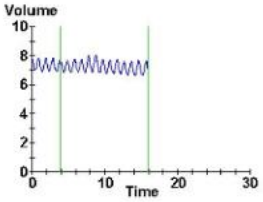


Spirometry

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	4.17	2.47	59	2.48	60	0
FEV.5	Liters	1.54	1.76	114	1.82	118	3
FEV1	Liters	2.52	1.98	79	2.06	82	4
FEV1/FVC	%	67	80		83		
FEV3/FVC	%	97	93		92		
FEF25-75%	L/sec	1.90	2.13	112	2.62	138	23
FEF25%	L/sec		7.91		6.98		-12
FEF75%	L/sec	0.78	0.52	67	0.68	88	31
FEF200-1200	L/sec	5.28	7.38	140	7.44	141	1
PEF	L/sec	6.75	8.78	130	8.87	131	1
MVV	L/min	97	59	61			

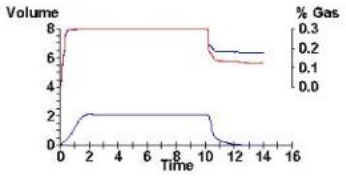
Lung Volumes

		Ref	Pre Meas	Pre % Ref
Vt	Liters			
ERV	Liters	1.17		
RV	Liters	2.75		
IC	Liters	2.35		
VC	Liters	3.39		
TLC	Liters	6.19		
RV/TLC	%	46		



Diffusion Capacity

		Ref	Pre Meas	Pre % Ref
DLCO	mL/min/mmHg	17.3	8.5	49
DL Adj	mL/min/mmHg	17.3	8.5	49
VA	Liters		3.30	
DLCO/VA	mL/min/mHg/L	3.37	2.59	77
DL/VA Adj	mL/min/mHg/L		2.59	
BHT	Sec		9.96	



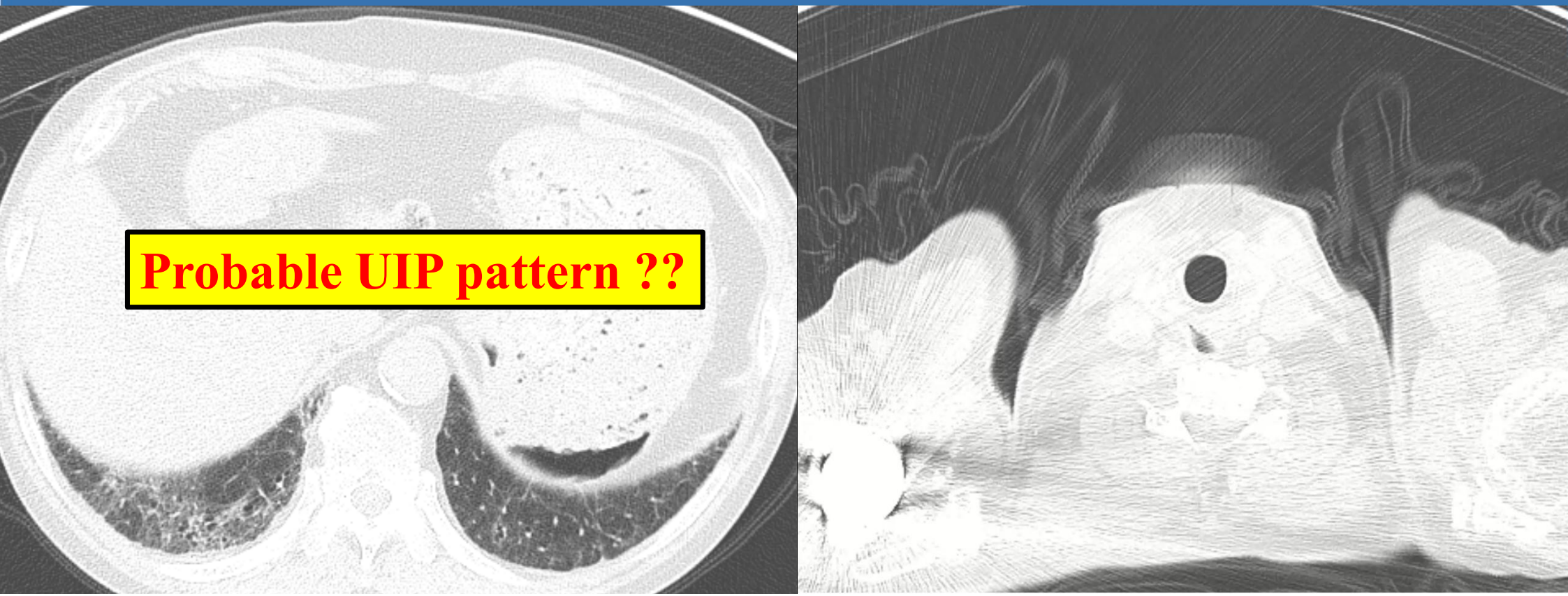
- Pre FVC 2.47 L (59%)
- Pre FEV1 1.98 L (79%)
- FEV1/FVC 80%
- DLco 49%

Restrictive pattern

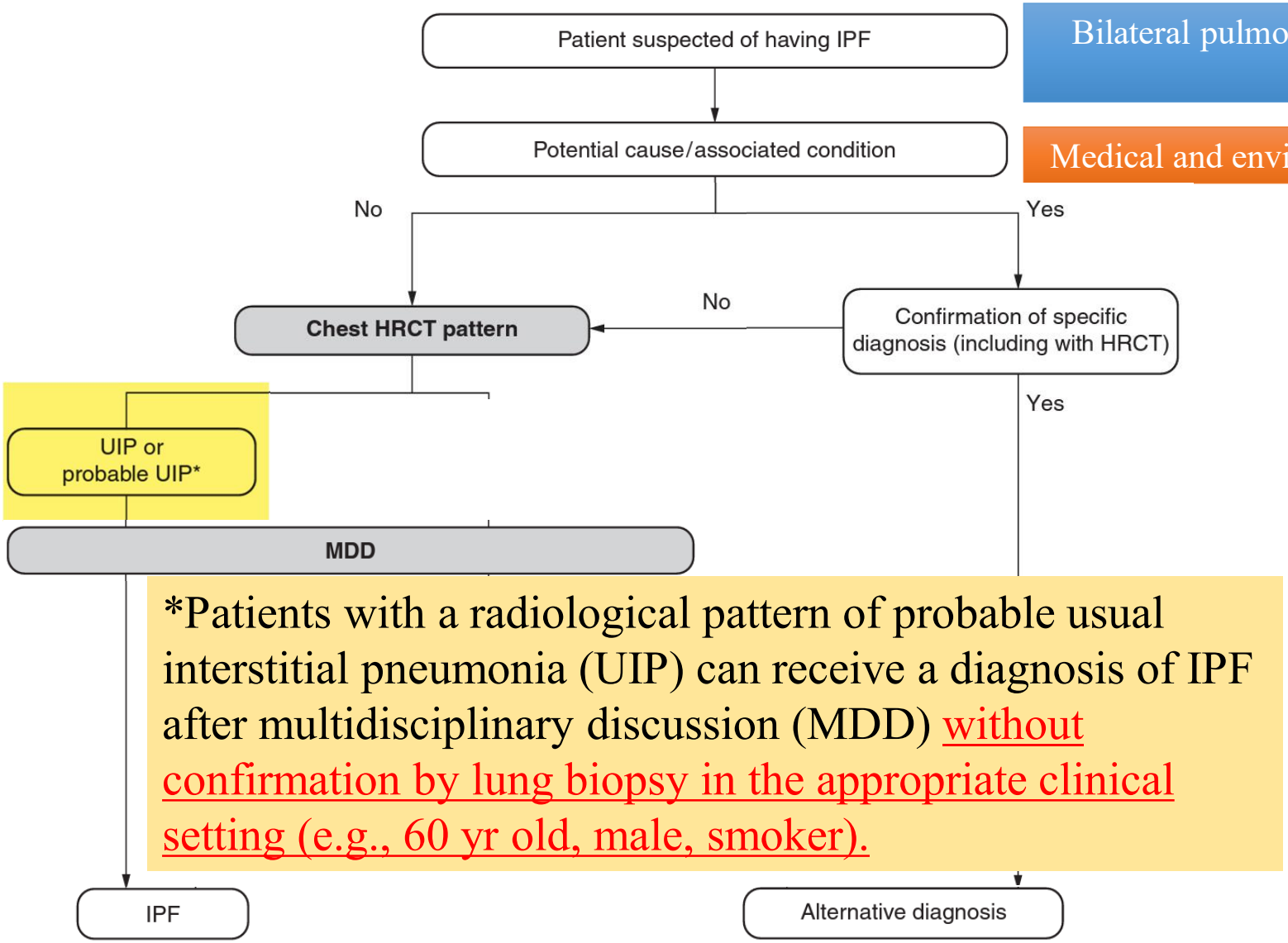
***Autoimmune marker (Screening)**

Anti-CCP	<0.5
ANA titer	Negative
ANCA	Negative
Rheumatoid factor titration	30.2
KL-6	2176

본원 Prone HRCT



1. Subpleural reticulation, GGO, traction bronchiectasis with honeycombing in both lungs with peripheral predominance, probably chronic fibrosing ILD (**UIP pattern**).



***MDD: multidisciplinary discussion**

Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

진단 및 치료

- Idiopathic pulmonary fibrosis [영상학적]

- 희귀질환 등록
- Pirfenidone start
- 연고지 병원으로 전원

Patient suspected of having IPF

Bilateral pulmonary fibrosis + bibasilar inspiratory crackles+ > 60yrs

Potential cause/associated condition

Medical and environmental exposure, excluding CTD

No

Yes

No

Chest HRCT pattern

Confirmation of specific diagnosis (including with HRCT)

Yes

UIP or probable UIP*

Indeterminate for UIP or alternate diagnosis

MDD

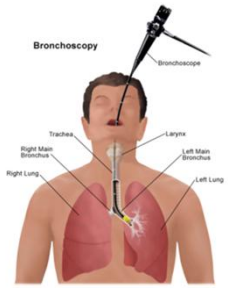
BAL† ± TBLC‡

SLB‡

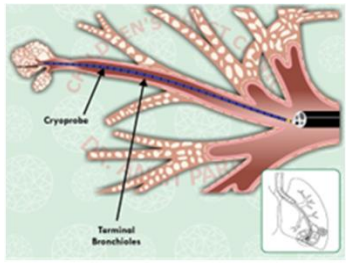
진단을 위해서는 대학병원 진료 필요

IPF

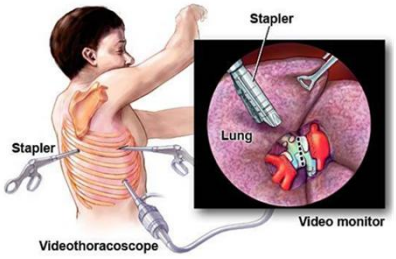
Alternative diagnosis



Bronchoscopy with bronchoalveolar lavage (BAL)



Cryobiopsy



Video-assist thoracic surgery (VATS)

***MDD: multidisciplinary discussion**

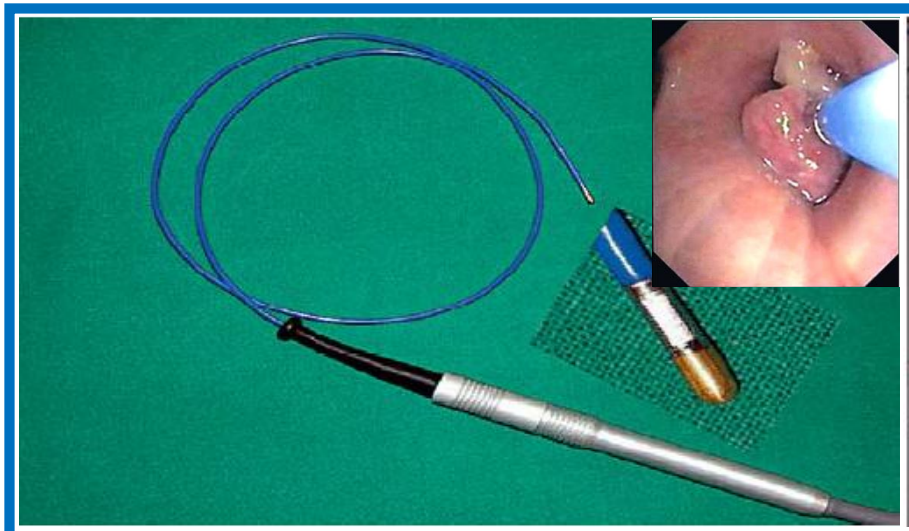
Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

Bronchoscopic transbronchial cryobiopsy

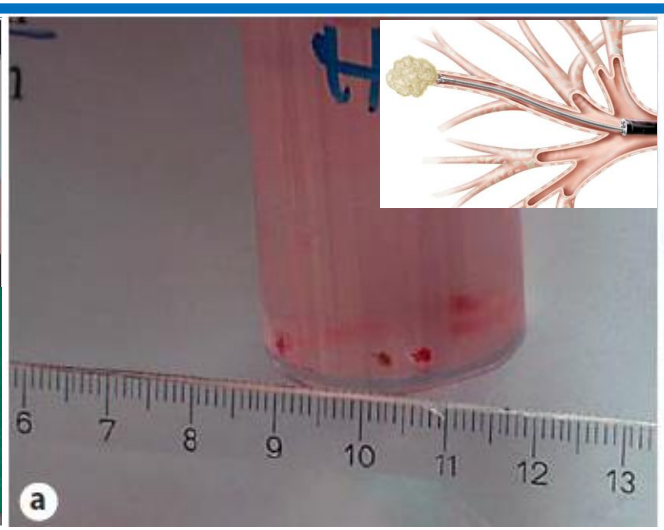
- Considered a safer, less morbid alternative to VATS biopsy.

조직학적 진단율 80%

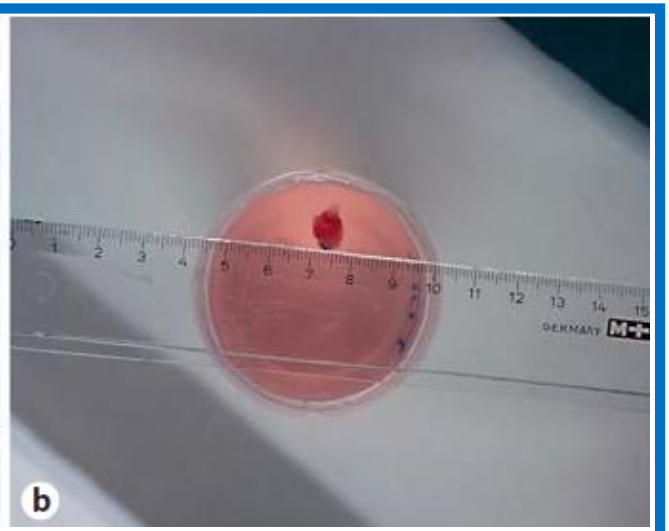
2008 Respiration



Flexible cryoprobe



Forcep biopsy



Cryoprobe biopsy

Cryobiopsy

- For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate for UIP, or an alternative diagnosis,
- **the panel made no recommendation regarding lung cryobiopsy.**

Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.

- We suggest that TBLC be regarded as an acceptable alternative to SLB for making a histopathological diagnosis in patients with ILD of undetermined type in medical centers with experience performing and interpreting TBLC (conditional recommendation, very low quality evidence).

Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

Histopathology Patterns and Features

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
• Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis	• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF *And* • Absence of features to suggest an alternative diagnosis *Or* • Honeycombing only	• Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause* • Some histologic features from column 1, but with other features suggesting an alternative diagnosis†	• Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies • Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

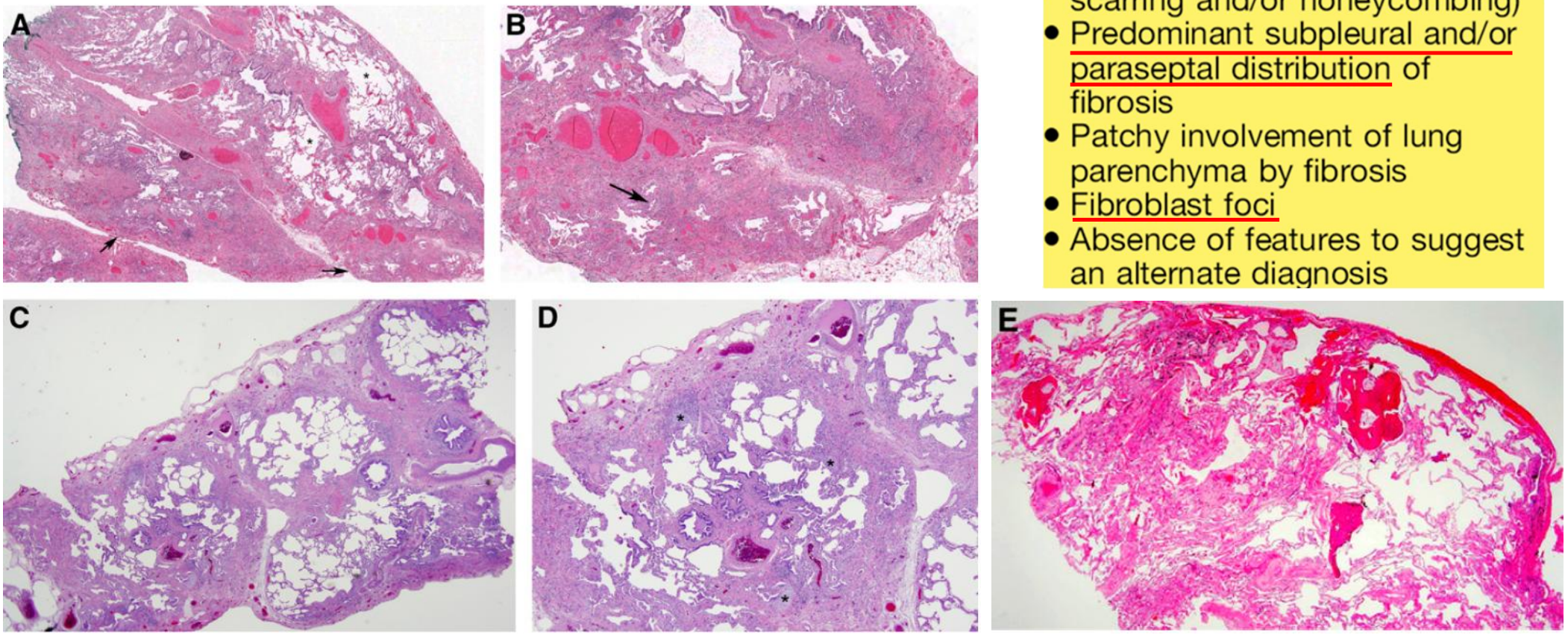
*UIP: Usual interstitial pneumonia

Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.

Histopathology demonstrating usual interstitial pneumonia (UIP)

UIP

- Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing)
- Predominant subpleural and/or paraseptal distribution of fibrosis
- Patchy involvement of lung parenchyma by fibrosis
- Fibroblast foci
- Absence of features to suggest an alternate diagnosis



***Fibroblast foci: scattered foci of proliferating fibroblasts**

Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.

Patient suspected of having IPF

Bilateral pulmonary fibrosis + bibasilar inspiratory crackles+ > 60yrs

Potential cause/associated condition

Medical and environmental exposure, excluding CTD

No

Yes

No

Chest HRCT pattern

Confirmation of specific diagnosis (including with HRCT)

Yes

UIP or probable UIP*

Indeterminate for UIP or alternate diagnosis

MDD

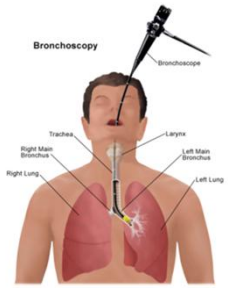
BAL† ± TBLC‡

SLB‡

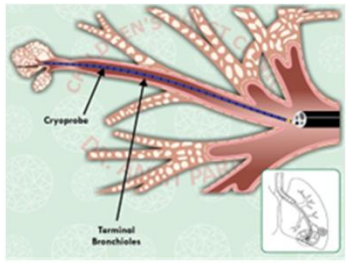
MDD

IPF

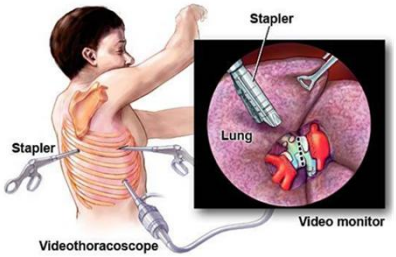
Alternative diagnosis



Bronchoscopy with bronchoalveolar lavage (BAL)



Cryobiopsy

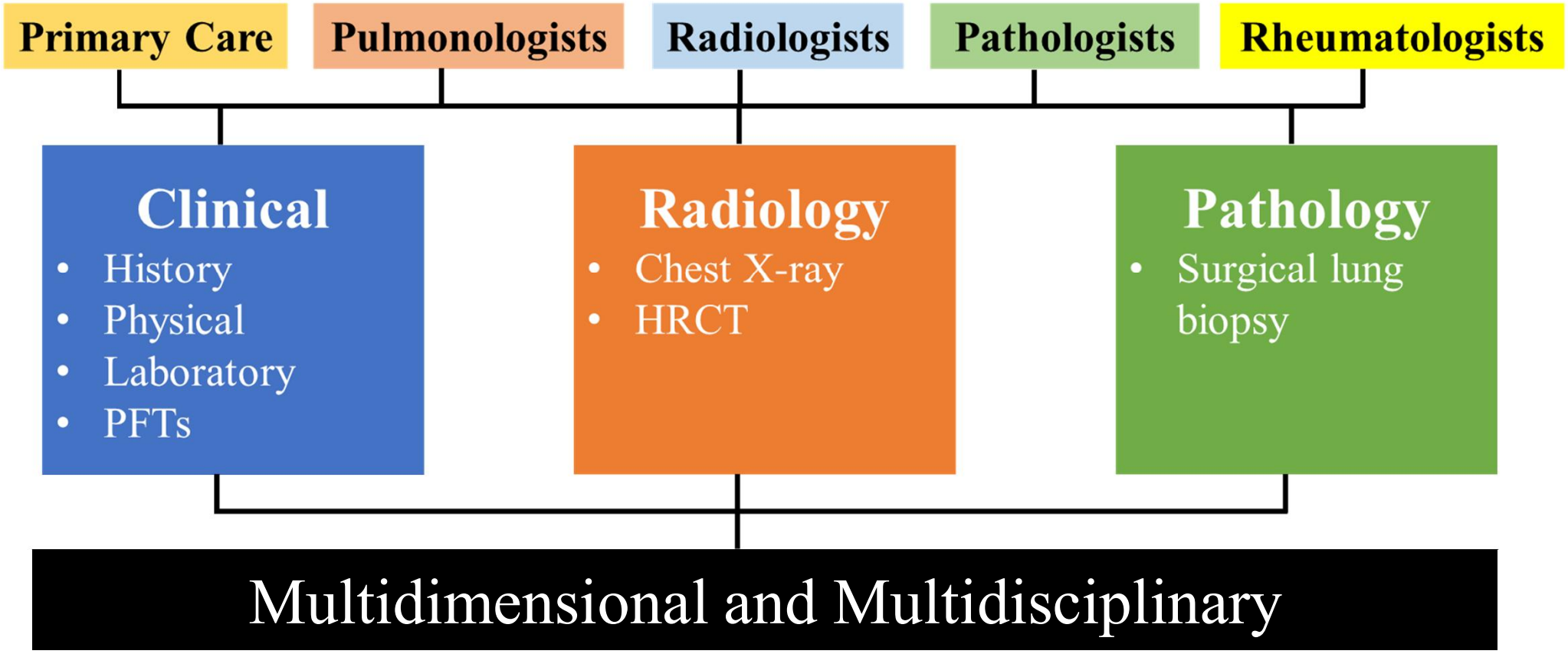


Video-assist thoracic surgery (VATS)

***MDD: multidisciplinary discussion**

Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

Multidisciplinary Discussion (MDD)



Idiopathic pulmonary fibrosis diagnosis based upon HRCT and biopsy patterns.

IPF suspected*		Histopathology pattern†			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)‡	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)‡	Indeterminate§	Non-IPF dx
	Alternative diagnosis	IPF (Likely)‡	Indeterminate§	Non-IPF dx	Non-IPF dx

*UIP: Usual interstitial pneumonia

Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.

전남대학교병원은 MDD ?

Chest conference

Pulmonologists

Chest conference
완전체

Radiologists

Pathologists

Rheumatologists

Surgeon

Pulmonologists

Rheumatologists

nference

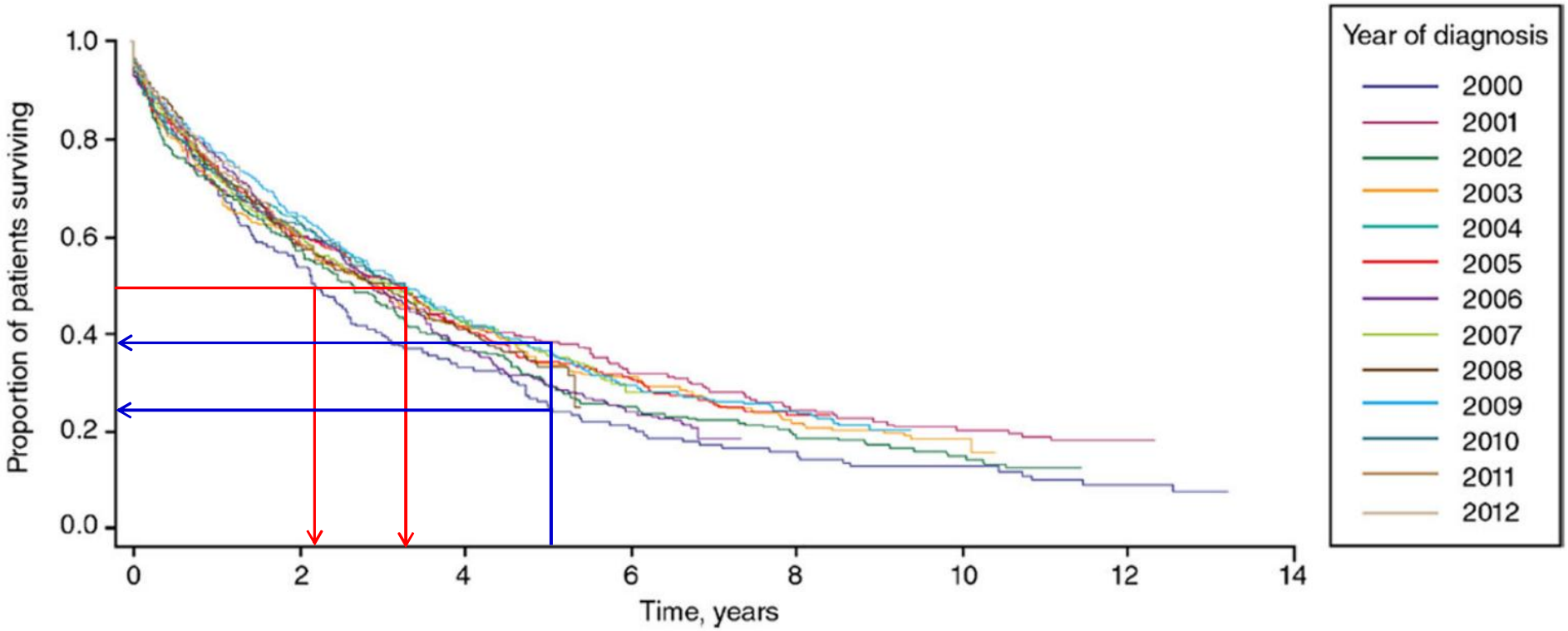
onologists

logists

logists

Surgeon

Survival in patients with incident IPF



Respir Res. 2019 Sep 6;20(1):205.

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis: An Update of the 2011 Clinical Practice Guideline

Agent	2015 Guideline
New and revised recommendations	
Anticoagulation (warfarin)	Strong recommendation against use
Selective endothelin receptor antagonist	Strong recommendation against use
Imatinib	Strong recommendation against use
Nintedanib	Conditional recommendation for use
Pirfenidone	Conditional recommendation for use
Dural endothelin receptor antagonists	Conditional recommendation against use
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use
Unchanged recommendations	
Antacid therapy	Conditional recommendation for use
N-acetylcysteine monotherapy	Conditional recommendation against use
Antipulmonary hypertension therapy	Deferred
Lung transplantation : single vs. bilateral lung transplantation	Deferred

새로운 약제가 없어 치료에 큰 변화가 없다.

Am J Respir Crit Care Med. 2015 Jul 15;192(2):e3-19

ILD 진료지침 (II. 특발성폐섬유증)

새로운 진료지침이 개정 중에 있음

권고사항

- 특발성폐섬유증(IPF) 환자에서 폐기능(FVC)의 감소로 정의되는 질환의 진행을 늦추기 위하여 Pirfenidone의 사용을 권장한다(근거수준: 보통, 권고수준: 강함)
- 특발성폐섬유증(IPF) 환자에서 폐기능(FVC)의 감소로 정의되는 질환의 진행을 늦추기 위하여 Nintedanib의 사용을 권장한다(근거수준: 보통, 권고수준: 강함)
- 특발성폐섬유증 환자에서 폐이식은 대조군(폐이식 받지 않은 군)에 비해 생존율을 증가시키므로 적절한 시기에 고려한다(근거수준: 보통, 권고수준: 약함)

2018 ILD 진료지침

Antifibrotic drugs for IPF treatment

- Pirfenidone

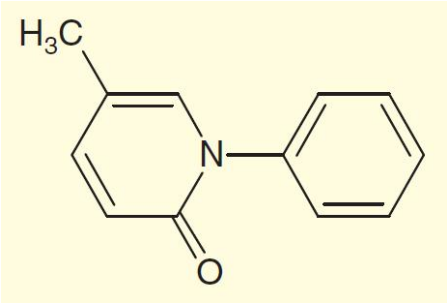
- Nintedanib

U.S. Food and Drug Administration

October 15, 2014

The FDA granted Esbriet (pirfenidone) and Ofev (nintedanib) fast track, priority review, orphan product, and breakthrough designations.

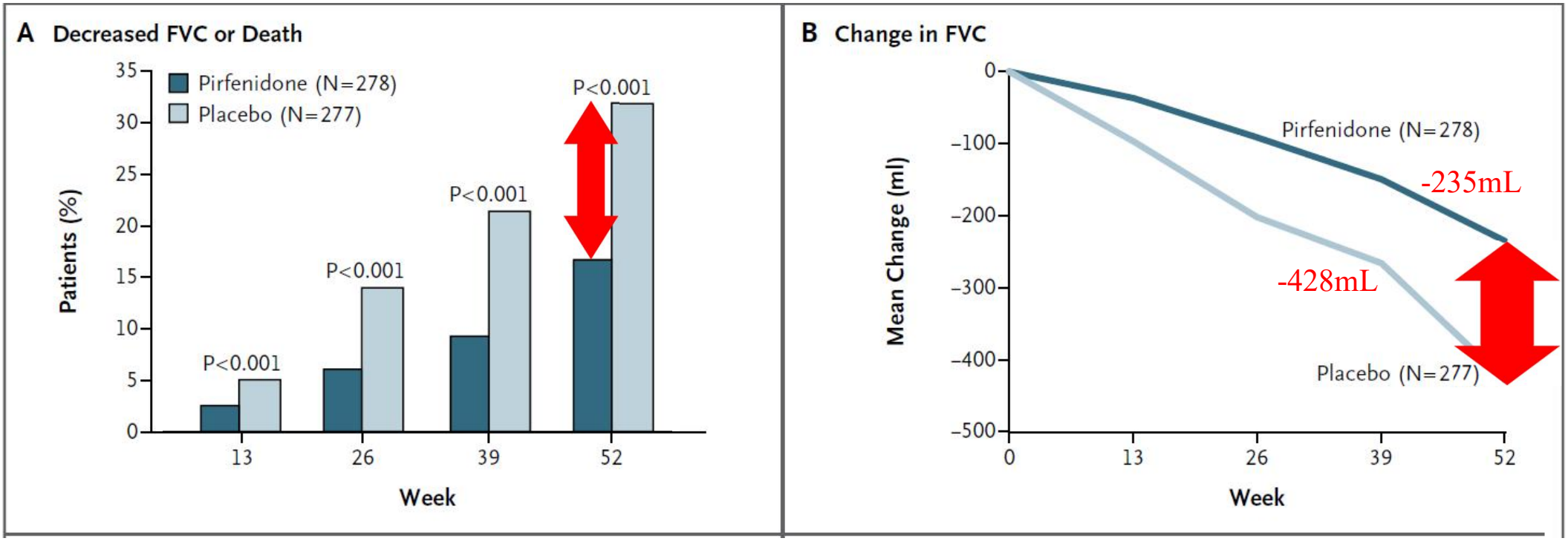
Pirfenidone



- Inhibits TGF-β production, downstream signaling
- Inhibits collagen synthesis
- Inhibits fibroblast proliferation

- 용법
  - 200 mg x tid for 14days
  - 400 mg x tid for 14days
  - 600 mg x tid ~

Pirfenidone significantly reduced pulmonary function decline in IPF patients compared with placebo in 52-week- phase III trial.



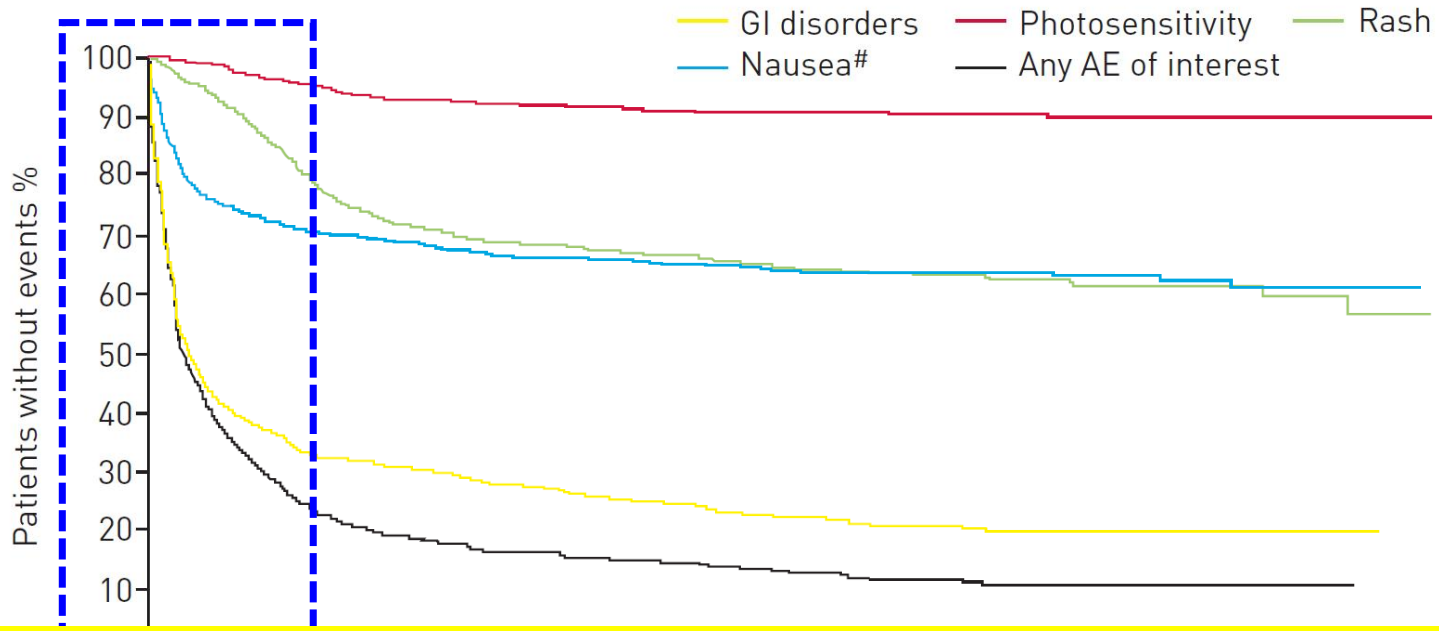
*Proportion of patients with FVC % predicted decline ⩾10% or death

N Engl J Med 2014;370:2083-92.

Pirfenidone 경구제 보험인정기준 변경 대비표 *보건복지부 고시 제2018-280호 기준* (시행일자 2019.1.1)

현 보험인정기준	새로운 보험인정기준
아래와 같은 기준으로 투여시 요양급여를 인정하며, 허가사항 범위이지만 동 인정기준 이외에 투여하는 경우에는 약값 전액을 환자가 부담토록 함. - 아 래 - ○ 투여대상: 고해상흉부전산화단층촬영(HRCT)과/또는 수술적폐조직생검(surgical lung biopsy)으로 확진된 특발성폐섬유증환자 중 **경증 및 중등도환자**로서 치료를 시작하기 전에 다음 **조건을 만족시켜야 함.** ① FVC ≤ 90%, or ② DLco ≤ 80%, or ③ 다음 중 2개 이상 만족 ▪ FVC ≥10% 감소/year ▪ FVC ≥ 200 mL 감소/year ▪ 임상증상 악화 ▪ 흉부영상 악화	허가사항 범위 내에서 아래와 같은 기준으로 투여시 요양급여를 인정하며, 동 인정기준 이외에는 약값 전액을 환자가 부담토록 함. - 아 래 - ○ 투여대상 -고해상 흉부전산화단층촬영(HRCT)과/또는 수술적 폐조직 생검(surgical lung biopsy)으로 확진된 특발성 폐섬유증 환자로서 치료를 시작하기 전 **다음에 해당하는 경우** **-단, 교원성 질환 또는 다른 원인으로 설명되는 간질성 폐질환은 제외함.** - 다 음 - **1) Predicted forced vital capacity(FVC) 90% 이하 이거나** **Predicted carbon monoxide diffusing capacity(DLco) 80% 이하** **2) Predicted FVC 90% 초과하면서 Predicted DLco 80% 초과한 환자 중** **아래 두 가지 이상에 해당되는 경우** **- 아 래 -** **가) 폐기능 저하: 연간 Predicted FVC 감소량이 10% 이상이거나** **연간 Predicted FVC 200ml 이상 감소** **나) 임상증상 악화** **다) 흉부영상 악화 소견**

Kaplan–Meier analysis of time to first occurrence of a pirfenidone-related adverse event



약제 투여 초기를 잘 버텨야 한다.

Time to first AEs months

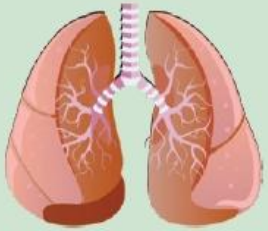
Patients at risk n									
GI disorders	623	199	166	139	86	64	25	12	0
Photosensitivity	623	574	530	499	343	258	118	66	6
Rash	623	478	395	366	244	176	81	36	5
Nausea#	623	427	385	361	248	188	87	43	4
Any AE of interest	623	143	100	87	56	38	12	5	0

Eur Respir Rev 2017; 26: 170057

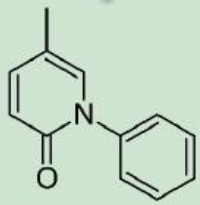
Efficacy of lower dose pirfenidone for idiopathic pulmonary fibrosis in real practice: a retrospective cohort study

Korean J Intern Med. 2022 Mar;37(2):366-376.

Patients



Idiopathic pulmonary fibrosis
3 referral centers
2012 to 2018



338 Patients
with pirfenidone

Table 2. Treatment duration and dose of pirfenidone in study patients (n = 338)

All patients	Value
Duration of total pirfenidone treatment, mo	16.1 ± 9.0
Maximum dose of pirfenidone, mg	
1,800	156 (46.2)
1,200–1,500	169 (50.0)
≤ 600	13 (3.8)
Final dose of pirfenidone, mg	
1,800	72 (21.3)
1,200–1,600	145 (42.9)
800–1,000	9 (2.7)
≤ 600	23 (6.8)
Discontinuation	89 (26.3)
Patients receiving standard dose (n = 68)	
Duration of total pirfenidone treatment, mo	18.2 ± 7.8

Values are presented as mean ± SD or number (%).

Efficacy of lower dose pirfenidone for idiopathic pulmonary fibrosis in real practice: a retrospective cohort study

Korean J Intern Med. 2022 Mar;37(2):366-376.

Table 5. Adverse events and mortality of enrolled patients (n = 338)

Variable	No. (%)
Adverse event	
Total	276 (81.7)
Anorexia	123 (36.4)
Skin rash	97 (28.7)
Dyspepsia	89 (26.3)
Nausea	65 (19.2)
General weakness	51 (15.1)
Liver function test abnormality	43 (12.7)
Photosensitivity	34 (10.1)
Fatigue	22 (6.5)
Diarrhoea	19 (5.6)
Others[a]	57 (16.9)
Discontinuation of treatment due to adverse event	83 (24.6)
Gastrointestinal-related	33 (9.8)
Skin-related	23 (6.8)
Liver function test abnormality	12 (3.6)
General weakness and fatigue	6 (1.8)
Others[a]	9 (2.7)
Overall death	36 (10.7)
IPF related death	31 (9.2)

Efficacy of lower dose pirfenidone for idiopathic pulmonary fibrosis in real practice: a retrospective cohort study

Korean J Intern Med. 2022 Mar;37(2):366-376.

Table 4. Comparison of FVC and DL_{CO} decline rate before and after treatment according to the dose of pirfenidone

Parameter	Time	Standard dose (n = 32)			Non-standard dose (n = 82[a] or 75[b])		
		Mean	95% CI	*p* value	Mean	95% CI	*p* value
Δ FVC/year[c] (n = 114)	Pre-treatment	−6.56	−9.26 to −3.87		−4.96	−6.82 to −3.09	
	Post-treatment	−4.43	−5.87 to −3.00		−1.79	−2.75 to −0.83	
	Difference	2.13		0.010	3.17		< 0.001
p value for homogeneity of difference in parameter between two groups: 0.307							
Δ DL_{CO}/year[c] (n = 107)	Pre-treatment	−8.03	−11.93 to −4.13		−7.69	−10.68 to −4.70	
	Post-treatment	−4.38	−6.44 to −2.31		−3.12	−4.34 to −1.90	
	Difference	3.65		0.008	4.57		< 0.001
p value for homogeneity of difference in parameters between two groups: 0.536							

FVC, forced vital capacity; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; CI, confidence interval.

[a]Δ FVC/year.

[b]Δ DL_{CO}/year.

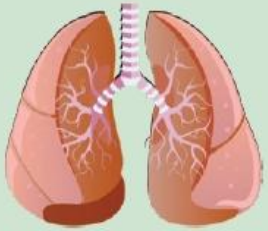
[c]Change in % predicted per year.

with pirfenidone

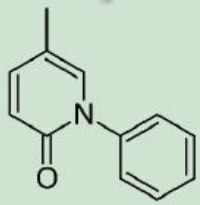
Efficacy of lower dose pirfenidone for idiopathic pulmonary fibrosis in real practice: a retrospective cohort study

Korean J Intern Med. 2022 Mar;37(2):366-376.

Patients



Idiopathic pulmonary fibrosis
3 referral centers
2012 to 2018



338 Patients
with pirfenidone

Outcome

Efficacy

The differences in pulmonary function changes after treatment with pirfenidone

Pirfenidone	Differences of Δ FVC/year	Differences of Δ DL_{CO}/year
All	+ 2.45 %	+ 3.79 %
Standard dose	+ 2.13 %	+ 3.65 %
Lower dose	+ 3.17 %	+ 4.57 %

Adverse events (AE)

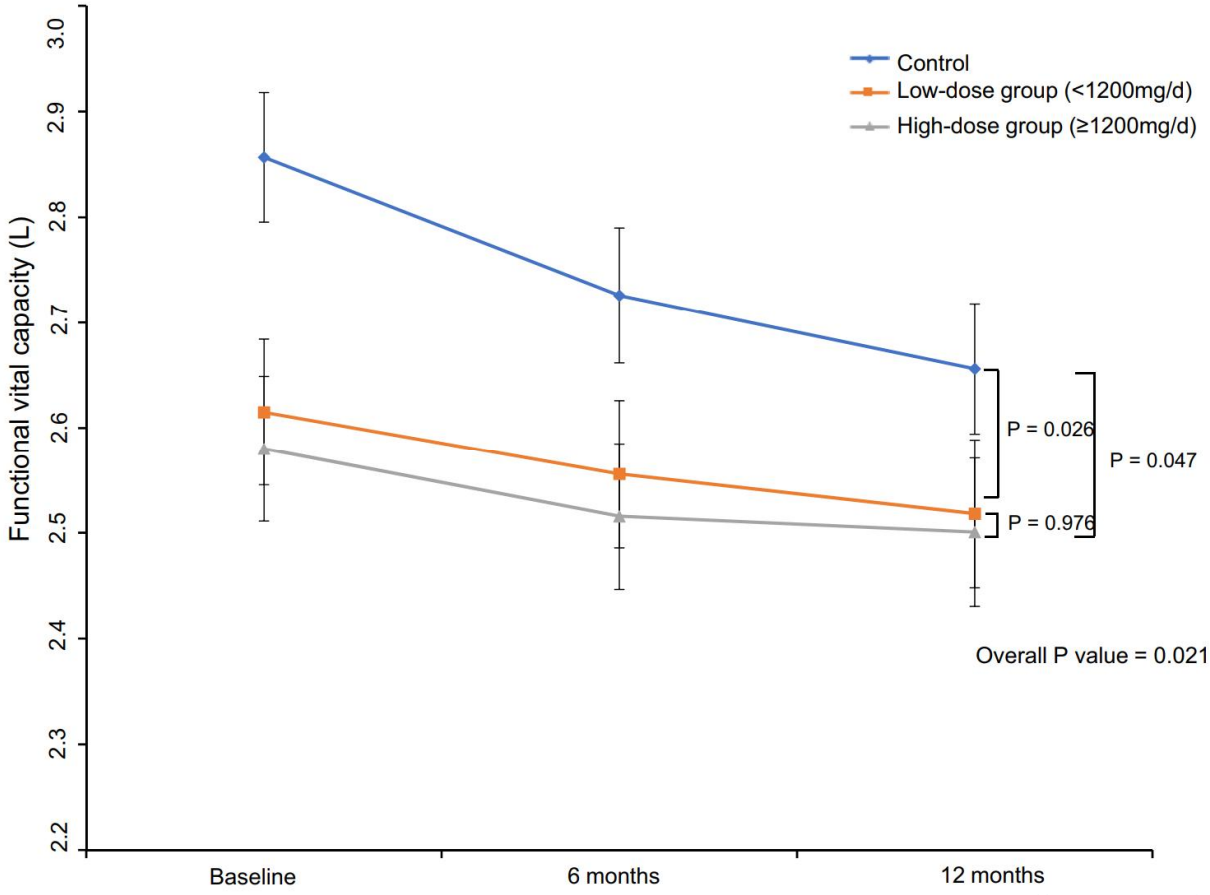
Any type of AE 81.7%

Discontinuation 24.6%

Conclusion

The effect of pirfenidone on reducing disease progression of idiopathic pulmonary fibrosis persisted even with a consistently lower dose.

Low-dose group (<1200 mg/d) vs. High-dose group (≥1200 mg/d)

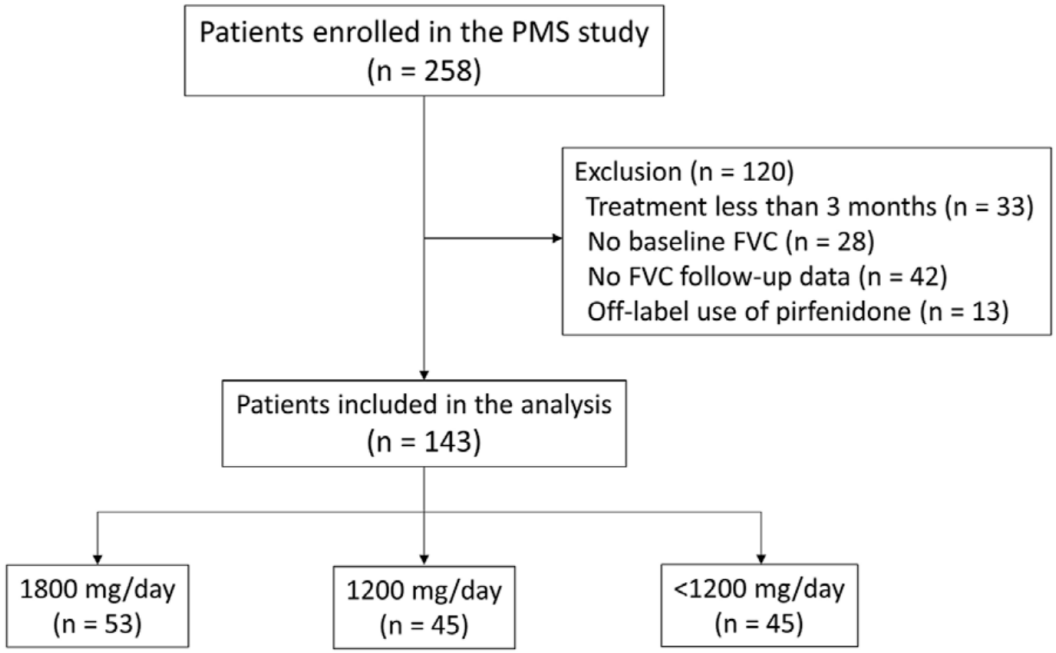


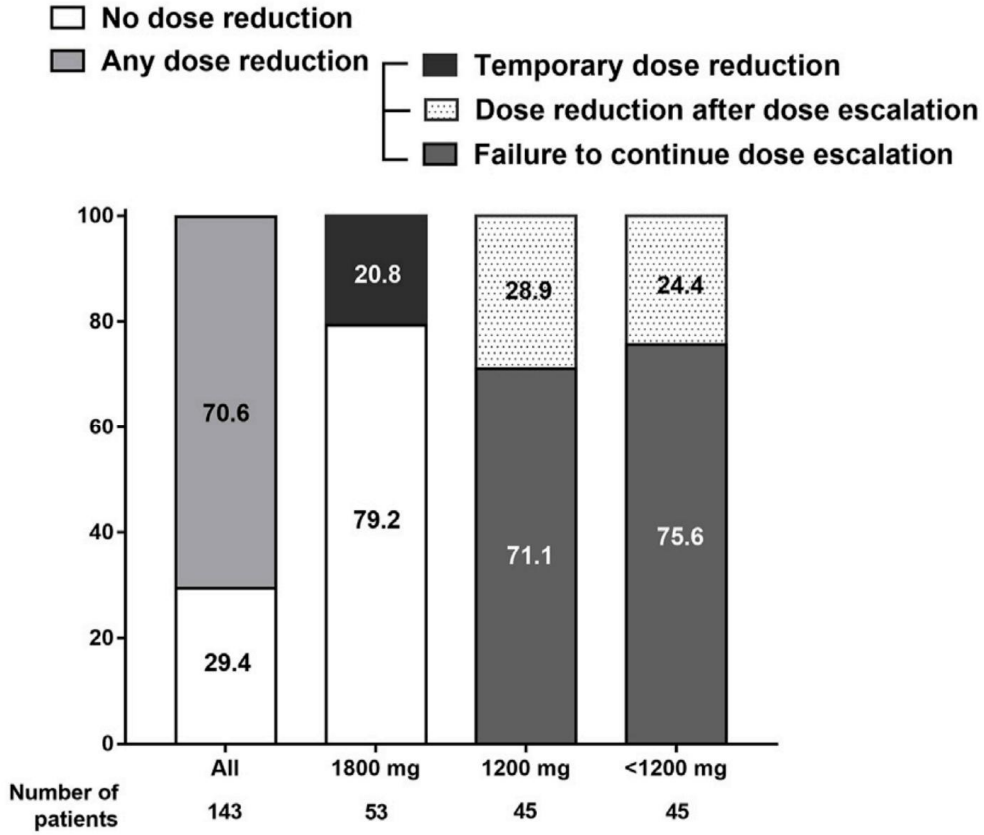
Sci Rep . 2020 Dec 4;10(1):21218.

Clinical outcomes of dose modification during pirfenidone treatment for IPF: A nationwide post-marketing surveillance study

Jieun Kang[1], Man Pyo Chung[2], Moo Suk Park[3], In Jae Oh[4], Heung Bum Lee[5], Young Whan Kim[6], Jong Sun Park[7], Soo Taek Uh[8], Yun Seong Kim[9], Yangjin Jegal[10] and Jin Woo Song[11]*

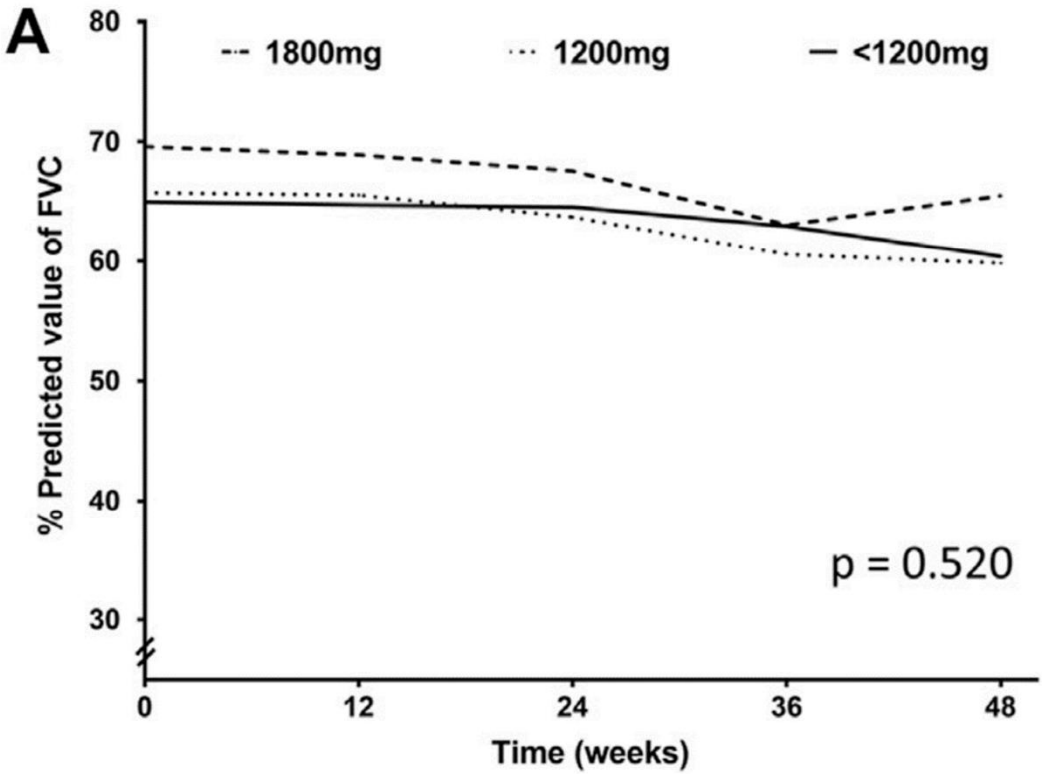
- 2014-2017, 10 hospitals
- 48 weeks f/u

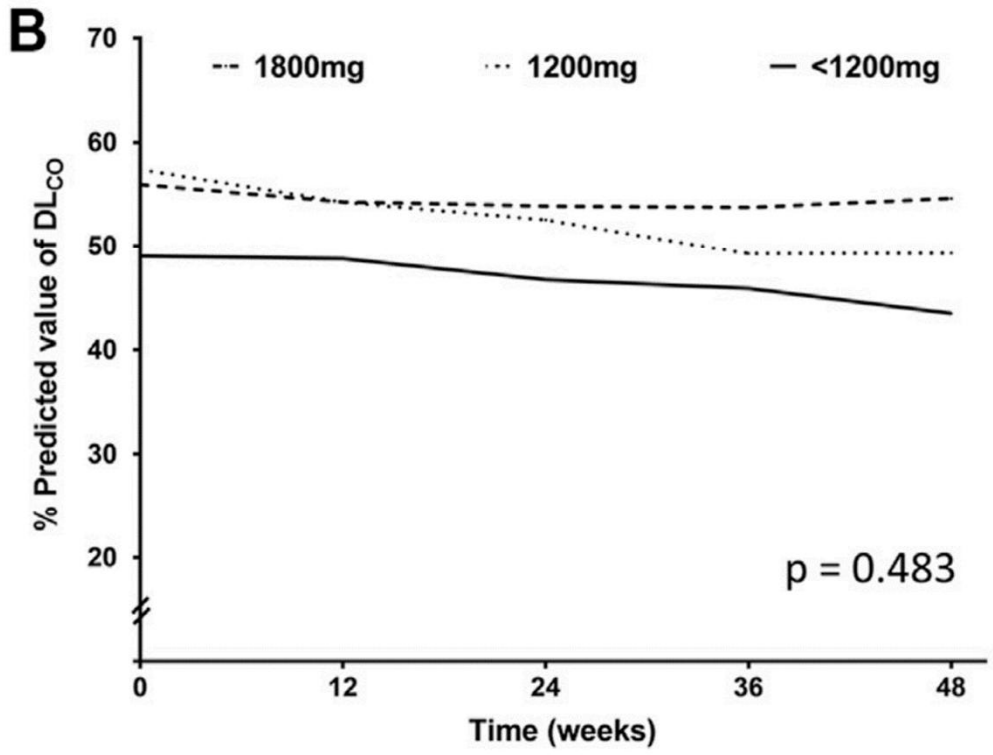




Front Pharmacol . 2023 Jan 10;13:1025947

Pulmonary function changes





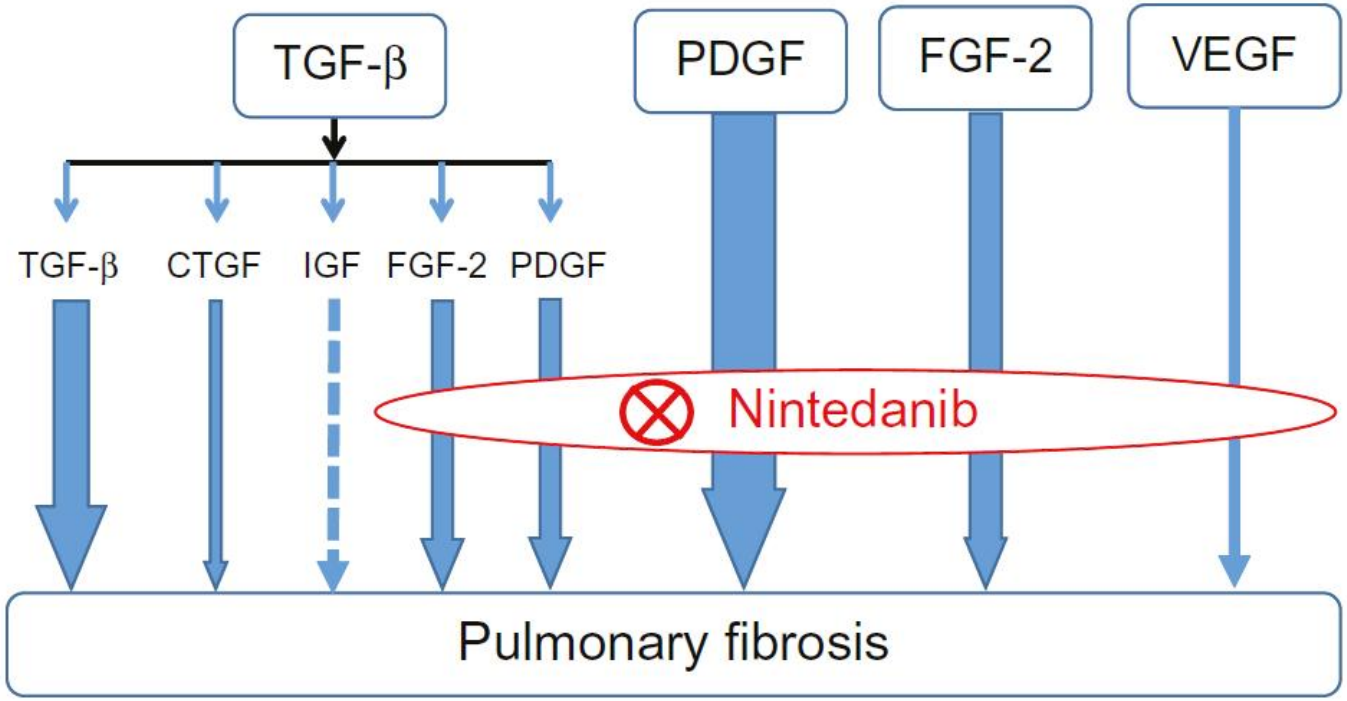
Front Pharmacol . 2023 Jan 10;13:1025947

Nintedanib (Ofev®)

- A small molecule originally designed as an anti-angiogenic drug for cancer indications
- Intracellular inhibitor of tyrosine kinases
  - FGFR (FGFR-1, FGFR-2, FGFR-3)
  - VEGFR (VEGFR-1, VEGFR-2, VEGFR-3)
  - PDGFR-α, PDGFR-β
- 150mg bid/100mg bid

- PDGF: platelet-derived growth factor
- FGF: fibroblast growth factor
- VEGF: vascular endothelial growth factor

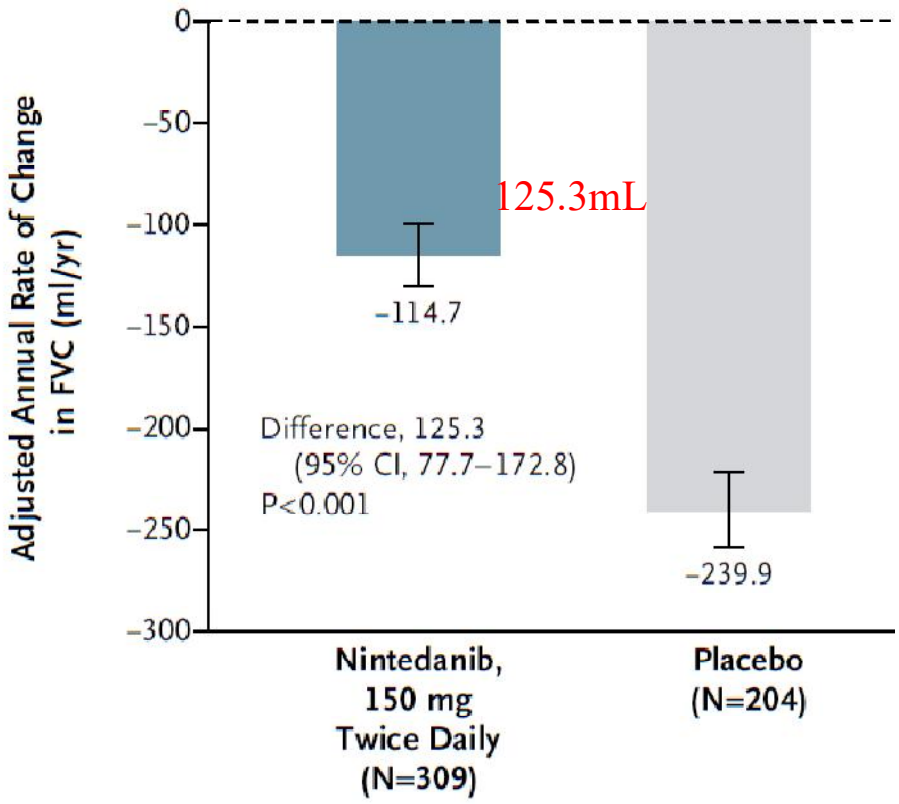
Nintedanib (Ofev®)

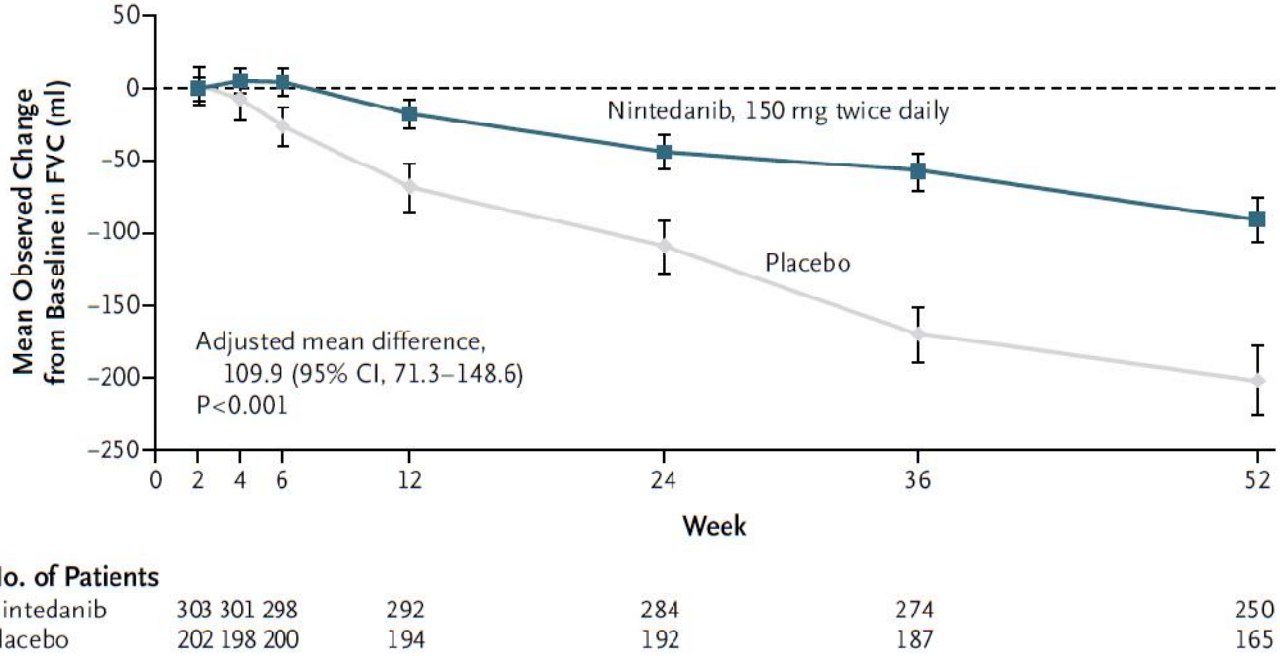


- PDGF: platelet-derived growth factor
- FGF: fibroblast growth factor
- VEGF: vascular endothelial growth factor

Core Evid. 2015 Aug 27;10:89-98

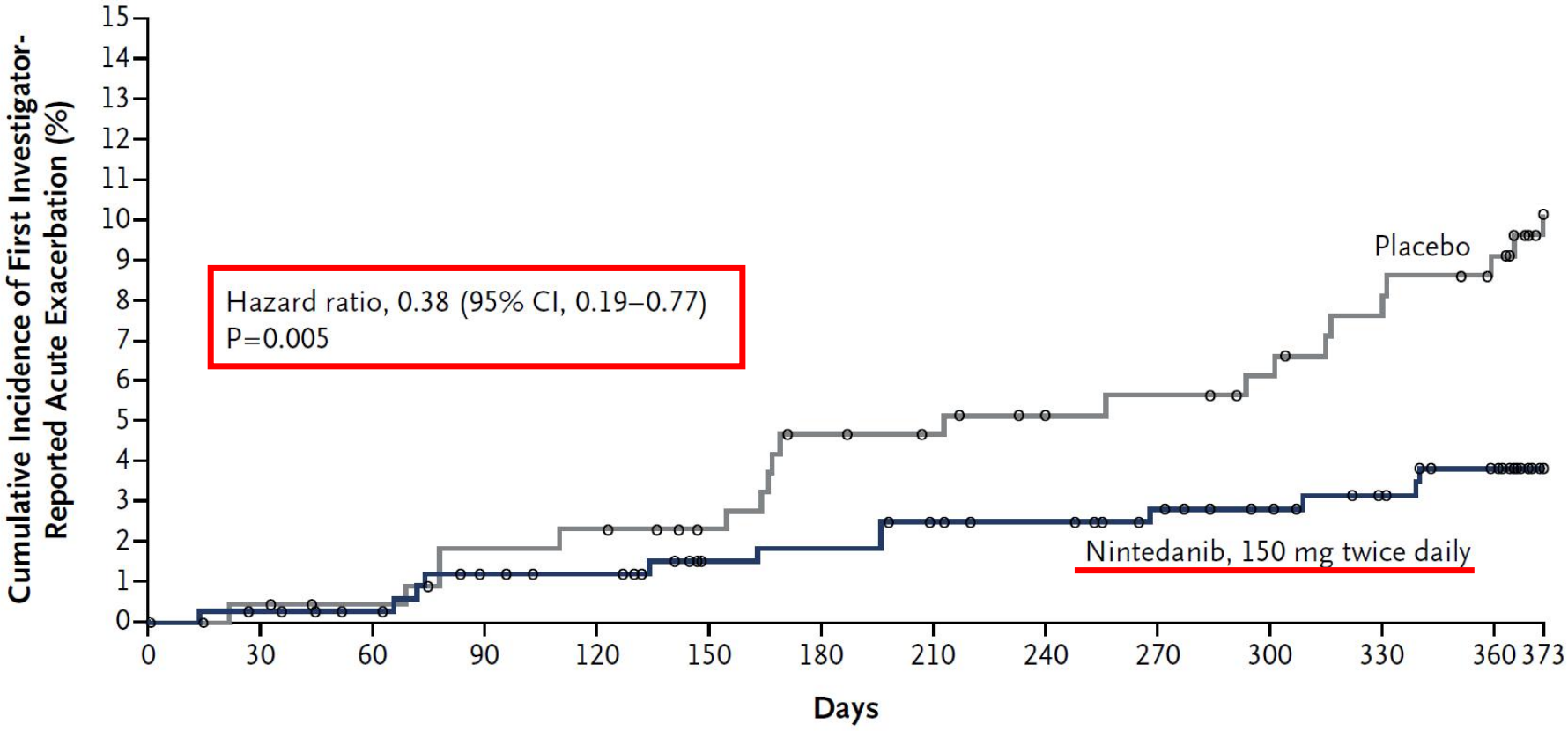
Nintedanib significantly reduced pulmonary function decline in IPF patients compared with placebo in 52-week- phase III trial.





N Engl J Med 2014;370:2071-82.

Nintedanib also reduced acute exacerbations compared with placebo by 62%



N Engl J Med 2014;370:2071-82.

Disease-modifying therapies : Nintedanib, Pirfenidone

Panel: Therapies identified in clinical trials as harmful, ineffective, or effective in the treatment of idiopathic pulmonary fibrosis

Potentially harmful therapies

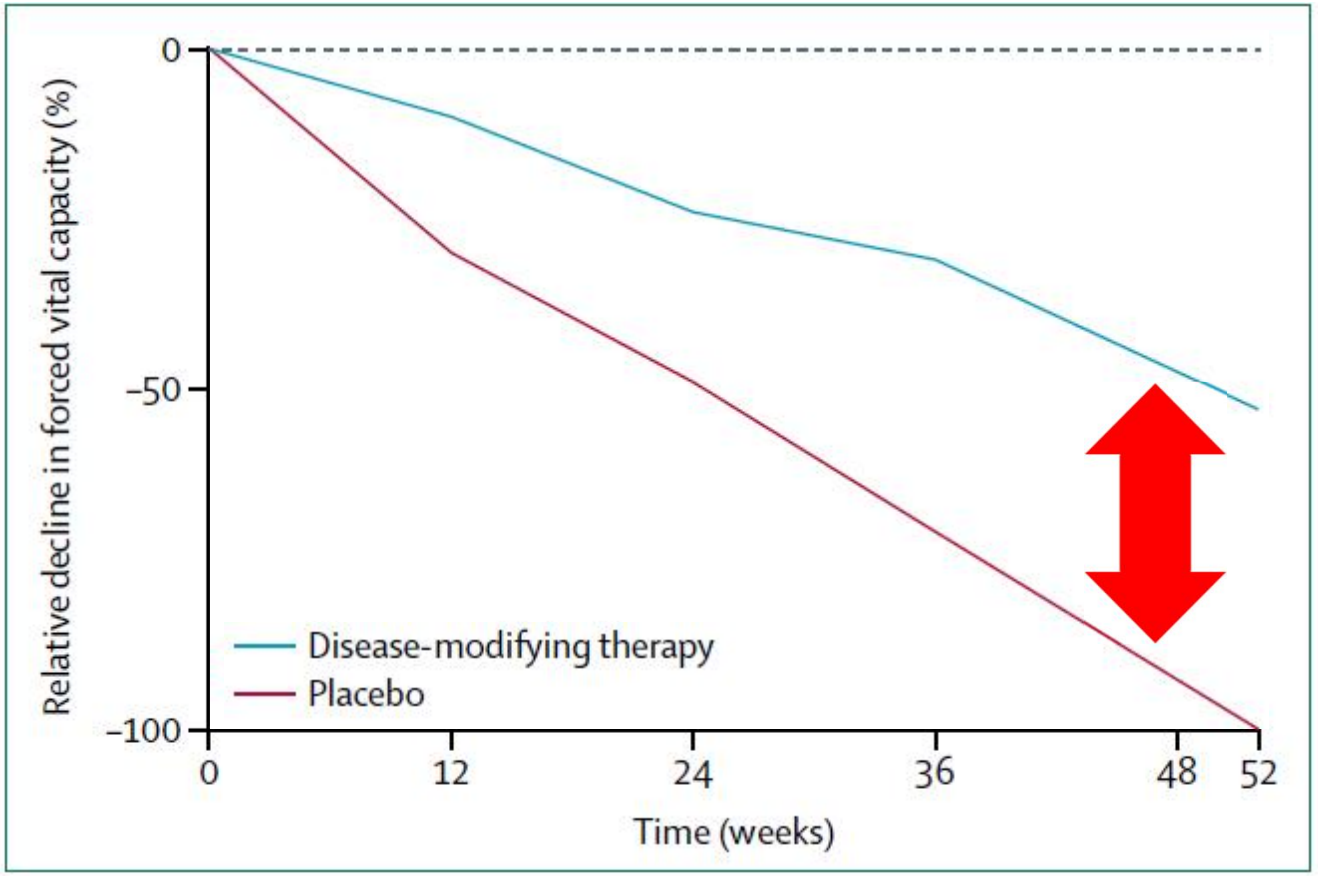
- Ambrisentan[81]
- Everolimus[82]
- Prednisolone, azathioprine, acetylcysteine[9]
- Warfarin[83]

Potentially ineffective therapies

- Bosentan[84]
- Imatinib[85]
- Macitentan[86]
- Acetylcysteine[87]
- Sildenafil[88]

Effective disease-modifying therapies

- Nintedanib[89]
- Pirfenidone[90,91]



the most important medications for IPF treatment.

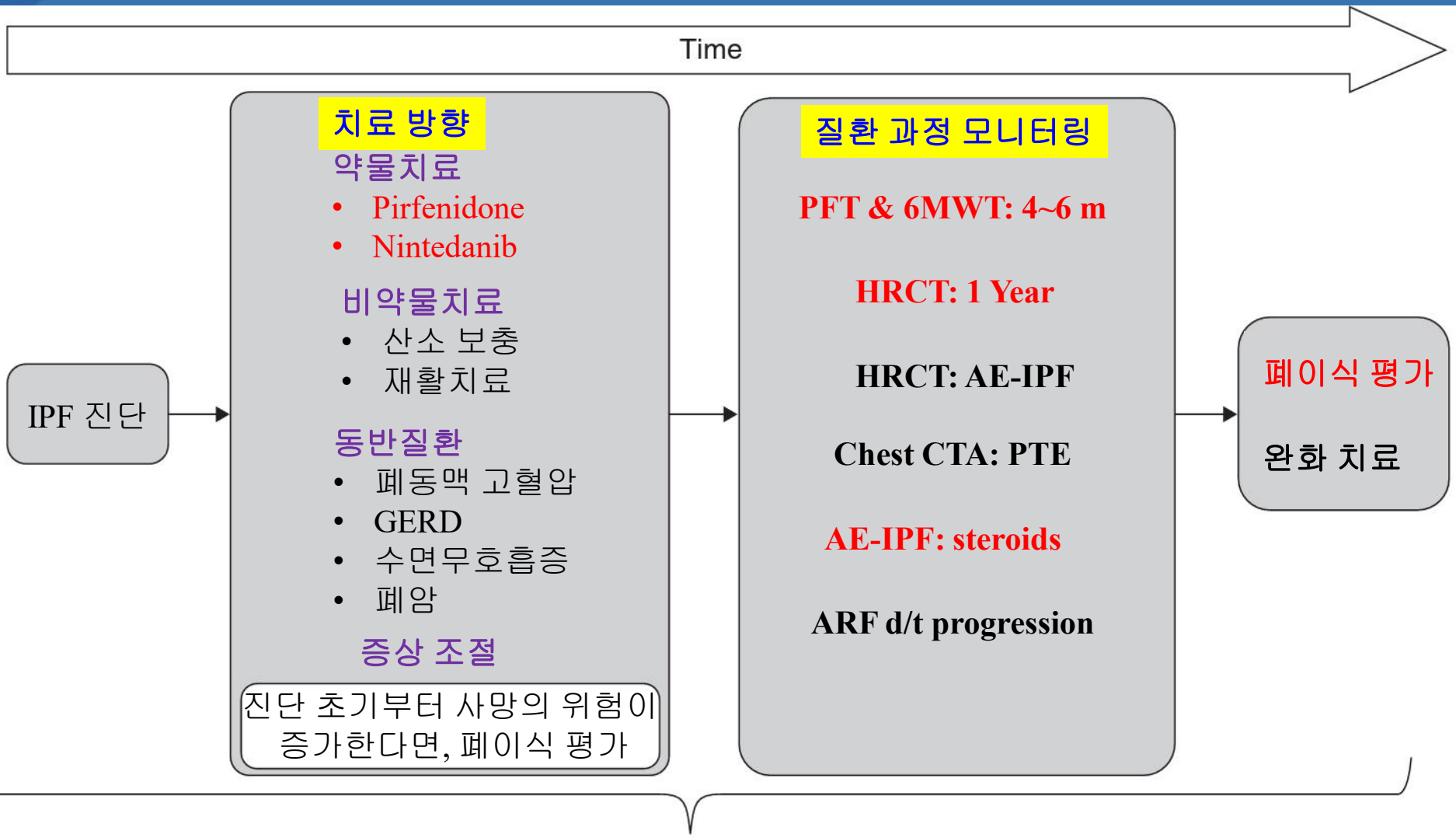
Lancet. 2017 Mar 29. pii: S0140-6736(17)30866-8.

There is no study to evaluate the superiority between pirfenidone and nintedanib.

Table 3. Pharmacologic Management of IPF.*

Variable	Nintedanib	Pirfenidone
Mechanism of action	Tyrosine kinase inhibition	Inhibition of TGF-β production and downstream signaling, collagen synthesis, and fibroblast proliferation (selected list)
Efficacy	Slows FVC decline by 50%	Slows FVC decline by 50%
FDA-approved dose	150 mg by mouth twice daily	801 mg by mouth thrice daily
Common side effects	Diarrhea	Anorexia, nausea, photosensitivity
Enzyme metabolism	Ester cleavage (major), CYP 3A4 (minor)	CYP 1A2 (major), other CYP enzymes (minor)
Cautions	Risks of both bleeding and arterial thrombosis; risk of gastrointestinal perforation (rare); anticoagulant and prothrombotic drugs should be avoided	CYP 1A2 inhibitors (e.g., fluvoxamine and ciprofloxacin) can raise pirfenidone levels; CYP 1A2 inducers (e.g., omeprazole and smoking) can lower pirfenidone levels
Need for liver-function monitoring	Yes†	Yes‡
Clinical strategies to minimize side effects	Use of antidiarrheal agents, temporary dose reduction to 100 mg twice daily	Slow dose increase over 14-day period, medication to be taken with food, use of antacids, use of antiemetic agents, sun avoidance

N Engl J Med 2014;370:2071-82.

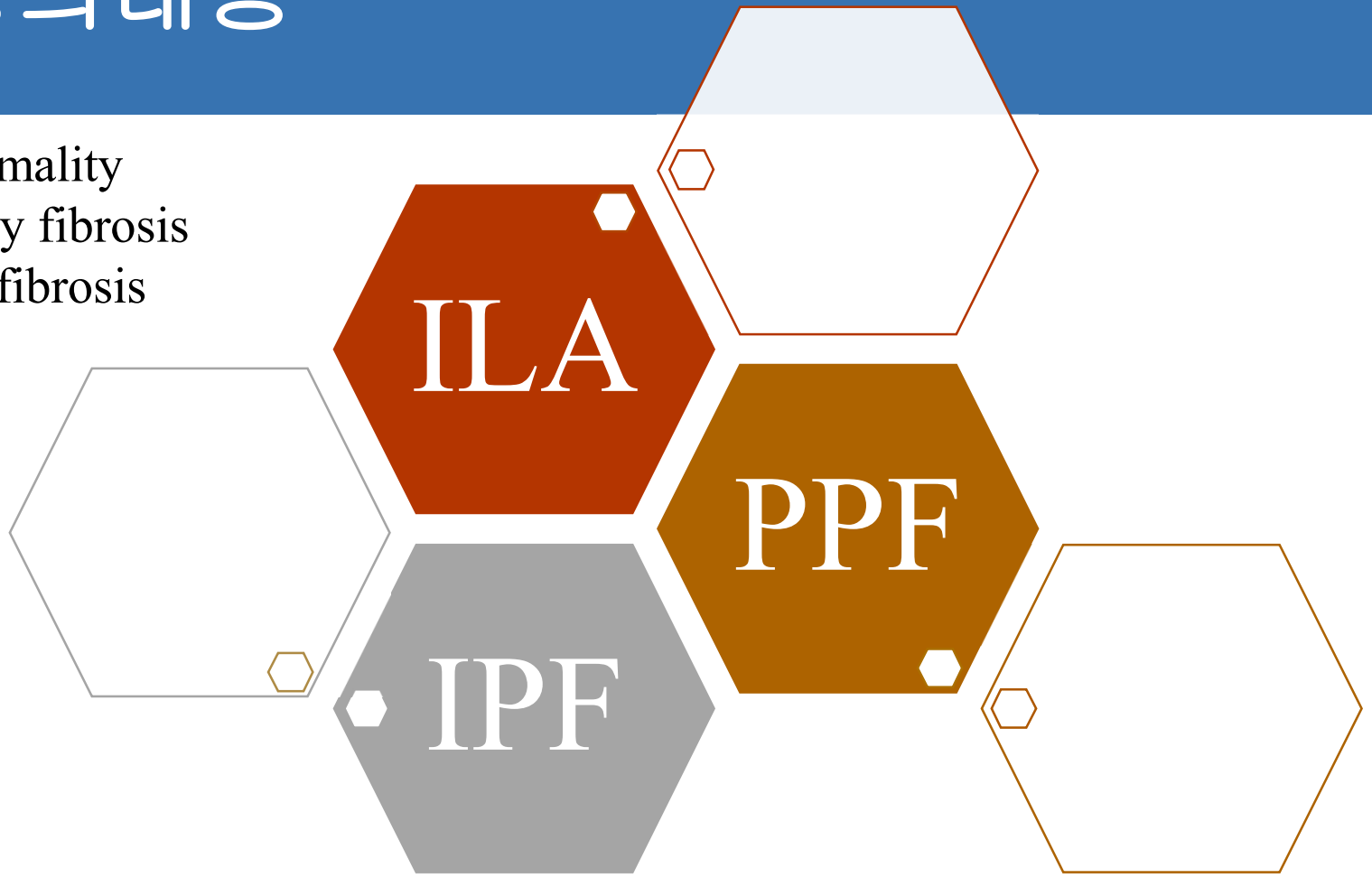


가능한 임상시험이 있다면 참가

Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

강의내용

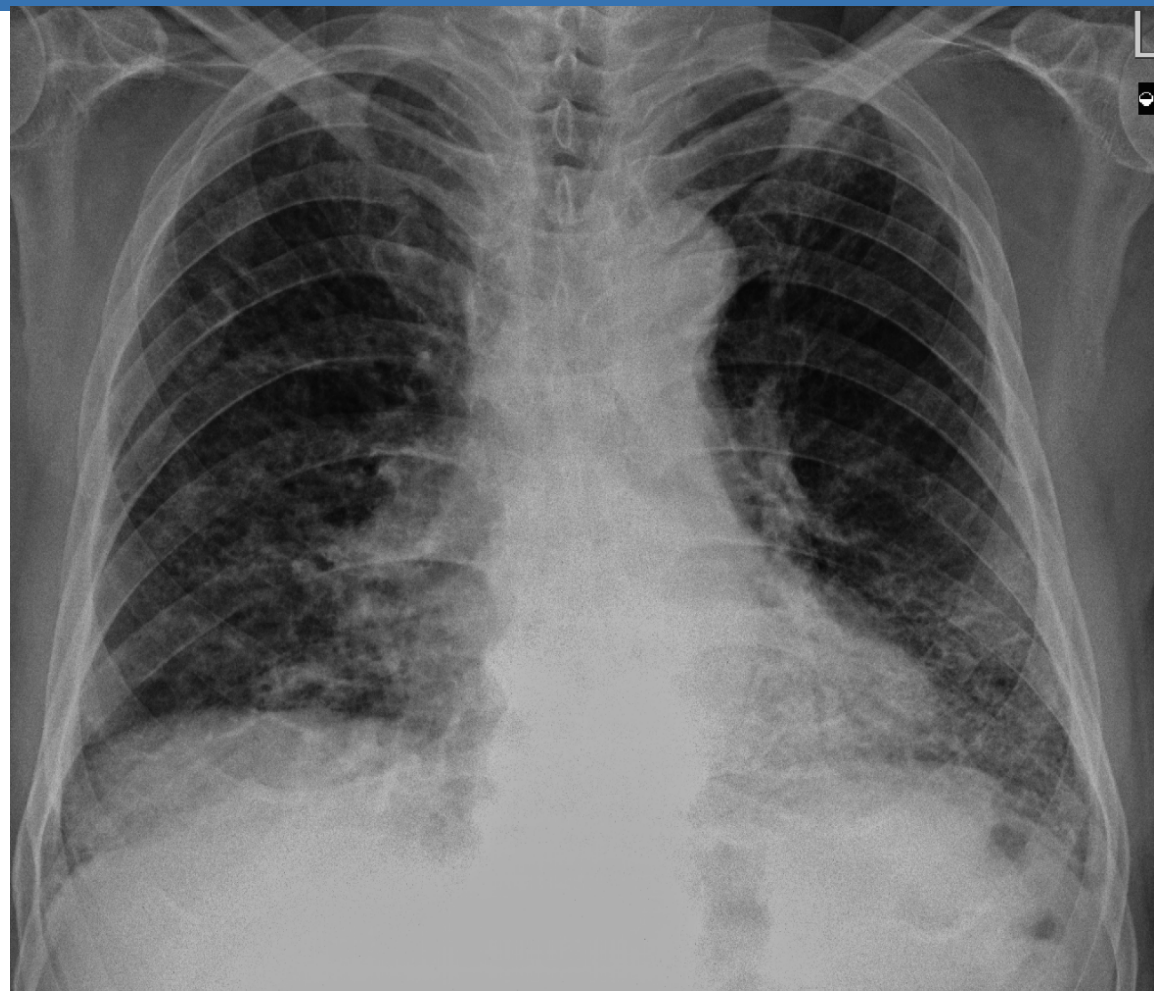
ILA: interstitial lung abnormality
PPF: progressive pulmonary fibrosis
IPF: idiopathic pulmonary fibrosis



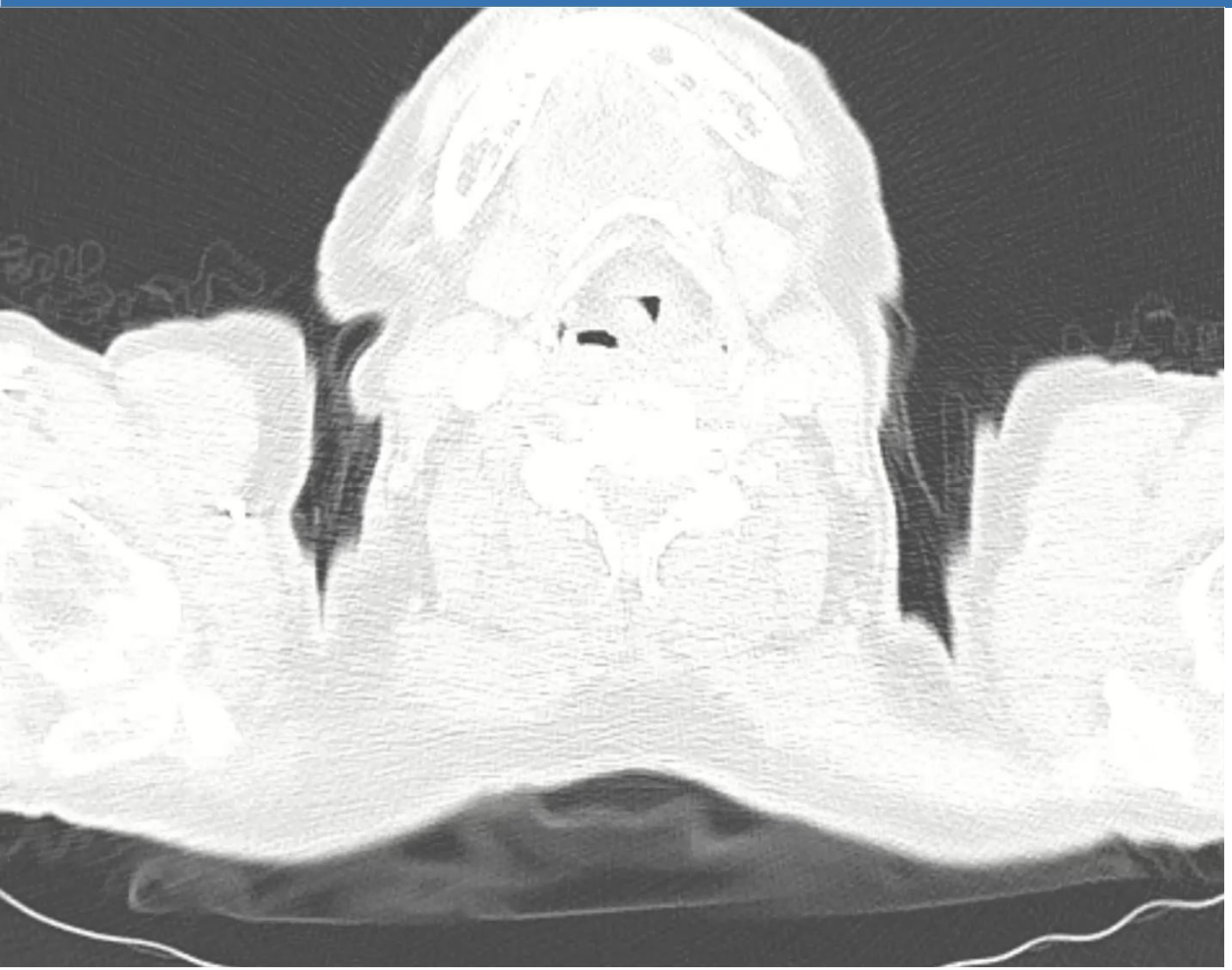
CASE 4. 85/M

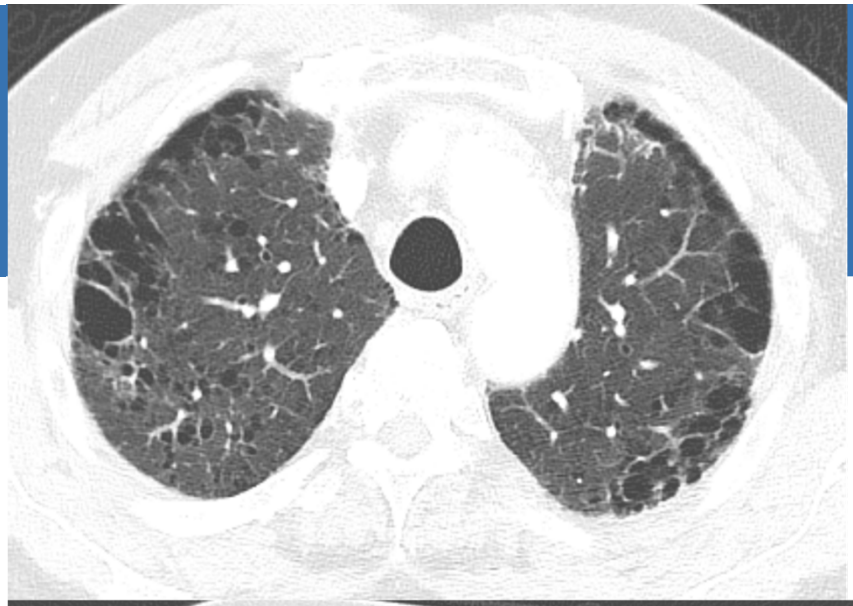
- C/C 호흡곤란으로 타원들러 시행한 CXR상 ILD 의심되어 내원함
- No underlying disease
- Ex, 15년전 quit, 100 PYs
- 공무원(사무직)

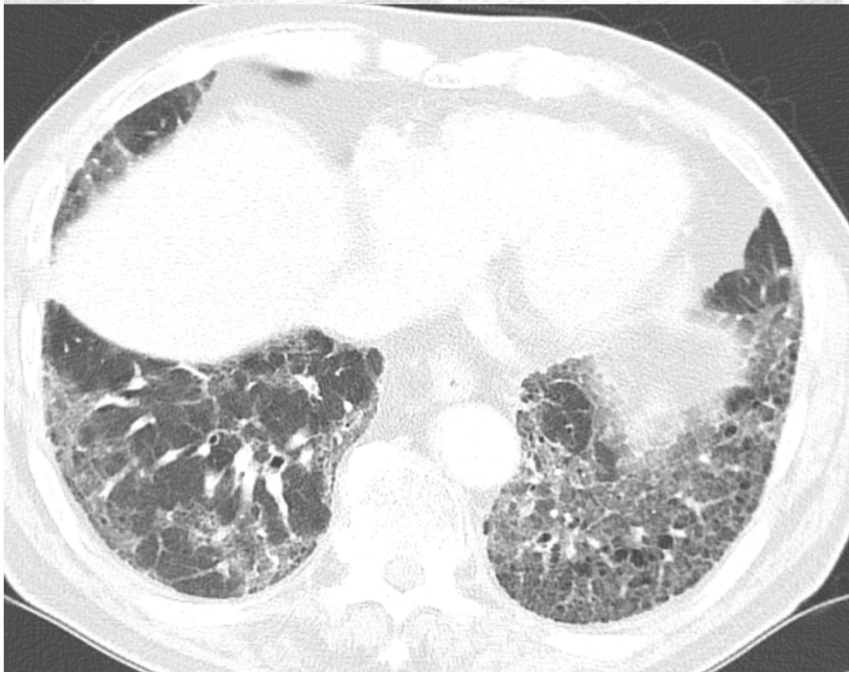
- C/S +/- mMRC 2-3



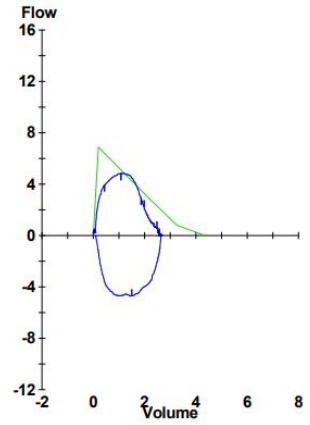
본원 HRCT



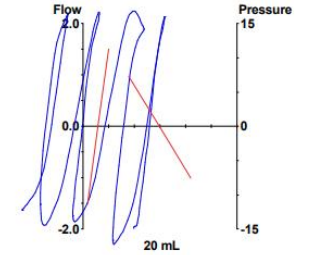


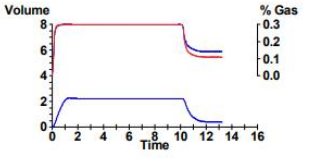


Plethysmography Report



Age: 84 Height(cm): 168 Weight(kg): 85.0 Gender: Male Race: Asian
Room: PD Medication:
Dyspnea Rest: No Dyspnea Exercise: No
Cough: No Persistent: No Productive (cc):
Smoker: No How Long(pk/yrs): Stopped(yrs): Cigarettes: No
Technician: kyoung min jeong Temp: 24 PBar: 754





Spirometry

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	4.37	2.65	61			
FEV1	Liters	2.53	2.51	100			
FEV1/FVC	%	66	95				
FEF25-75%	L/sec	1.84	4.05	220			
PEF	L/sec	6.85	4.87	71			
FET100%	Sec		5.89				
FIVC	Liters	3.44	2.53	74			
FIF50%	L/sec		4.70				
FVL ECode			000001				
MVV	L/min	97	95	98			

Lung Volumes

TLC	Liters	6.35	4.69	74
VC	Liters	3.44	2.65	77
RV	Liters	2.82	2.04	72
FRC PL	Liters	3.61	2.56	71
ERV	Liters	1.20		
IC	Liters	2.40	2.13	89
RV/TLC	%	46	44	
Raw	cmH2O/L/sec	1.56	1.41	90
Vtg	Liters		3.33	
sGaw	L/s/cmH2O/L	0.212	0.213	100

Diffusion

Hb:

DLCO	mL/min/mmHg	17.6	9.7	55
DL Adj	mL/min/mmHg	17.6	9.7	55
VA	Liters		4.38	
DLCO/VA	mL/min/mHg/L	3.27	2.22	68
DL/VA Adj	mL/min/mHg/L		2.22	
IVC	Liters		2.34	

- Pre FVC 2.65 L (61%)
- Pre FEV1 2.51 L (100%)
- FEV1/FVC 95%
- DLco 55%

Restrictive pattern

***Autoimmune marker (Screening)**

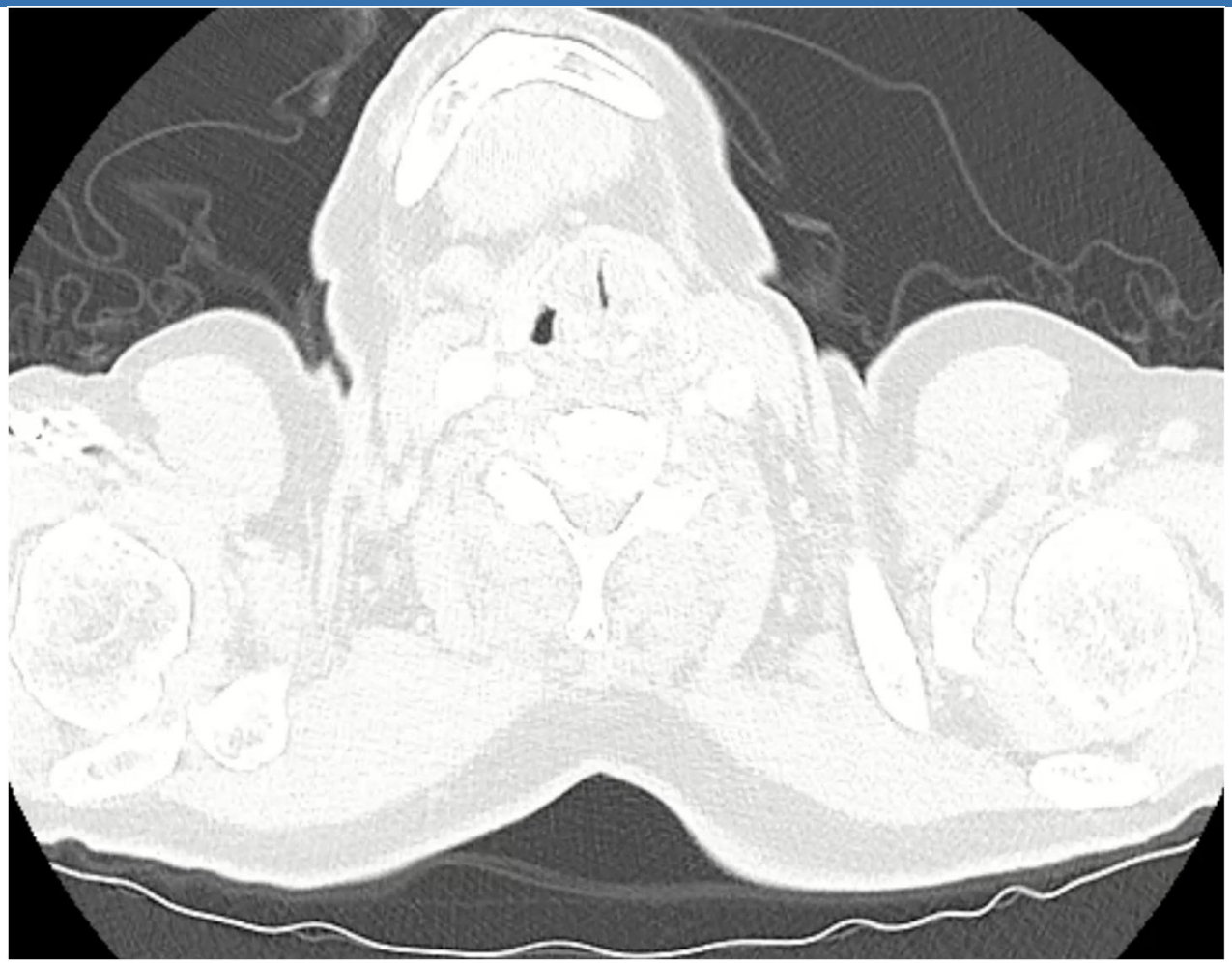
Anti-CCP	<0.5
ANA titer	Negative
ANCA	p-ANCA 1+
Rheumatoid factor titration	10.3
KL-6	1934.2

진단

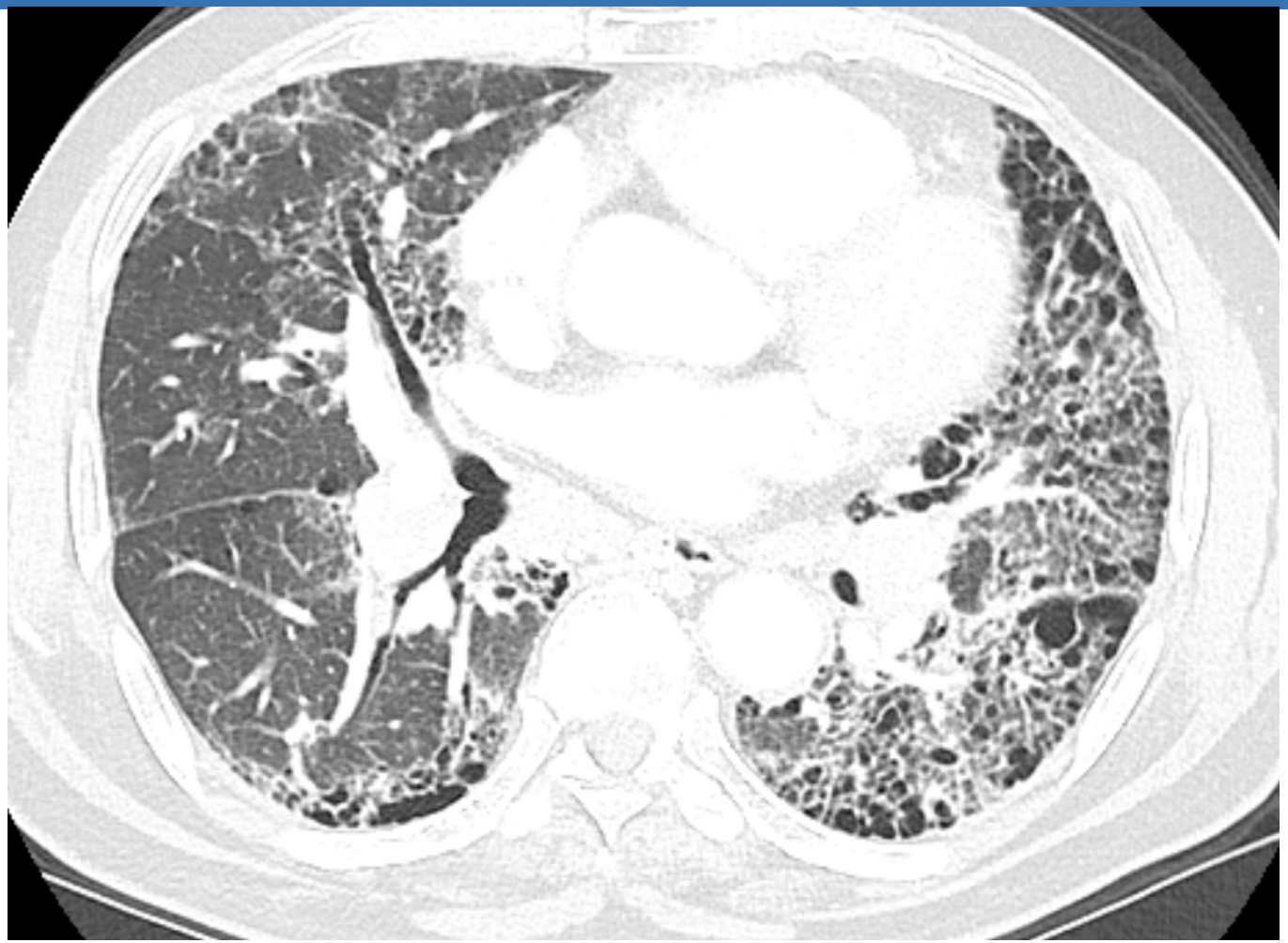
- Idiopathic interstitial pneumonia
- Indeterminate for UIP
- Emphysema
- Combined pulmonary fibrosis and emphysema (CPFE)

- VATS biopsy recommend - refuse

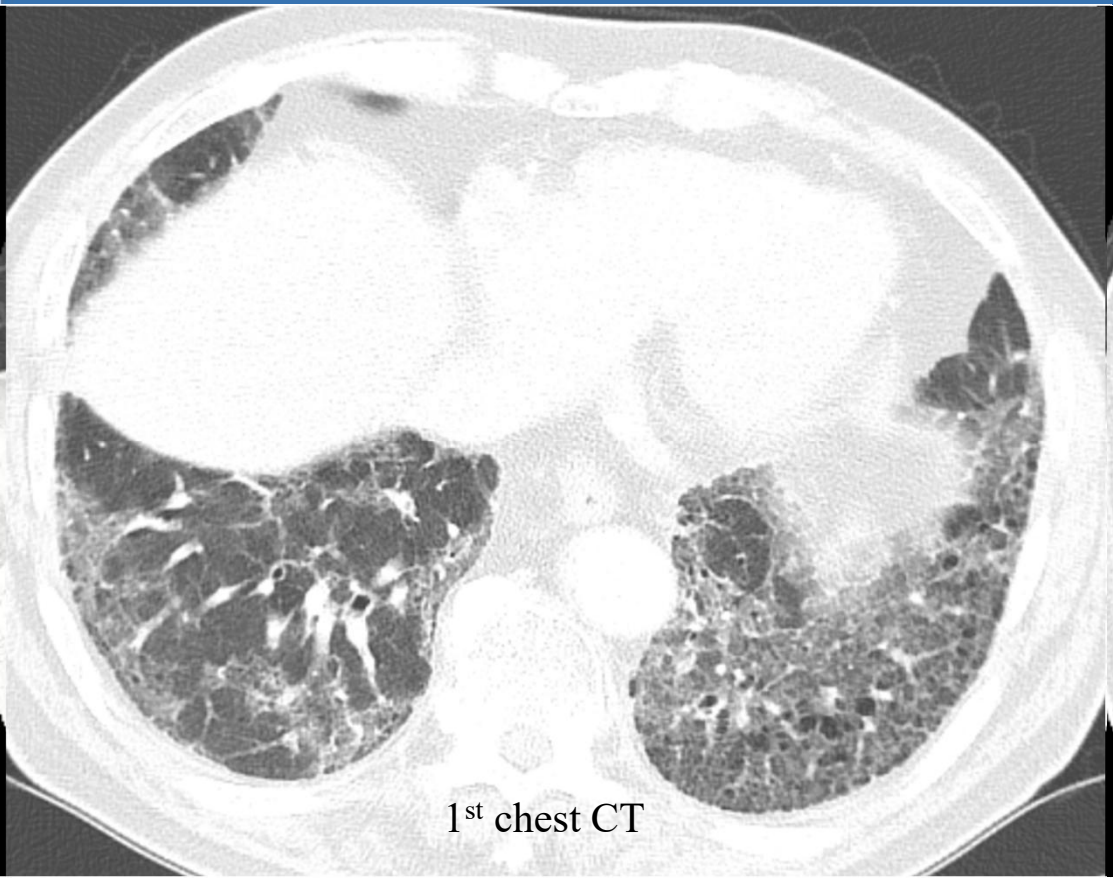
6개월 뒤 HRCT



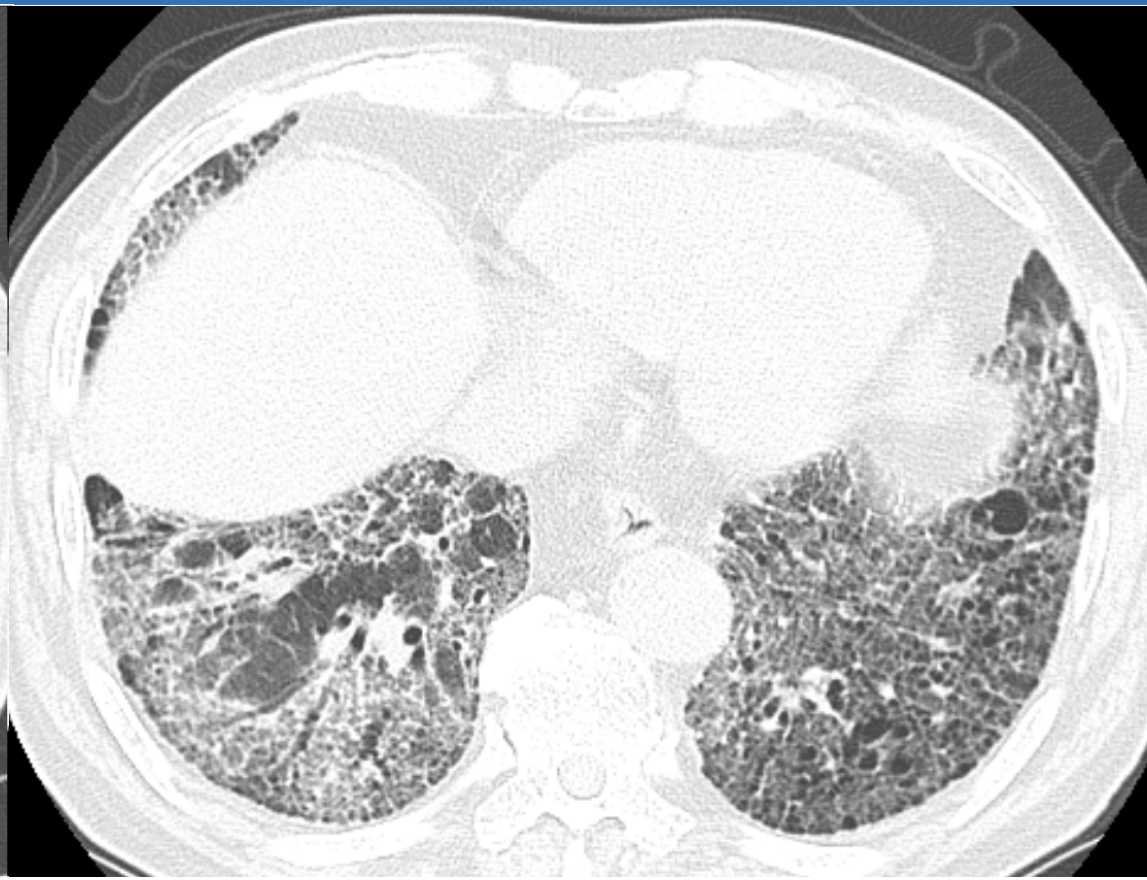
Acute exacerbation of IPF



AE-IPF 치료 후 6개월 뒤 HRCT



1st chest CT



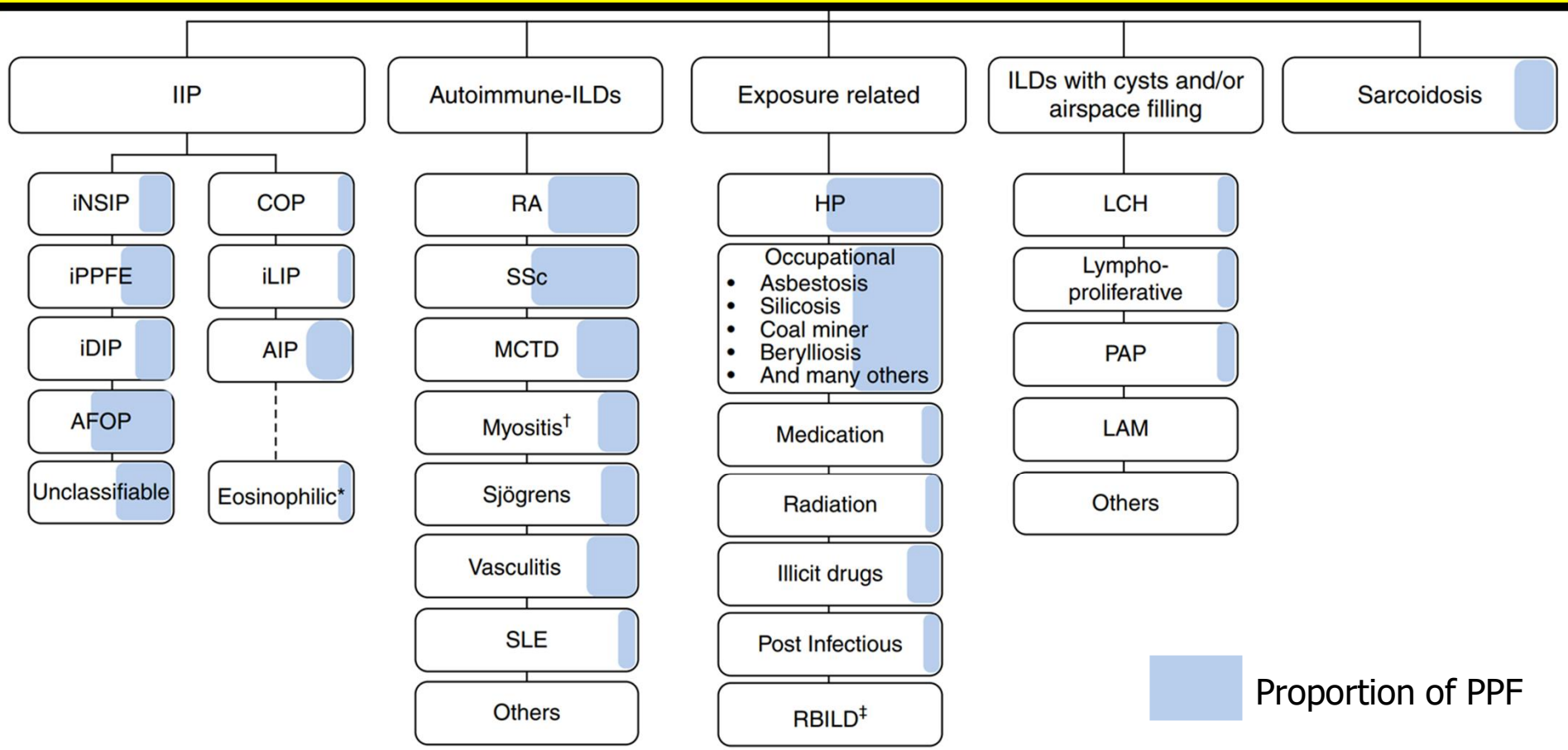
임상진단

- Progressive fibrosing ILD (PF-ILD)
- Progressive pulmonary fibrosis (PPF)
- Idiopathic interstitial pneumonia

- Pirfenidone (임의비급여) 시작

- 치료받지 않은 IPF의 자연경과는 확실한 진단을 받은 경우, 거의 모든 환자가 progression
- IPF 이외의 폐섬유증 환자의 **절반 이상이 stable 하거나, immunomodulatory Tx에 호전**

- **일부 환자들은 적절한 치료에 불구하고 폐 섬유증이 진행하여, 호흡기 증상 악화, 폐기능 저하, 삶의 질 저하, 조기 사망위험 발생**



Ganesh Raghu, Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

Definition of PF-ILD

- Progressive fibrosing interstitial lung diseases (PF-ILDs) are a diverse group of ILDs that share a similar disease behavior, are characterized by a progressive disease course, and overlapping genetic, pathophysiological, and clinical features.

- Features of PF-ILD include progressive fibrosis on HRCT scan, lung function decline resulting in respiratory failure, progressive symptom worsening, and early mortality.

Ganesh Raghu, Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

France cohort
2010.1.1 – 2017.12.31

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

CrossMark

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

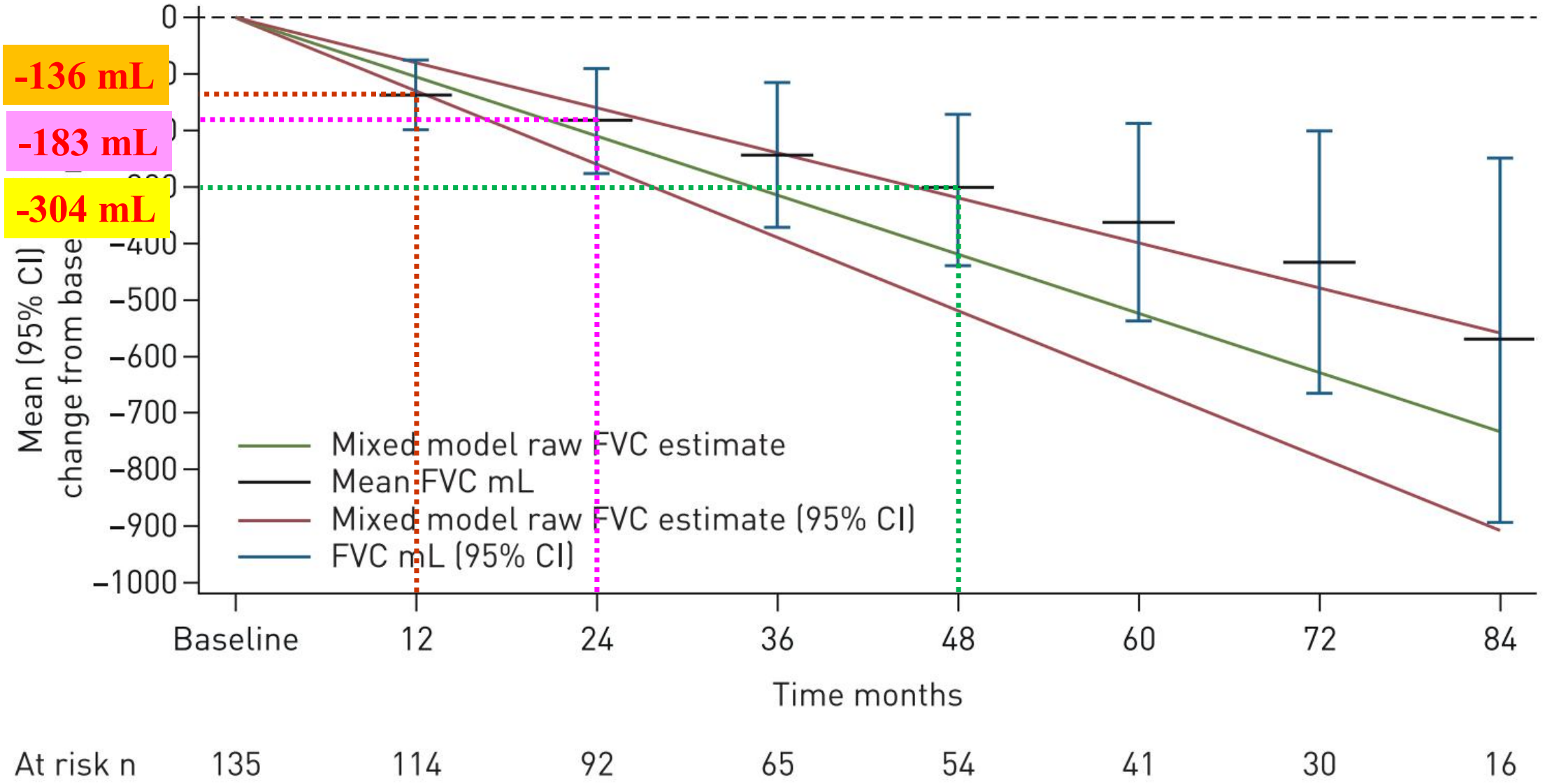
Retrospective, observational study
165명의 IPF가 아닌 ILD 환자 중 PF-ILD

- 스크리닝 24개월 이내에 다음 3가지 중 1가지 이상 만족

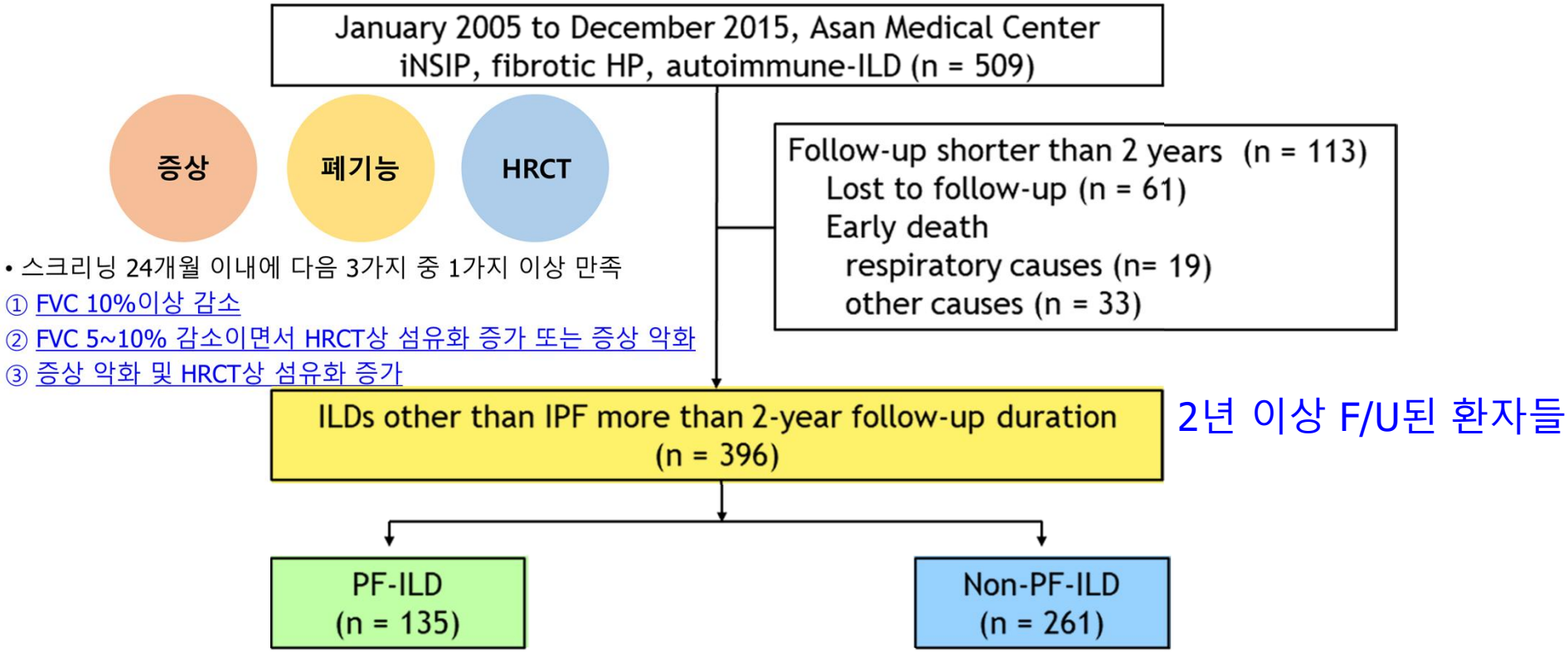
① FVC 10%이상 감소
② FVC 5~10% 감소이면서 HRCT상 섬유화 증가 또는 증상 악화
③ 증상 악화 및 HRCT상 섬유화 증가

Mouhamad Nasser, Eur Respir J . 2021 Feb 11;57(2):2002718

The linear mixed model



아산병원 코호트 (2005-2015)

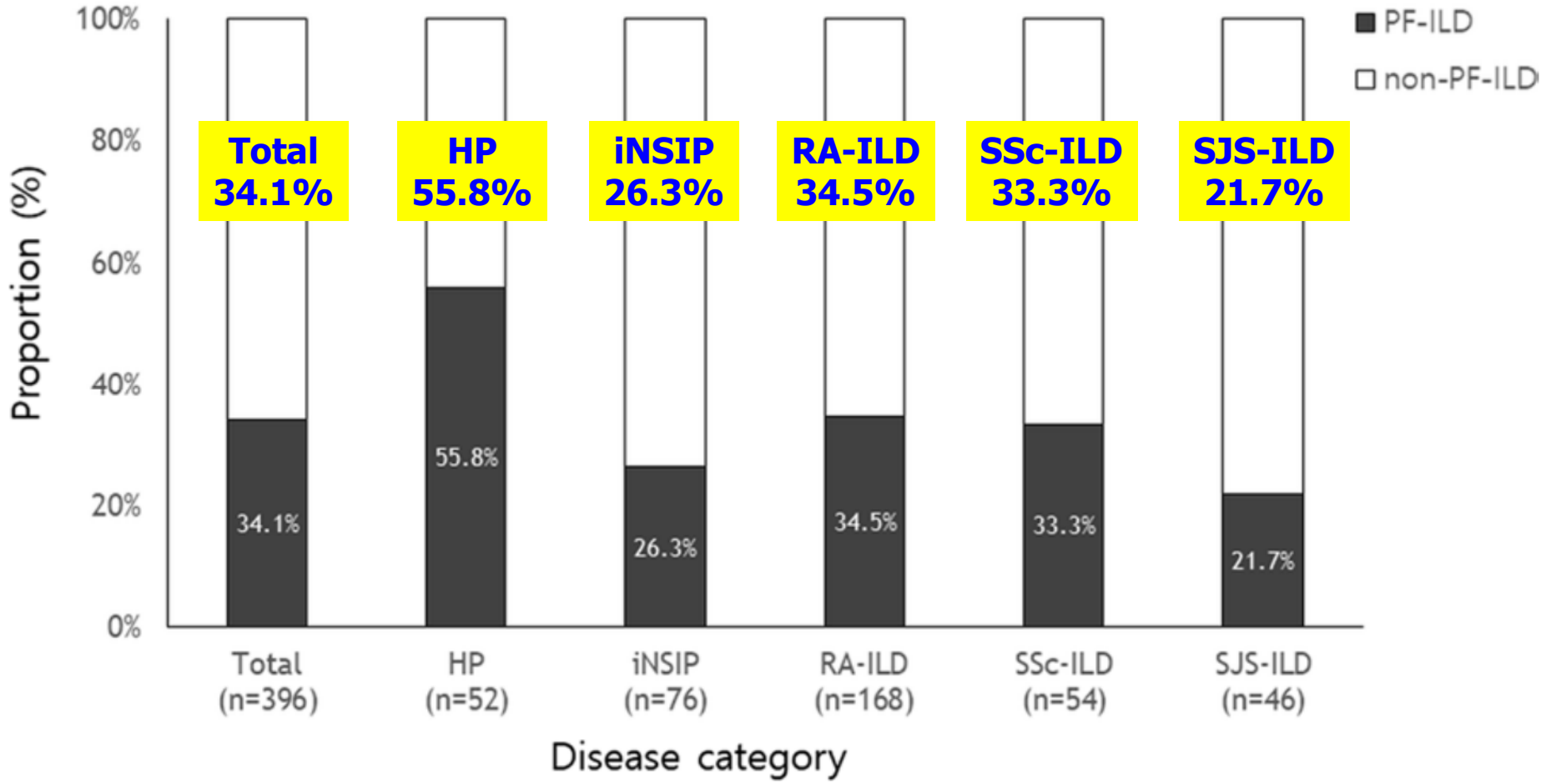


2년 이상 F/U된 환자들

A progressive phenotype was identified in about **34% of patients with non-IPF fibrosing ILD**

Kwon et al. Respir Res (2021) 22:282

아산병원 코호트 (2005-2015)



아산병원 코호트 (2005-2015)

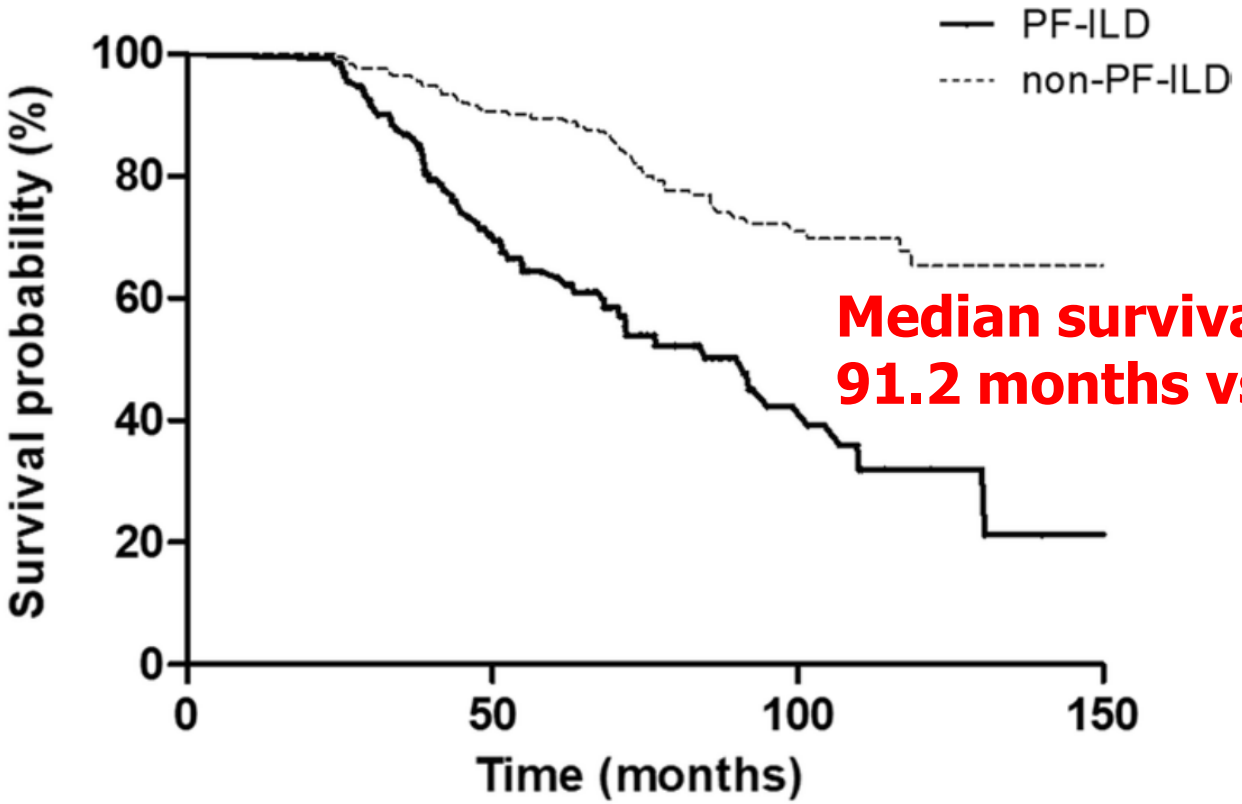
- **Complications: PF-ILD vs. non-PF-ILD groups**

	Total	PF-ILD	Non-PF-ILD	*P*-value
Number of patients	396	135	261	
Follow-up duration, months	68.9 ± 32.5	59.9 ± 28.4	73.5 ± 33.5	< 0.001
Unexpected respiratory hospitalisation	120 (30.3)	62 (45.9)	58 (22.2)	< 0.001
Acute exacerbation[a]	74 (18.7)	38 (28.1)	36 (13.8)	0.001
Time interval from diagnosis (months)	34.6 ± 28.2	29.3 ± 20.5	40.2 ± 33.9	0.037
Pneumonia	35 (8.8)	16 (11.9)	19 (7.3)	0.138
Pneumothorax	7 (1.8)	5 (3.7)	2 (0.8)	0.048
Pulmonary hypertension	89 (22.5)	45 (33.3)	44 (16.9)	< 0.001
Lung cancer	28 (7.1)	14 (10.4)	14 (5.4)	0.065

Hospitalization, AE, pneumothorax, pul HTN

아산병원 코호트 (2005-2015)

- **Survival curves: PF-ILD VS. non-PF-ILD**

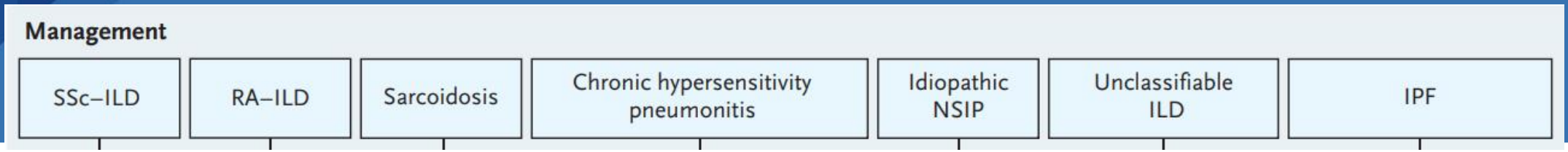


Median survival
91.2 months vs. not reached; P <0.001

아산병원 코호트 (2005-2015)

- **Prognostic factors for mortality**

Variables	Odds ratio (95% CI)	P-value
Age	1.075 (1.050-1.100)	<0.001
DLco	0.982 (0.971-0.993)	0.001
UIP-like pattern	1.458 (0.960-2.212)	0.077
PF-ILD	3.053 (2.066-4.512)	<0.001



- **치료 목표**
- 삶의 질 개선 또는 유지
- 질병의 개선 또는 진행을 지연

- 환자 교육 및 결정 공유 (Off-label treatment option)
- 항원 노출 제거
- 금연
- 폐렴구균 및 인플루엔자 예방접종
- 산소공급 (PaO2 <55mmHg, SaO2 <89%, or PaO2 <60mmHg + cor pulmonale or polycythemia)
- 호흡재활
- 폐이식

- **약물적 치료 ??? (항섬유제제)**

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

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY, EUROPEAN RESPIRATORY SOCIETY, JAPANESE RESPIRATORY SOCIETY, AND ASOCIACIÓN LATINOAMERICANA DE TÓRAX FEBRUARY 2022

Ganesh Raghu, Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.

PF-ILD ➔ PPF (Progressive Pulmonary Fibrosis)

Definition of PPF

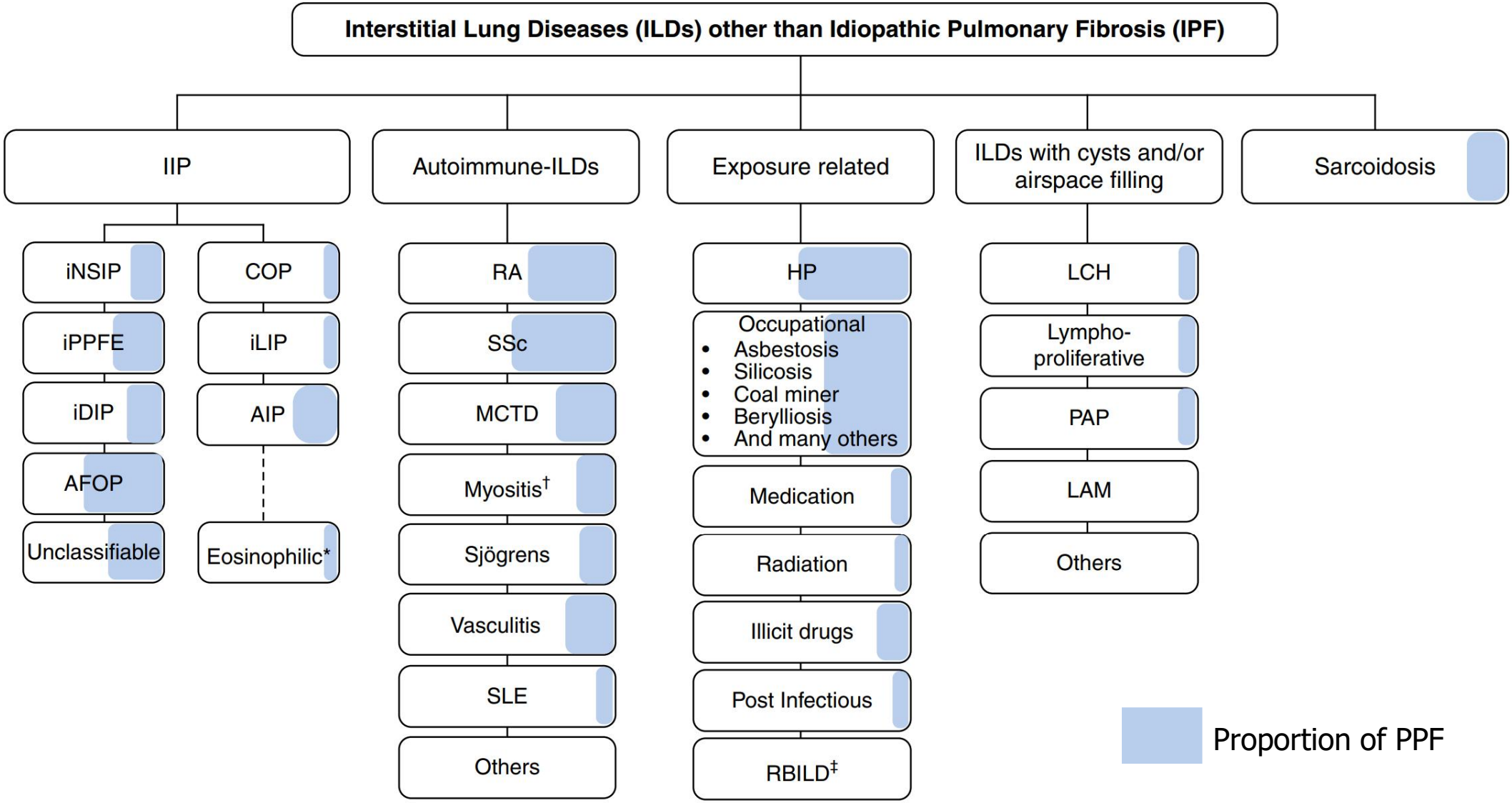
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:

1 Worsening respiratory symptoms

2 Physiological evidence of disease progression (either of the following):
- a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up
- b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up

3 Radiological evidence of disease progression (one or more of the following):
- a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
- b. New ground-glass opacity with traction bronchiectasis
- c. New fine reticulation
- d. Increased extent or increased coarseness of reticular abnormality
- e. New or increased honeycombing
- f. Increased lobar volume loss

Ganesh Raghu, Am J Respir Crit Care Med . 2022 May 1;205(9):e18-e47.


Interstitial Lung Diseases (ILDs) other than Idiopathic Pulmonary Fibrosis (IPF)
IIP
Autoimmune-ILDs
Exposure related
ILDs with cysts and/or airspace filling
Sarcoidosis
iNSIP
iPPFE
iDIP
AFOP
Unclassifiable
COP
iLIP
AIP
Eosinophilic*
RA
SSc
MCTD
Myositis†
Sjögrens
Vasculitis
SLE
Others
HP
Occupational
Asbestosis
Silicosis
Coal miner
Berylliosis
And many others
Medication
Radiation
Illicit drugs
Post Infectious
RBILD‡
LCH
Lympho-proliferative
PAP
LAM
Others
Proportion of PPF

Question: PPF (PF-ILD) 환자에서 Pirfenidone을 사용할 것인가?

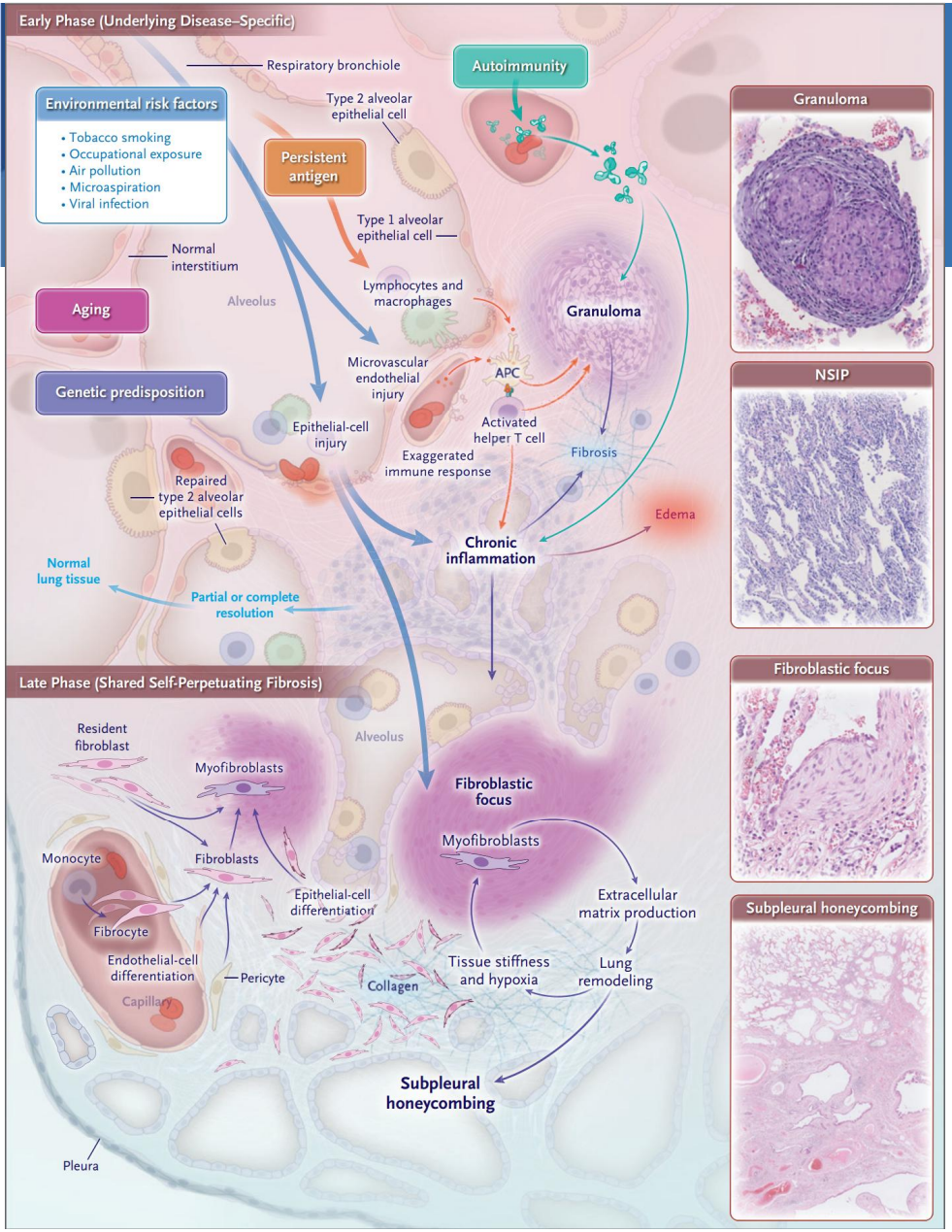
	Pirfenidone
Disease progression	**24주에 걸쳐 placebo 대비 FVC감소를 100mL↓** **uILD 환자에서 progression↓ [FVC>5%: 1.6배↓, FVC>10%: 1.9배↓]**
Mortality	uILD, RELIFE ➔ 통계적으로 유의하지 않음.
Lung function	**DLco 감소를 ↓[RELIFE, uILD]**
Respiratory symptoms	통계적으로 유의하지 않음.
AE	GI Sx x 8배 ↑ Photosensitivity x 4.9배 ↑

- We recommend further research into the efficacy, effectiveness, and safety of pirfenidone in both 1) non-IPF ILD manifesting PPF in general and 2) specific types of non-IPF ILD manifesting PPF.

Question: PPF (PF-ILD) 환자에서 Nintedanib을 사용할 것인가?

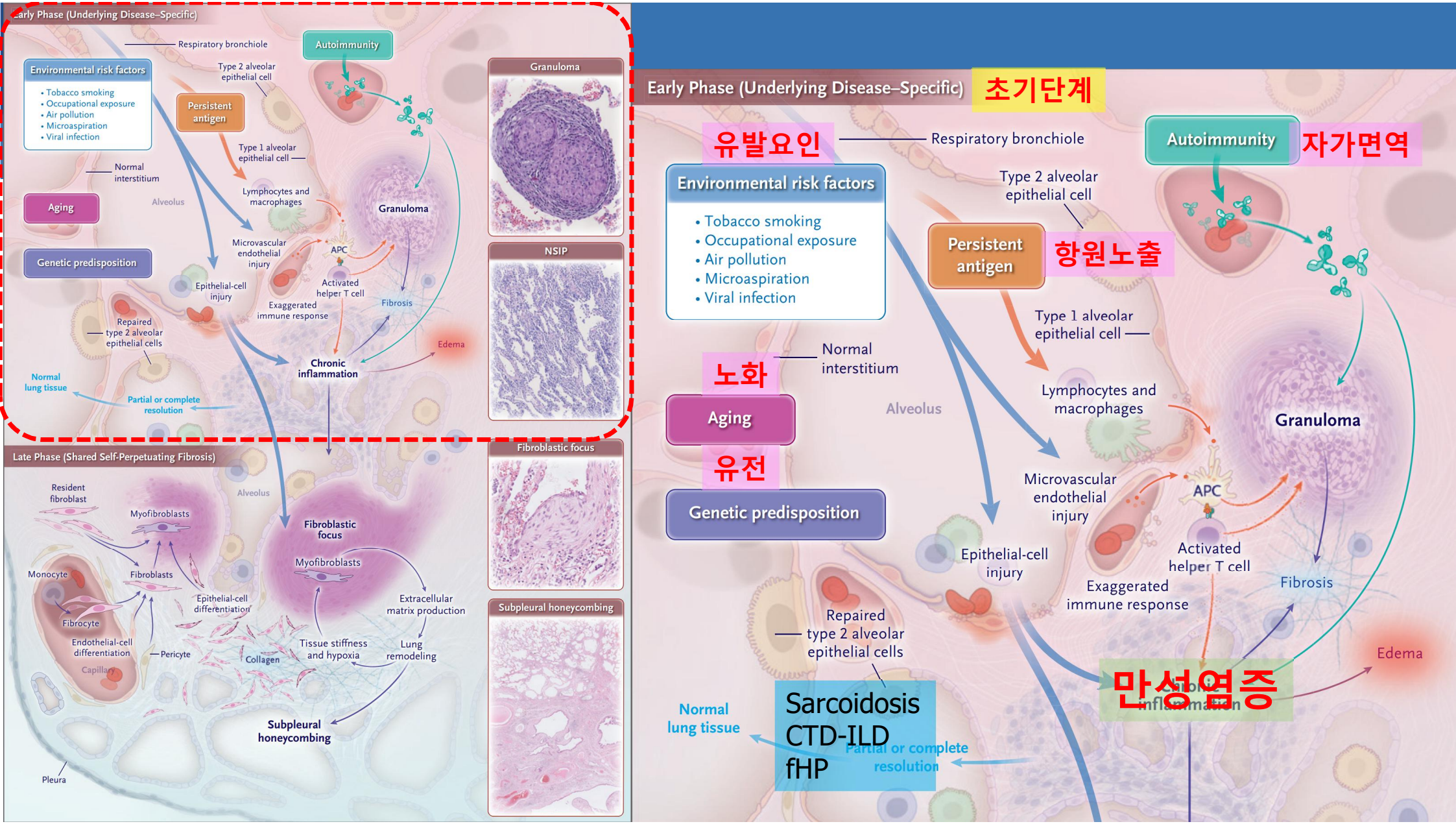
	Nintedanib
Disease progression	**52주에 걸쳐 placebo 대비 FVC감소를 107mL↓** **Disease progression x 2.4배↓**
Mortality	통계적으로 유의하지 않음.
AE	Abdominal pain (x4.2), nausea (x3.1), vomiting (x3.6), diarrhea (x2.8), anorexia (x2.8), weight loss (x3.7)

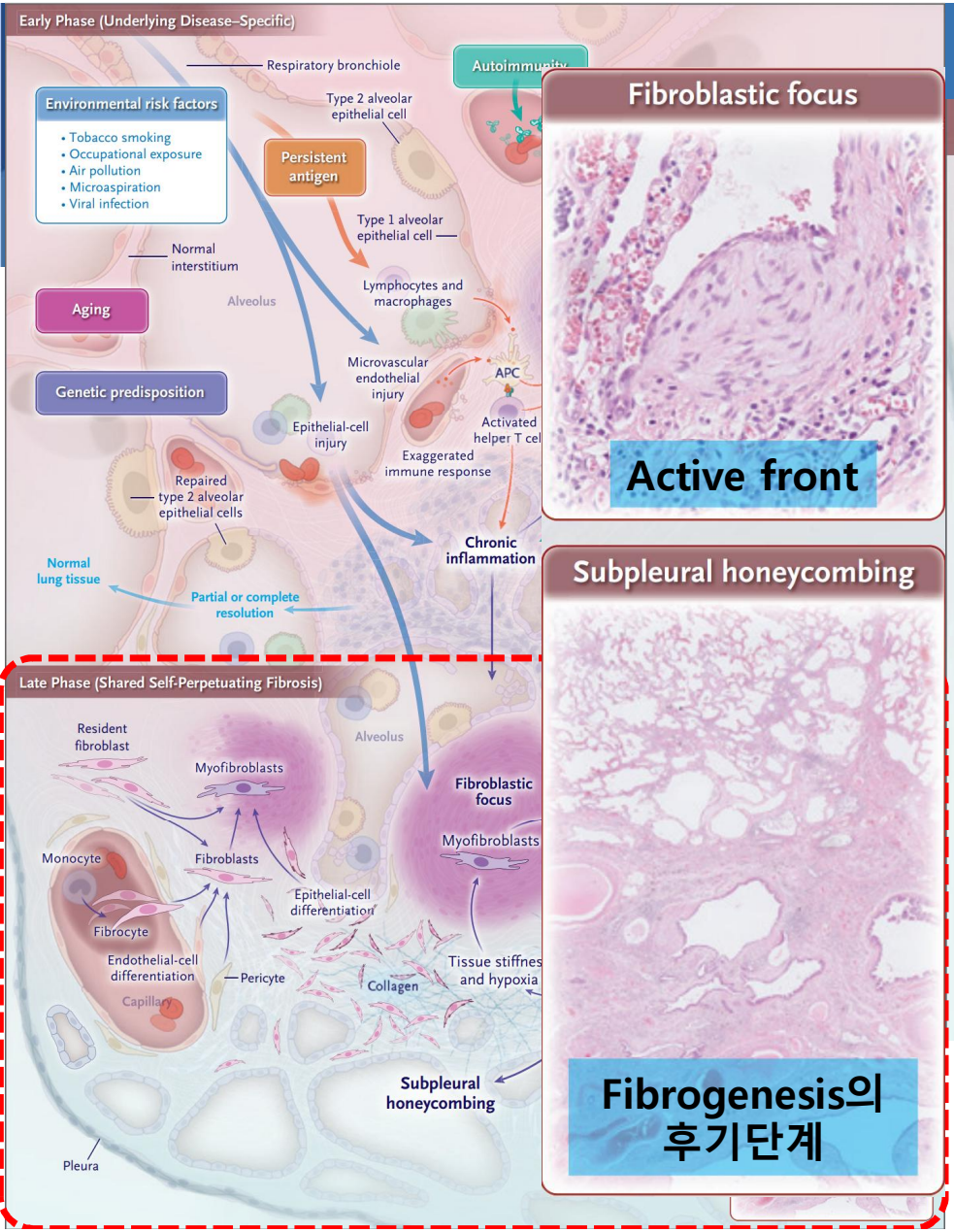
- We suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF (**conditional recommendation, low-quality evidence**).
- We recommend research into the efficacy, effectiveness, and safety of nintedanib in specific types of non-IPF ILD manifesting PPF.

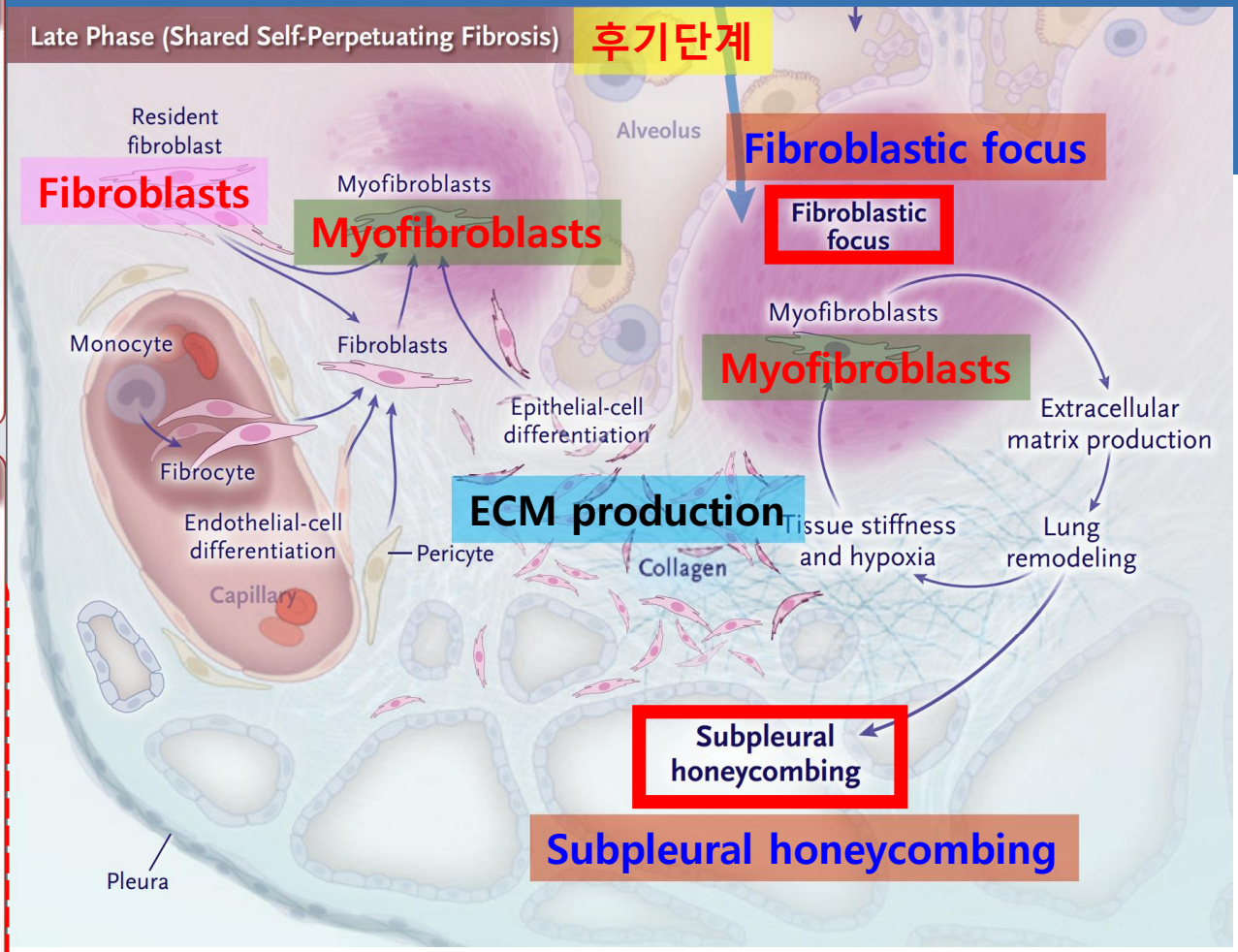


Pathogenesis and Self-Perpetuation of Pulmonary Fibrosis

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


Early Phase (Underlying Disease–Specific)
초기단계
유발요인
Respiratory bronchiole
Environmental risk factors
• Tobacco smoking
• Occupational exposure
• Air pollution
• Microaspiration
• Viral infection
Autoimmunity
자가면역
Type 2 alveolar epithelial cell
Persistent antigen
항원노출
Type 1 alveolar epithelial cell
Normal interstitium
노화
Aging
Alveolus
Lymphocytes and macrophages
Granuloma
유전
Genetic predisposition
Microvascular endothelial injury
APC
Activated helper T cell
Epithelial-cell injury
Exaggerated immune response
Fibrosis
Repaired type 2 alveolar epithelial cells
Edema
Chronic inflammation
만성염증
Normal lung tissue
Partial or complete resolution
Sarcoidosis
CTD-ILD
fHP
Granuloma
NSIP
Late Phase (Shared Self-Perpetuating Fibrosis)
Fibroblastic focus
Subpleural honeycombing
Resident fibroblast
Myofibroblasts
Alveolus
Fibroblastic focus
Monocyte
Fibroblasts
Epithelial-cell differentiation
Extracellular matrix production
Fibrocyte
Endothelial-cell differentiation
Pericyte
Tissue stiffness and hypoxia
Lung remodeling
Capillary
Collagen
Subpleural honeycombing
Pleura

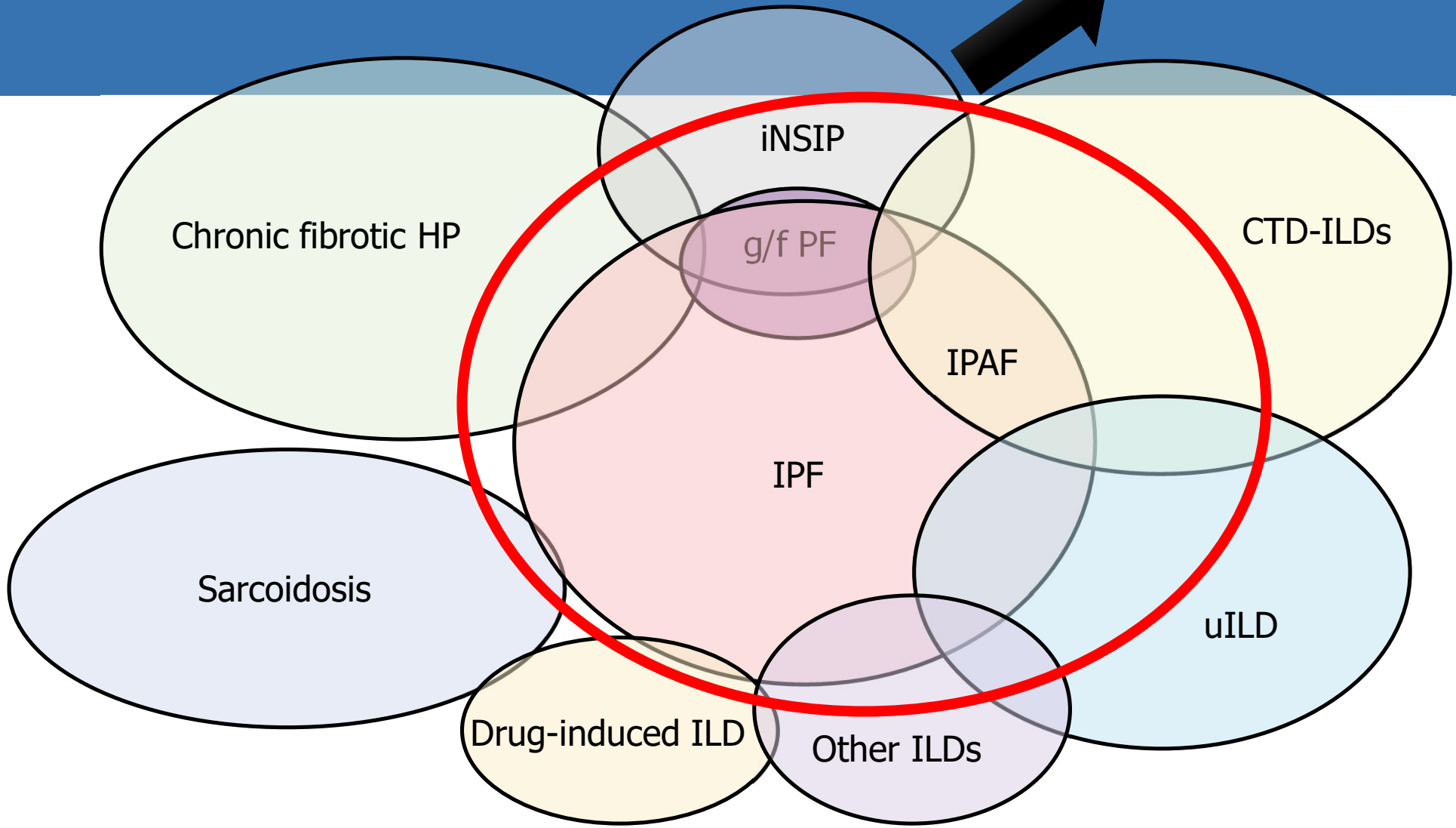




후기단계 = common mechanism (pathway)

IPF를 제외하고 만성적으로 섬유화가 진행되는 ILD

PF-ILDs



The NEW ENGLAND JOURNAL of MEDICINE

INBUILD trial

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

Kevin R Flaherty, N Engl J Med . 2019 Oct 31;381(18):1718-1727.

Non-IPF PF-ILD 기준

- 스크리닝 24개월 이내에 다음 3가지 중 1가지 이상 만족

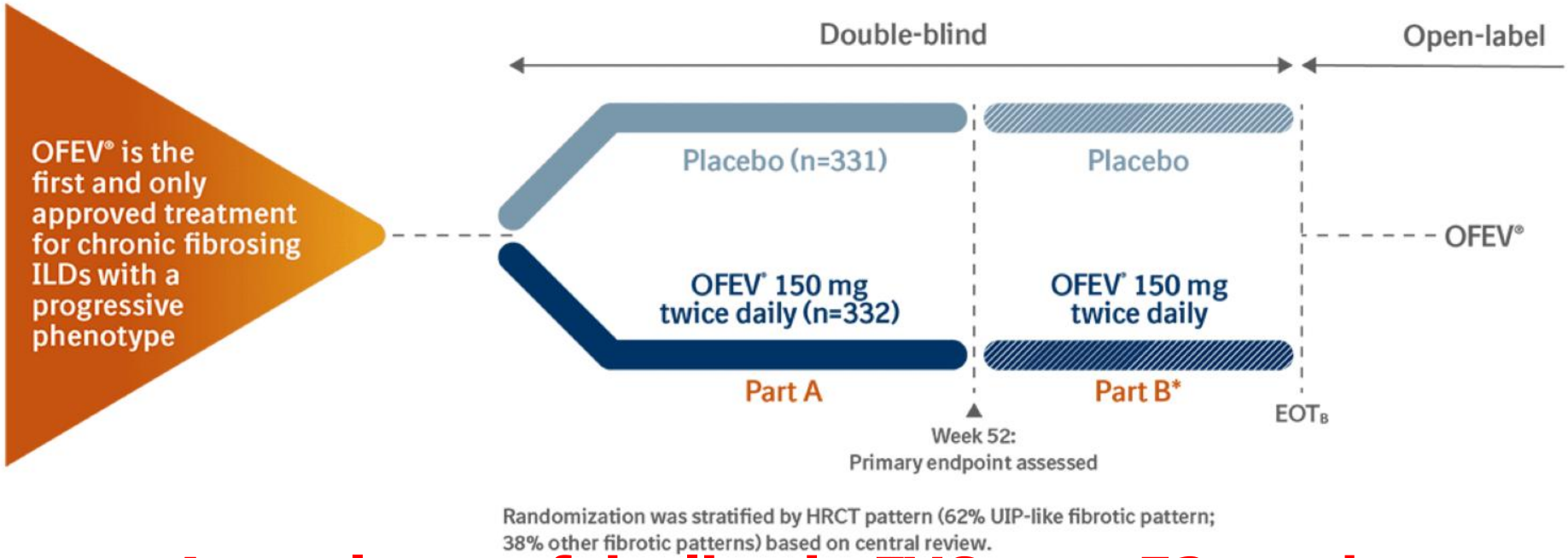
① **FVC 10%이상 감소**

② **FVC 5~10% 감소이면서 HRCT상 섬유화 증가 또는 증상 악화**

③ **증상 악화 및 HRCT상 섬유화 증가**

- FVC ≥45%, DLco 30~80%

INBUILD trial design

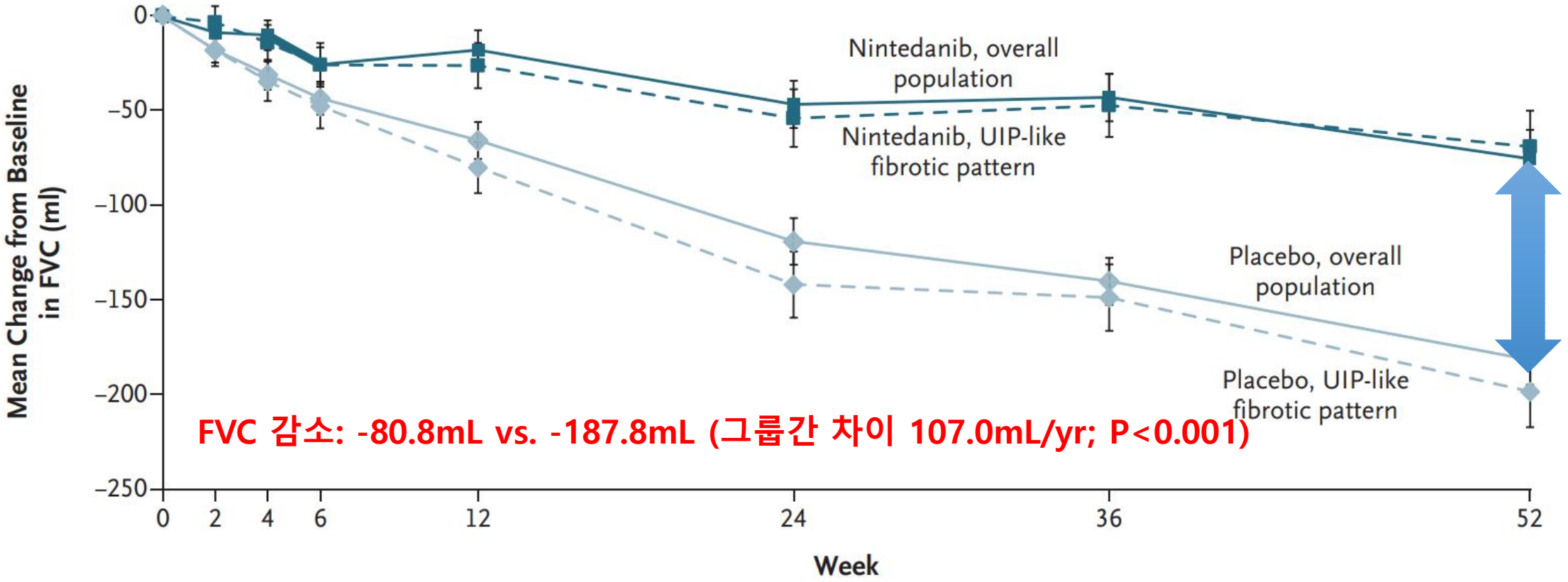


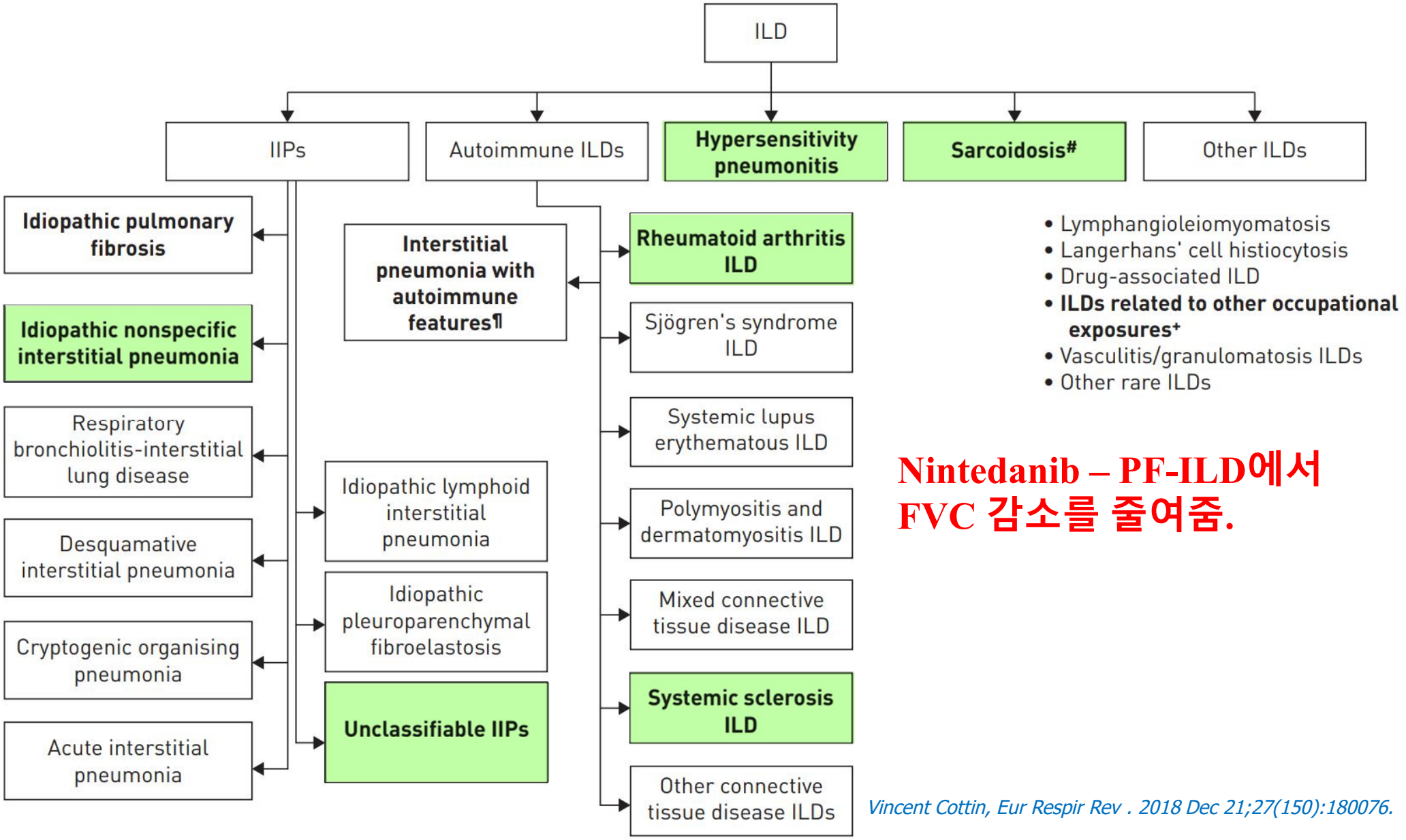
Randomization was stratified by HRCT pattern (62% UIP-like fibrotic pattern; 38% other fibrotic patterns) based on central review.

Annual rate of decline in FVC over 52 weeks

https://pro.boehringer-ingelheim.com/products/ofev/progressive-fibrosing-ild-overview/efficacy-trial-design

Decline from Baseline in FVC





Nintedanib – PF-ILD에서 FVC 감소를 줄여줌.

Vincent Cottin, Eur Respir Rev . 2018 Dec 21;27(150):180076.

Pirfenidone

Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial

Toby M Maher, Tamera J Corte, Aryeh Fischer, Michael Kreuter, David J Lederer, Maria Molina-Molina, Judit Axmann, Klaus-Uwe Kirchgaessler, Katerina Samara, Frank Gilberg, Vincent Cottin

Toby M Maher, Lancet Respir Med . 2020 Feb;8(2):147-157.

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

*Jürgen Behr, Antje Prasse, Michael Kreuter, Johannes Johow, Klaus F Rabe, Francesco Bonella, Reiner Bonnet, Christian Grohe, Matthias Held, Heinrike Wilkens, Peter Hammerl, Dirk Koschel, Stefan Blaas, Hubert Wirtz, Joachim H Ficker, Wolfgang Neumeister, Nicolas Schönfeld, Martin Claussen, Nikolaus Kneidinger, Marion Frankenberger, Simone Hummler, Nicolas Kahn, Silke Tello, Julia Freise, Tobias Welte, Petra Neuser, Andreas Günther, on behalf of the RELIEF investigators**

Jürgen Behr, Lancet Respir Med . 2021 May;9(5):476-486

Nintedanib (Ofev®) 허가 사항

- Treatment of idiopathic pulmonary fibrosis (IPF).
- Treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.
- Slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

오페브는?

• 오페브는 특발성 폐섬유증 치료, 전신경화증 연관 간질성폐질환 환자의 폐 기능 감소 지연 및 진행성 표현형을 나타내는 만성 섬유성 간질성폐질환의 치료를 위해 사용되는 처방의약품입니다.

- 오페브연질캡슐 100밀리그램
  주성분 : 닌테다닙에실산염 120.40mg (닌테다닙으로서 100mg)
  성상 : 밝은 황색의 점성 현탁액을 포함하고 있는 타원형의 불투명한 연한 분홍색 젤라틴 연질 캡슐.

- 오페브연질캡슐 150밀리그램
  주성분: 닌테다닙에실산염 180.60mg (닌테다닙으로서 150mg)
  성상 : 밝은 황색의 점성 현탁액을 포함하고 있는 타원형의 불투명한 갈색 젤라틴 연질 캡슐.

https://www.bikr.co.kr/sites/kr/files/files/pdf/ofev_patient_leaflet.pdf

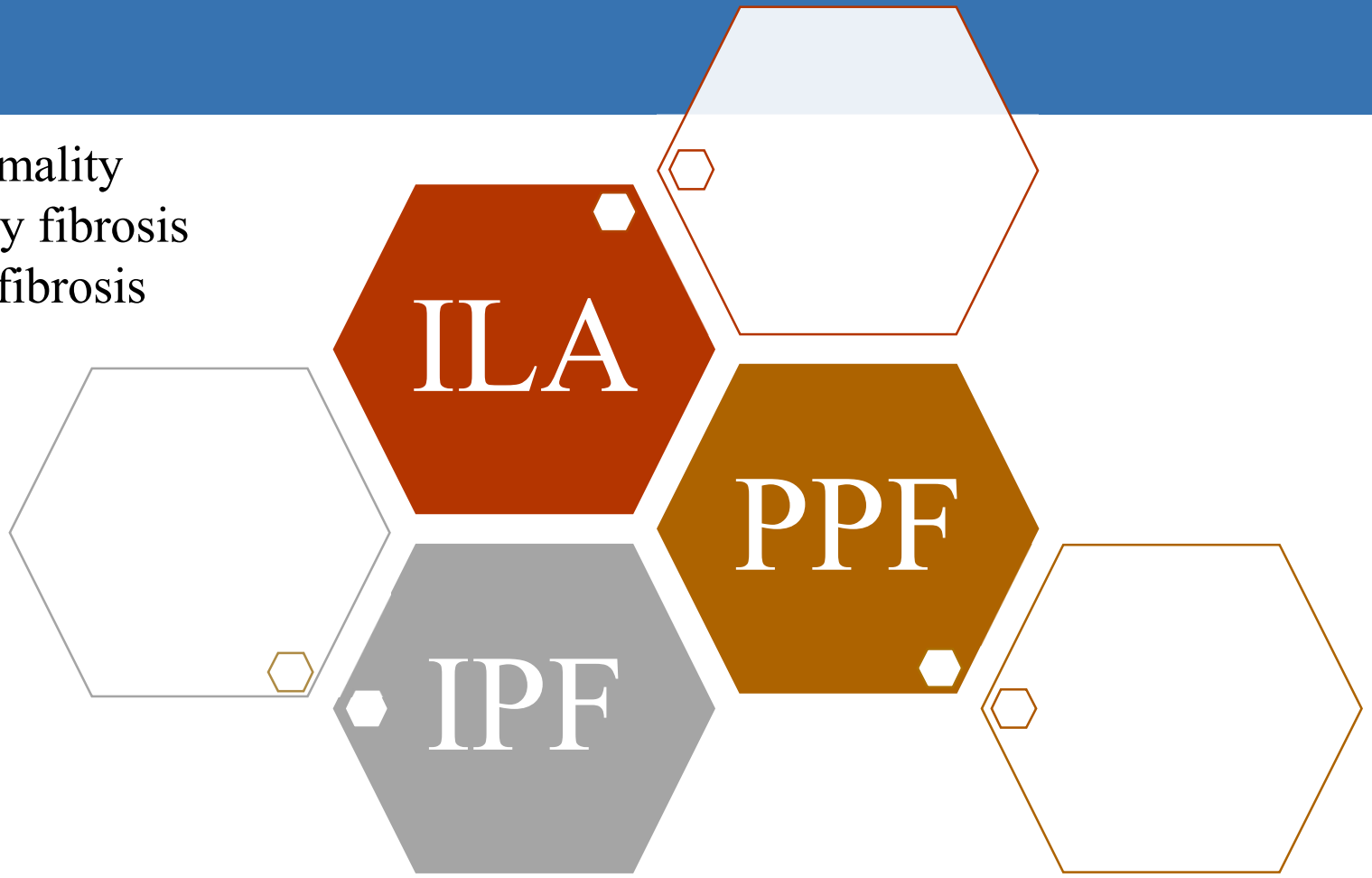
현실적인 문제

Ongoing studies on pirfenidone use in non-IPF ILD

National Clinical Trial Identifier (Reference)	Study Name	ILD Type	Number of Participants	Study Duration	Primary Endpoint	Projected End Date
NCT03385668 (25)	PIRFENIVAS (Pilot Study of Pirfenidone in Pulmonary Fibrosis with Anti-MPO Antibodies)	Anti-MPO–associated	15	52 wk	Absolute change in FVC% predicted	February 2021
NCT03856853 (26)	Efficacy and Safety of Pirfenidone in Patient with Systemic Sclerosis–associated ILD	Systemic sclerosis–associated	144	52 wk	Relative change from baseline of FVC%	May 2021
NCT03857854 (27)	Efficacy and Safety of Pirfenidone in Patient with Dm-ILD	Dermatomyositis-associated	152	52 wk	Relative change from baseline of FVC%	May 2021
NCT02808871 (28)	TRAIL1 (Phase II Study of Pirfenidone in Patients with RAILD)	Rheumatoid arthritis–associated	270	52 wk	Progression (FVC decline of 10% or greater)–free survival	November 2021
NCT02958917 (29)	Study of Efficacy and Safety of Pirfenidone in Patients with Fibrotic Hypersensitivity Pneumonitis	Fibrotic hypersensitivity pneumonitis	40	52 wk	Mean change from baseline in FVC%	December 2021
NCT03221257 (30)	SLSIII (Scleroderma Lung Study III - Combining Pirfenidone with Mycophenolate)	Systemic sclerosis–associated	150	18 mo	Change from baseline in FVC% predicted	June 2022
NCT04193592 (31)	PEARL (Efficacy and Safety of Pirfenidone Treatment in HPS-ILD)	HPS-associated	50	52 wk	Incidence of decline in FVC% predicted >10%	December 2022

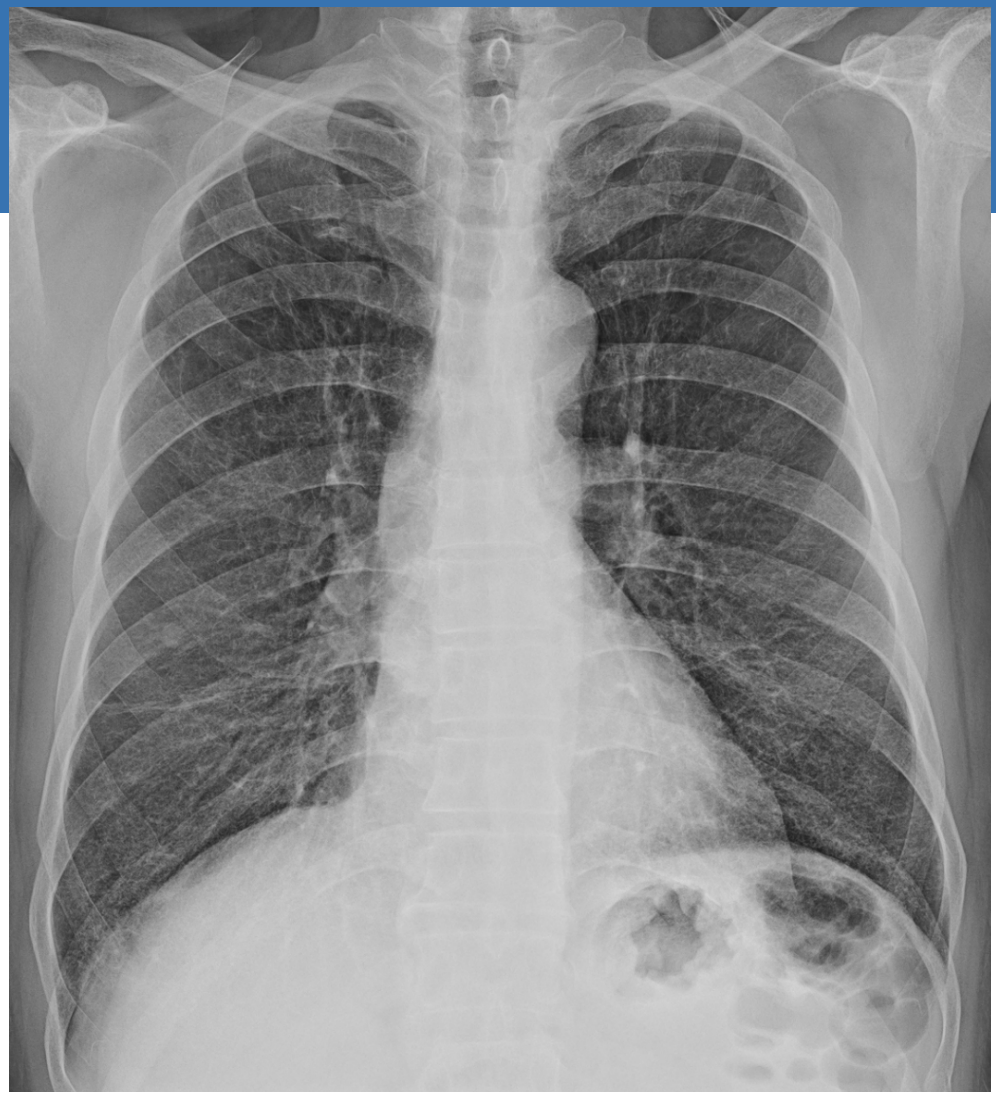
Ann Am Thorac Soc . 2022 Jun;19(6):1030-1039.

ILA: interstitial lung abnormality
PPF: progressive pulmonary fibrosis
IPF: idiopathic pulmonary fibrosis

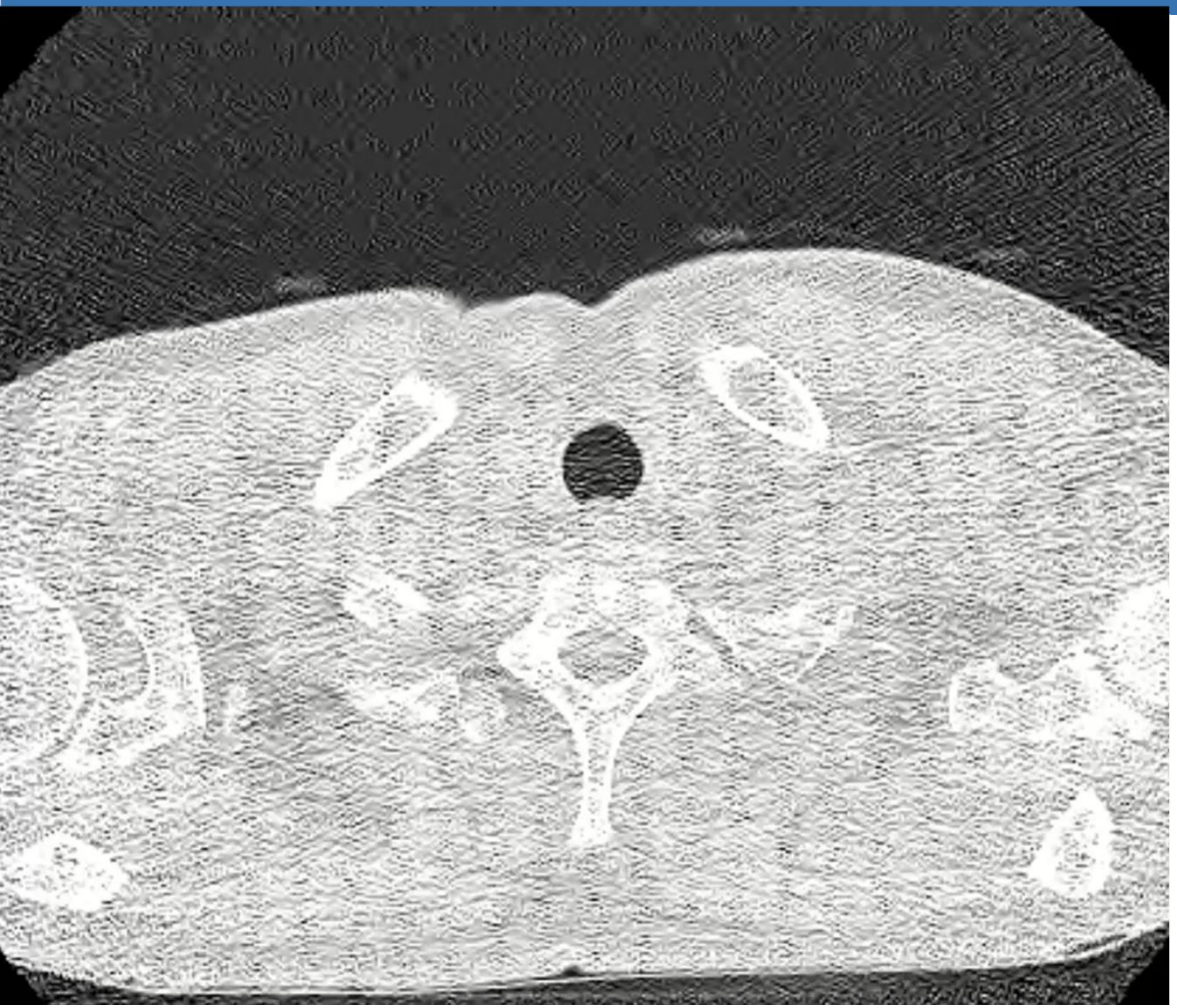


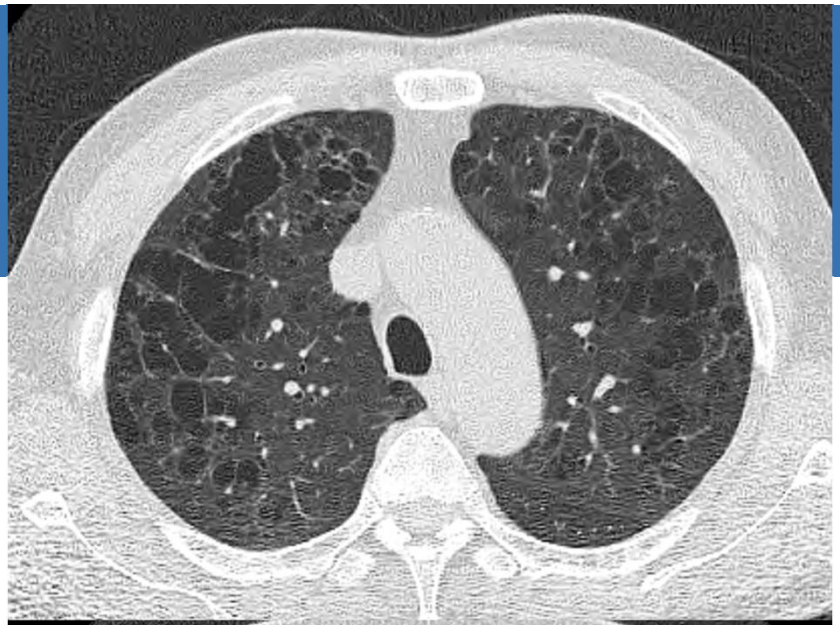
CASE 5. 69/M

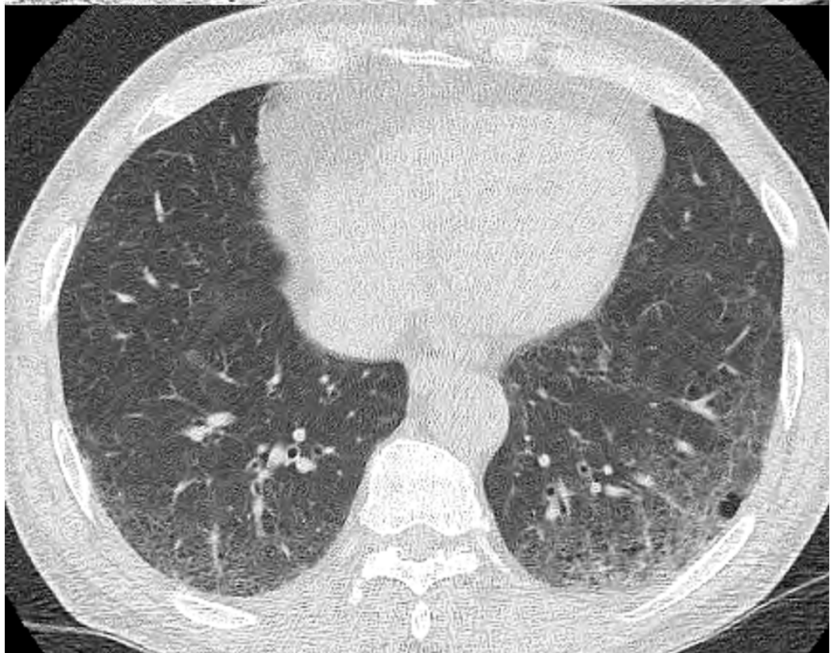
- C/C 검진으로 타원에서 시행한 chest CT상 ILD 의심되어 내원함
- HTN+, DL+
- C-smoker, 50 PYs
- C/S +/- mMRC 0-1
- 사무직



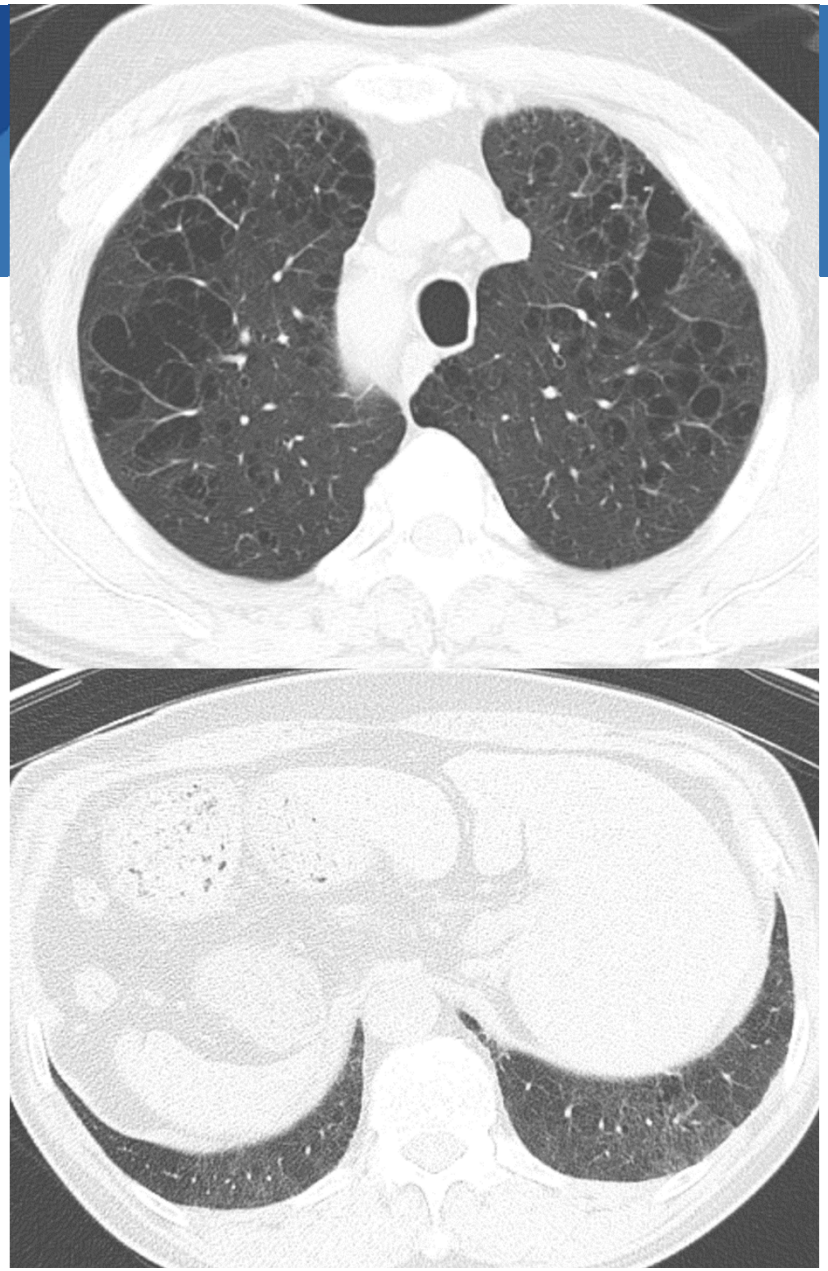
타원 chest CT

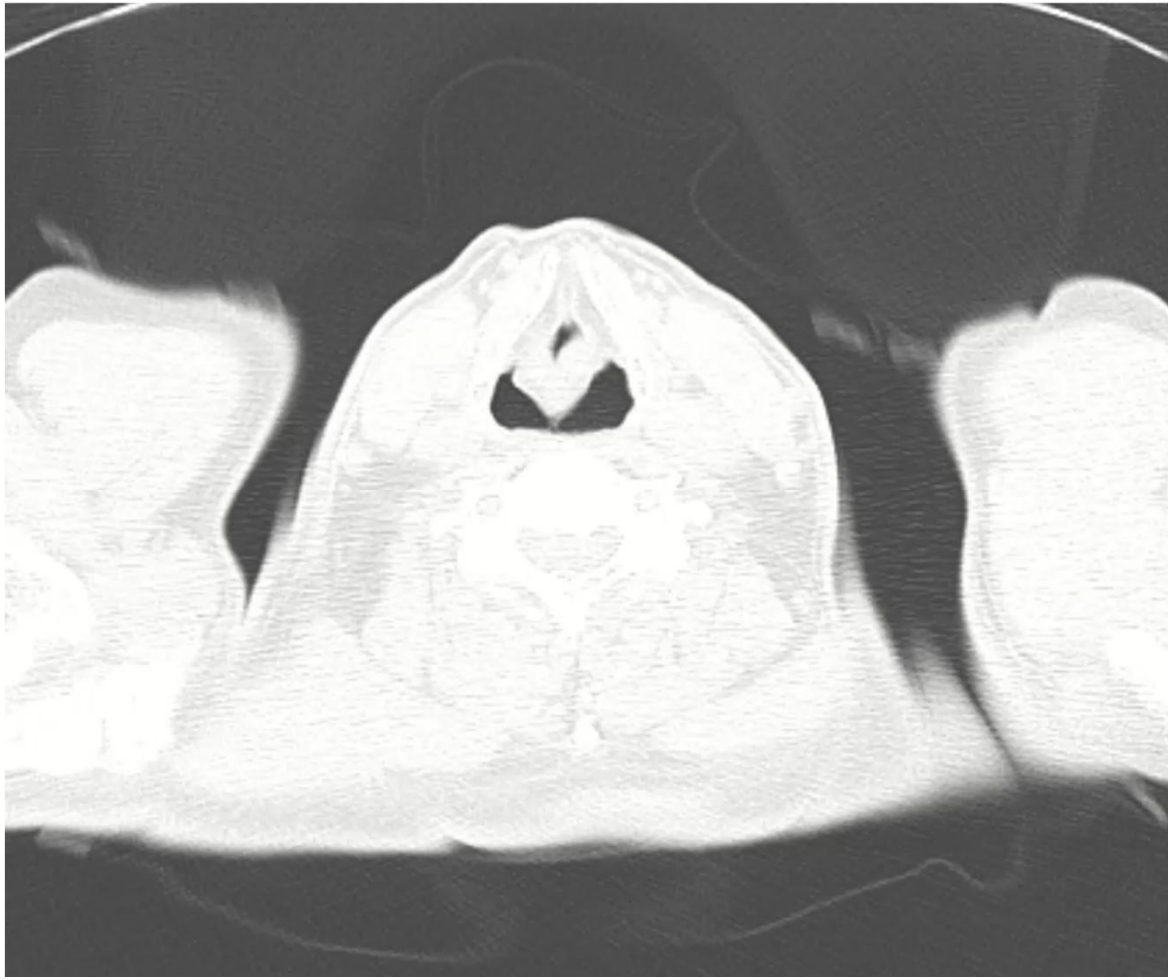




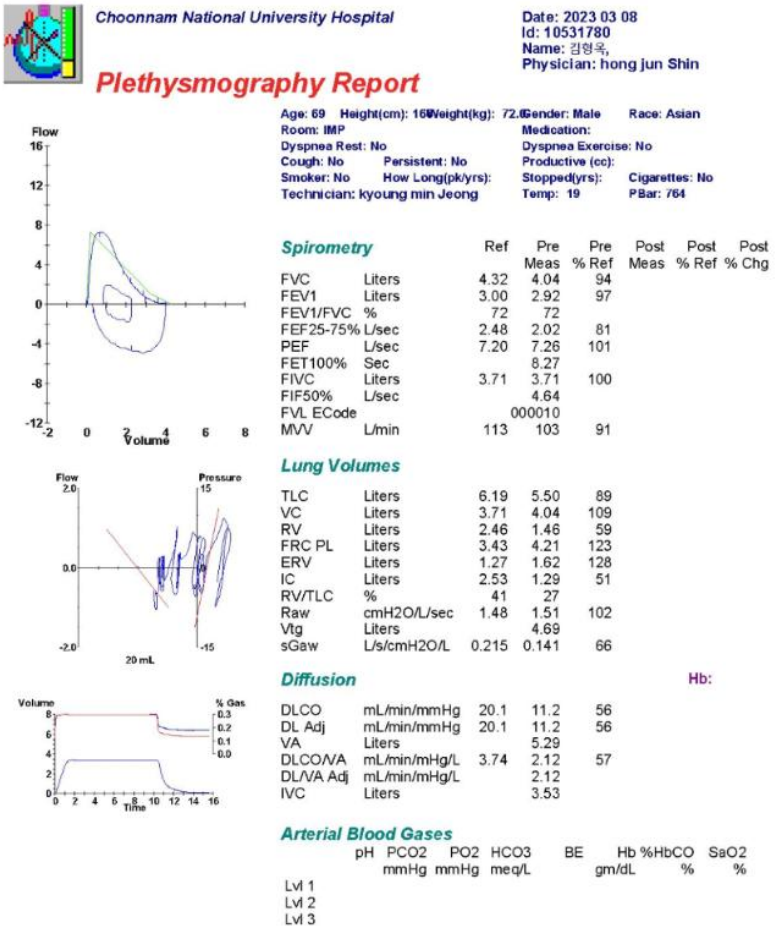


본원 Prone HRCT





폐기능 검사



Choonnam National University Hospital

Date: 2023 03 08
Id: 10531780
Name: 김형옥,
Physician: hong jun Shin

Plethysmography Report

Age: 69 Height(cm): 168 Weight(kg): 72.0 Gender: Male Race: Asian
Room: IMP Medication:
Dyspnea Rest: No Dyspnea Exercise: No
Cough: No Persistent: No Productive (cc):
Smoker: No How Long(pk/yrs): Stopped(yrs): Cigarettes: No
Technician: kyoung min Jeong Temp: 19 PBar: 764

Spirometry

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	4.32	4.04	94			
FEV1	Liters	3.00	2.92	97			
FEV1/FVC	%	72	72				
FEF25-75%	L/sec	2.48	2.02	81			
PEF	L/sec	7.20	7.26	101			
FET100%	Sec		8.27				
FIVC	Liters	3.71	3.71	100			
FIF50%	L/sec		4.64				
FVL ECode			000010				
MVV	L/min	113	103	91			

Lung Volumes

TLC	Liters	6.19	5.50	89
VC	Liters	3.71	4.04	109
RV	Liters	2.46	1.46	59
FRC PL	Liters	3.43	4.21	123
ERV	Liters	1.27	1.62	128
IC	Liters	2.53	1.29	51
RV/TLC	%	41	27	
Raw	cmH2O/L/sec	1.48	1.51	102
Vtg	Liters		4.69	
sGaw	L/s/cmH2O/L	0.215	0.141	66

Diffusion Hb:

DLCO	mL/min/mmHg	20.1	11.2	56
DL Adj	mL/min/mmHg	20.1	11.2	56
VA	Liters		5.29	
DLCO/VA	mL/min/mHg/L	3.74	2.12	57
DL/VA Adj	mL/min/mHg/L		2.12	
IVC	Liters		3.53	

Arterial Blood Gases

	pH	PCO2 mmHg	PO2 mmHg	HCO3 meq/L	BE	Hb gm/dL	%HbCO %	SaO2 %
Lvl 1								
Lvl 2								
Lvl 3								

- Pre FVC 4.04 L (94%)
- Pre FEV1 2.92 L (97%)
- FEV1/FVC 72%
- DLco 56%

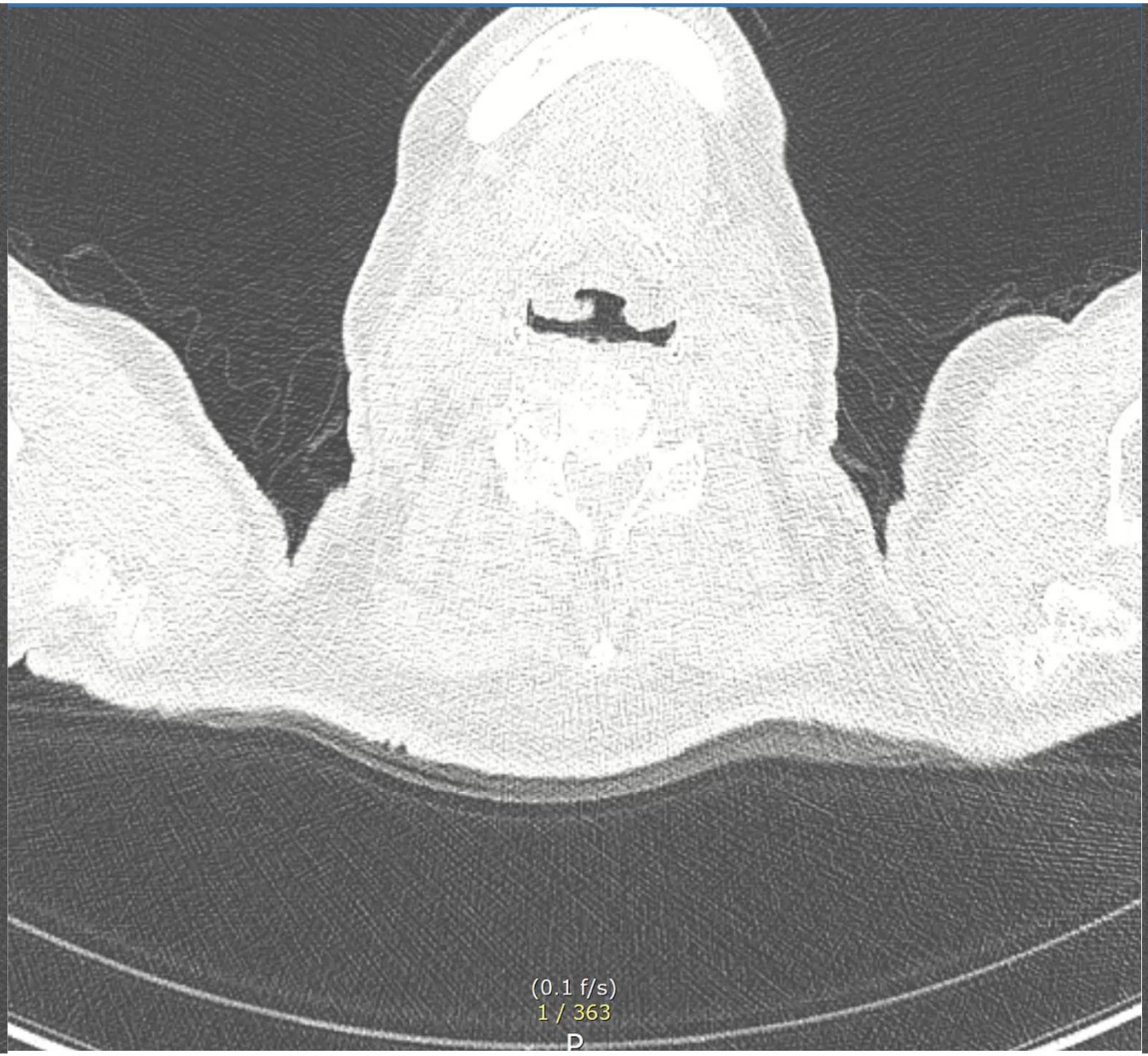
***Autoimmune marker (Screening)**

Anti-CCP	0.6
ANA titer	Negative
ANCA	Negative
Rheumatoid factor titration	3.0
KL-6	470

진단

- Subpleural non-fibrotic ILA

- 금연 권고
- 1년뒤 HRCT 및 PFT f/u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P

Interstitial Lung Abnormality (ILA)

Position Paper

The term interstitial lung abnormalities refers to specific CT findings that are potentially compatible with interstitial lung disease in patients without clinical suspicion of the disease.

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

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†*

Lancet Respir Med . 2020 Jul;8(7):726-737.

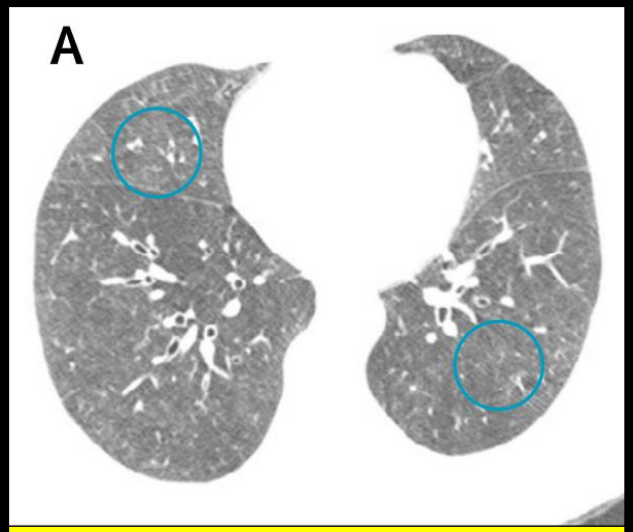
Definition of ILA

What are interstitial lung abnormalities (ILAs)?

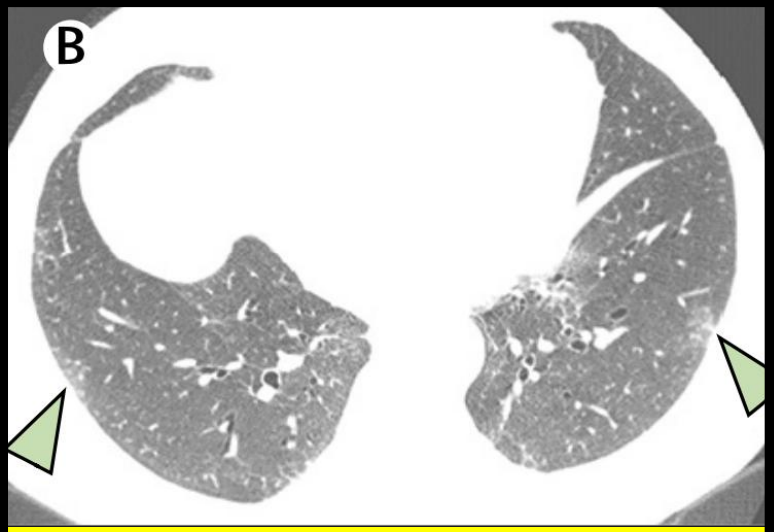
- Incidental identification of non-dependent abnormalities, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts
- Involving at least 5% of a lung zone (upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein)
- In individuals in whom interstitial lung disease is not suspected

Lancet Respir Med . 2020 Jul;8(7):726-737.

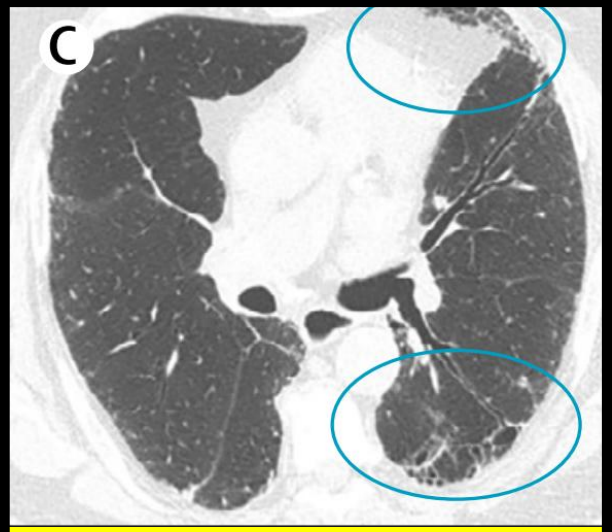
Subcategories of ILA



Non-subpleural ILA



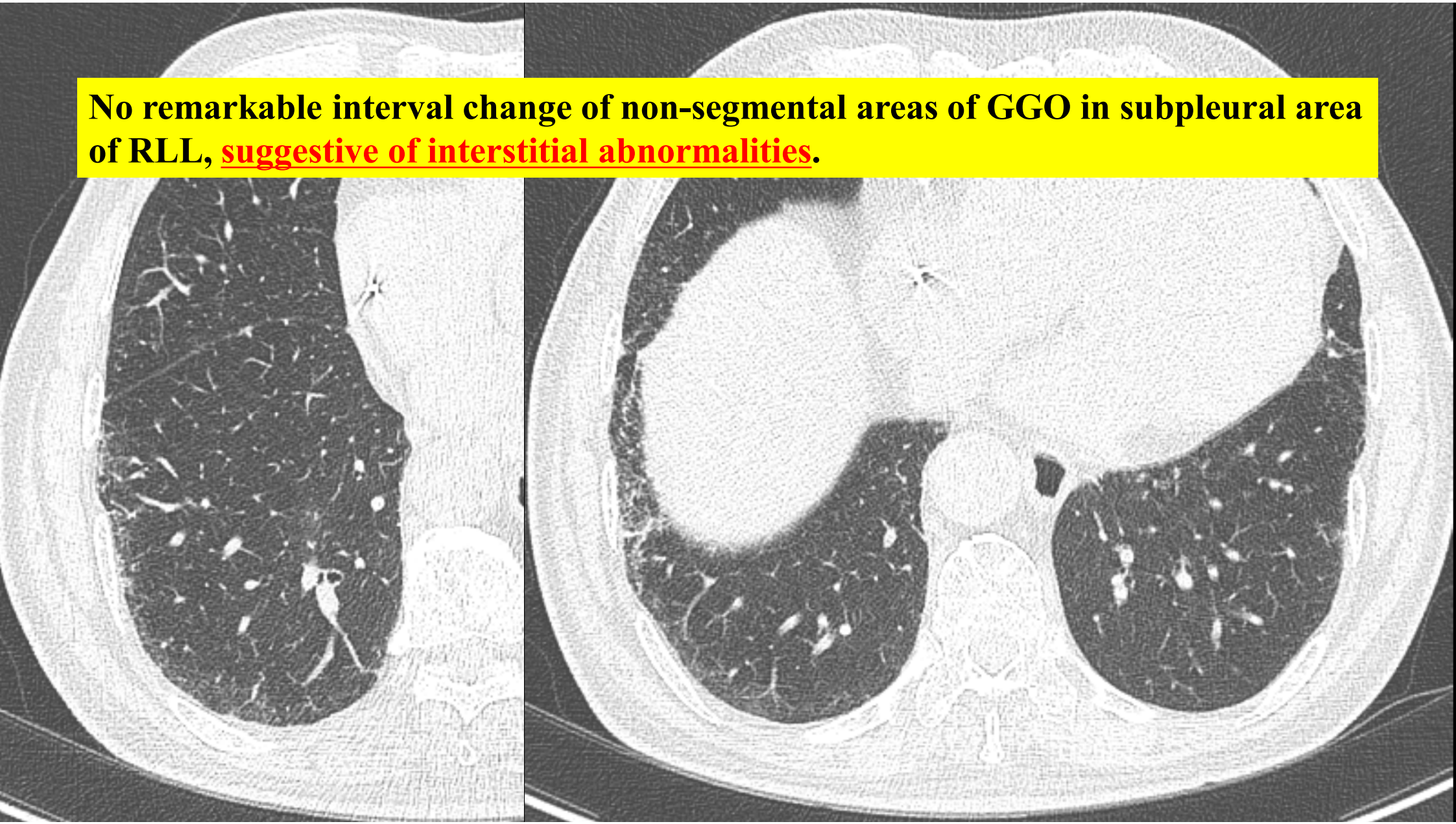
Subpleural non-fibrotic ILA



Subpleural fibrotic ILA

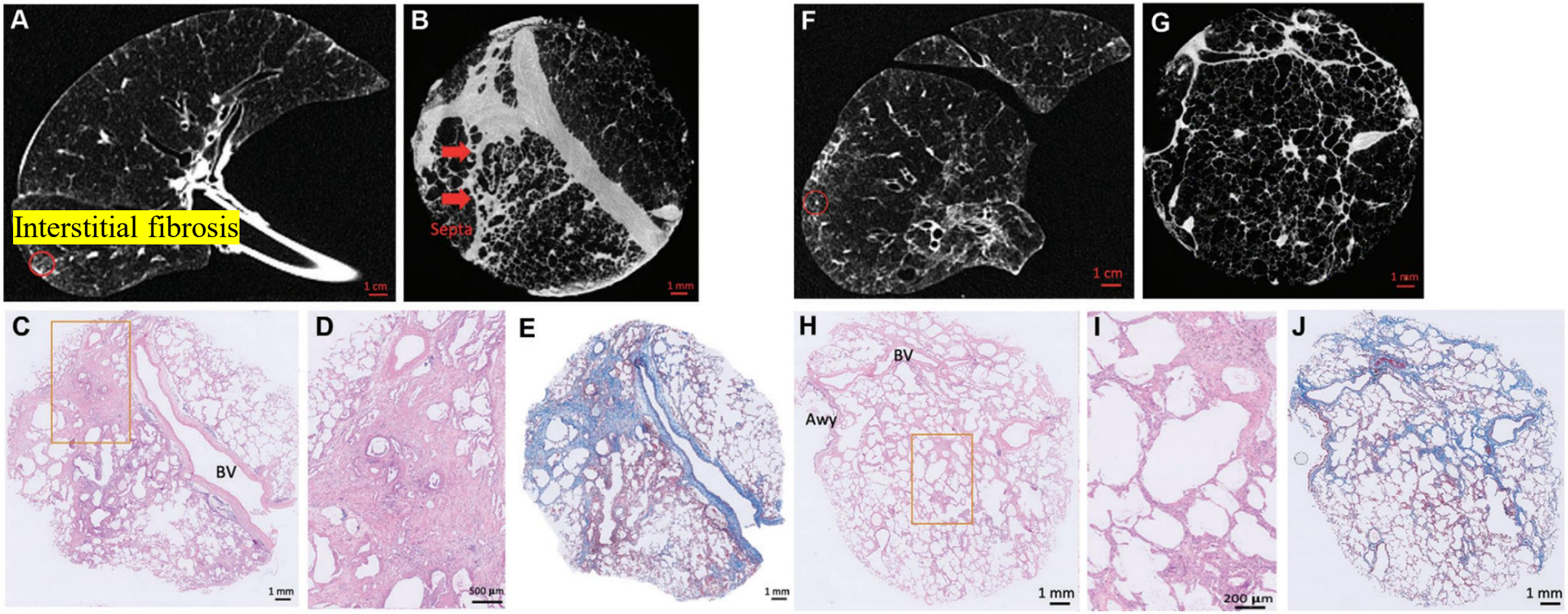
- Non-subpleural: ILAs without predominant subpleural localisation (figure 1A)
- Subpleural non-fibrotic: ILAs with a predominant subpleural localisation and without evidence of fibrosis* (figure 1B)
- Subpleural fibrotic: ILAs with a predominant subpleural localisation and with evidence of pulmonary fibrosis* (figure 1C)

Lancet Respir Med . 2020 Jul;8(7):726-737.



No remarkable interval change of non-segmental areas of GGO in subpleural area of RLL, suggestive of interstitial abnormalities.

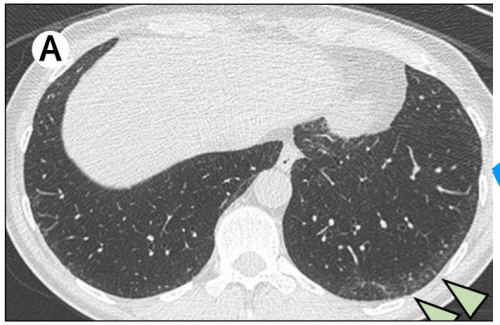
Radiologic and Histologic Correlates



Radiology . 2022 Dec 20;221145.

Differentiation between ILAs and clinical and subclinical ILD

Radiologists



ILA

Respiratory signs, symptoms, or functional impairment 에 대한 정보는 없음.

Clinicians

- ILA
- Subclinical ILD
- Clinical ILD

Prevalence, progreesion, and death

	Population-based cohorts				Smoking and lung cancer screening cohorts				
	MESA[11,12,13,14]	Nagano, Japan*[15]	FHS[6,8,9]	AGES-Reykjavik[9]	ECLIPSE[9]	NLST[7,16]	COPDGene[4,9,17]	MILD[18]	DLCST[19]
Study characteristics									
Total number of chest CT scans evaluated	3137	3061	2633	5320	1670	884	9292	692	1990
Prevalence of ILAs	310 (10%)	80 (3%)	177 (7%)	377 (7%)	157 (9%)	86 (10%)	708 (8%)	28 (4%)	332 (17%)
Mean age of those with ILAs (years)	75	62	70	78	64	62	64	60	60
Radiological progression									
Overall progression, follow-up time	NA	46%, 4 years	43%, 6 years	63%, 5 years	NA	20%, 2 years	NA	20%, 2 years	NA
Mortality									
Relative risk of death, (hazard ratio [95% CI])	NA	NA	2·7 (1·1–6·5)	1·3 (1·2–1·4)	1·4 (1·1–2·0)	NA	1·8 (1·1–2·8)	NA	2·0 (1·4–2·7)

ILAs=interstitial lung abnormalities. NA=not available. *Patients participating in a health screening programme from Nagano prefecture, Japan.

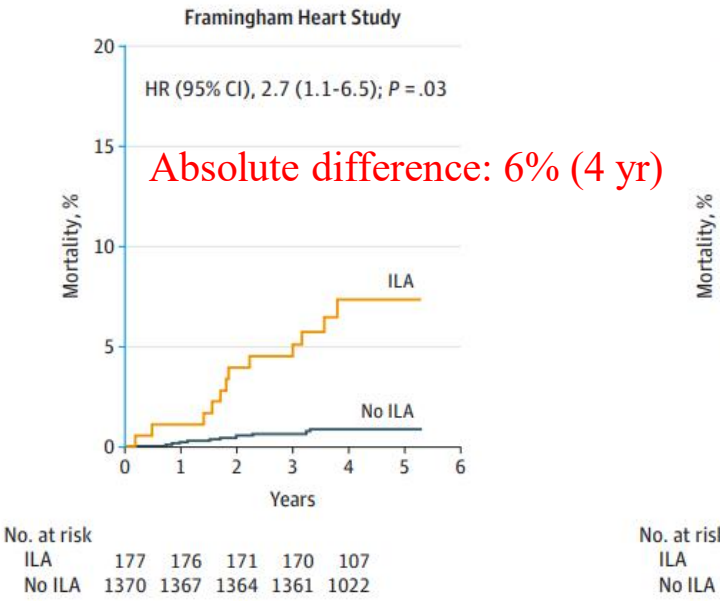
Lancet Respir Med . 2020 Jul;8(7):726-737.

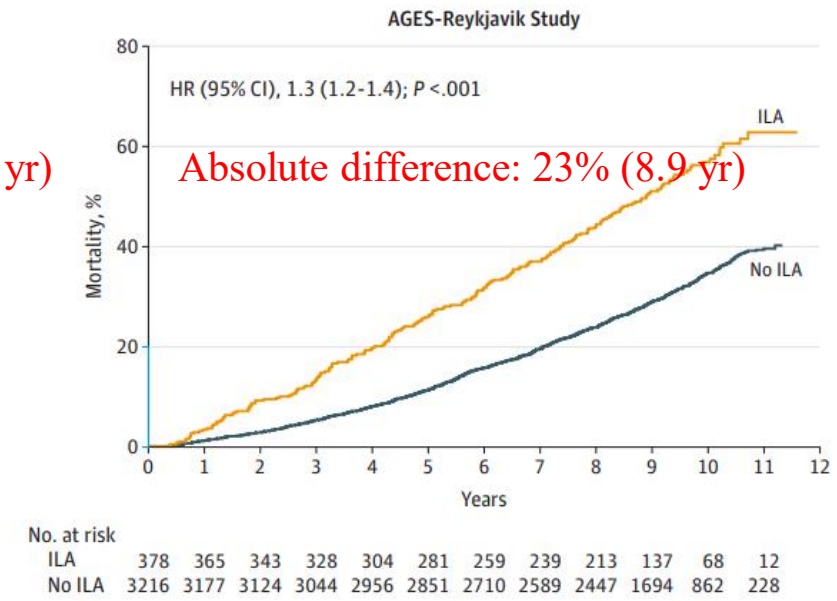
Risk factors for ILAs

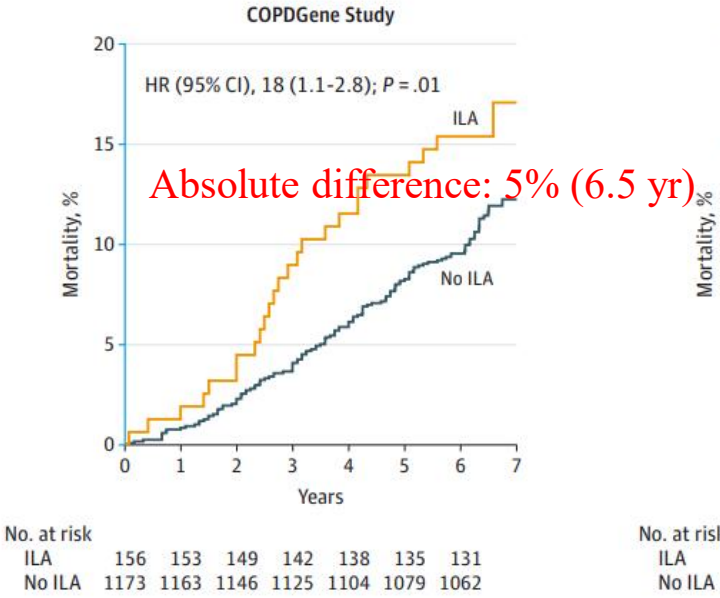
- Advanced age: OR 2.2 (per 10 year increase)
- Male sex: OR 1.7
- Smoking: OR 1.8
- Occupational exposure (vapours, gases, dusts, fumes)
- Air pollution (nitrogen oxides, elemental carbon)
- MUC5B promoter polymorphism: OR 2.8

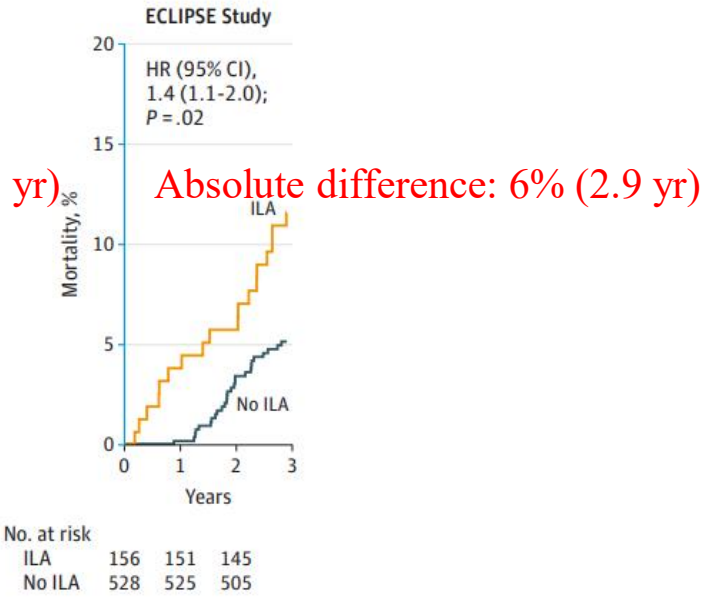
Lancet Respir Med . 2020 Jul;8(7):726-737.

Mortality Rates by ILA Status



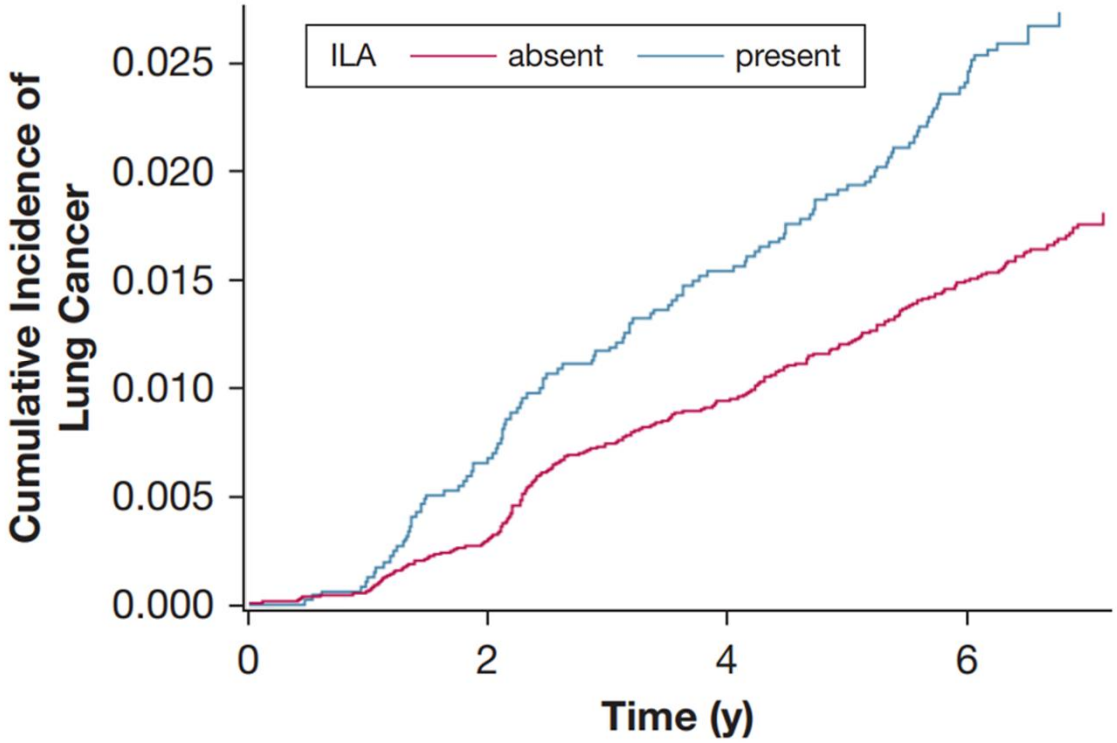






JAMA . 2016 Feb 16;315(7):672-81

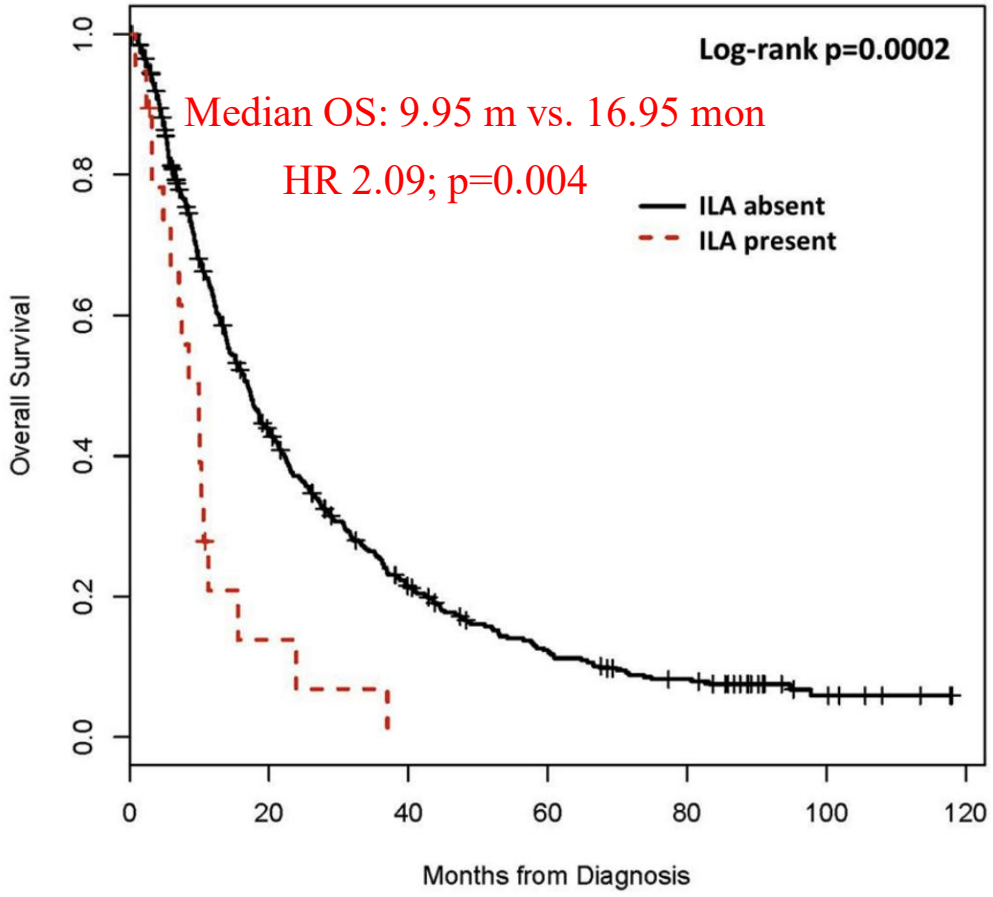
Lung cancer: development



- NLST: 25,041 patients with CT images
- ILA (20.2%): reticular/reticulonodular opacities, honeycombing, fibrosis, scarring on baseline CT

Variable	Lung Cancer Cases, No. (%)	*P* Value	Lung Cancer Incident Cases per 100,000 Person-Years (95% CI)	Unadjusted IRR (95% CI)
ILA	121 (2.4)	< .01	398 (333-476)	1.61 (1.30-1.99)
No ILA	304 (1.5)		248 (221-227)	Reference

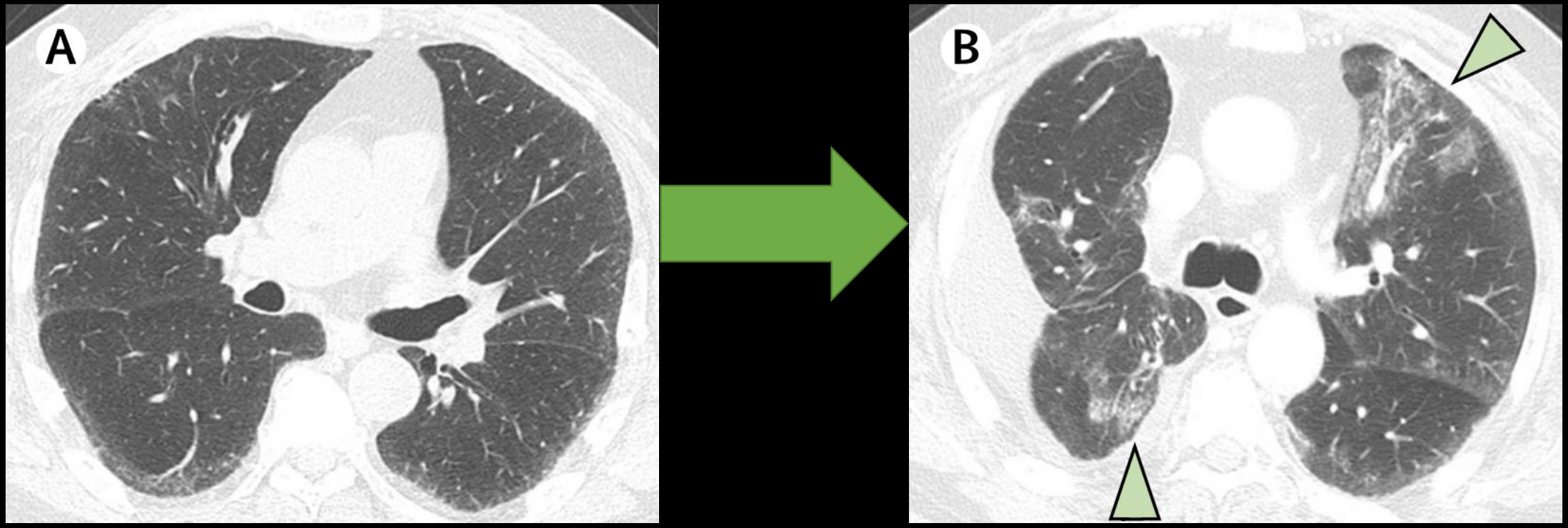
Lung cancer: survivor



- USA
- NSCLC, stage IV
- N=484

Eur J Radiol Open . 2019 Mar 29;6:128-131.

Lung cancer: treatment



- NSCLC with anti-PD-1 antibody → ILD development [OR 6.64 (1.7-24.7)]
- Other cancer with anti-PD-1 antibody → ILD development [OR 6.29 (2.3-16.9)]

Respir Investig . 2019 Sep;57(5):451-459.
Lancet Respir Med . 2020 Jul;8(7):726-737.

Impact of ILA on postoperative pulmonary complications and survival of lung cancer

Table 2 Univariable and multivariable logistic regression analysis for factors related to PPCs in study patients (n=300)

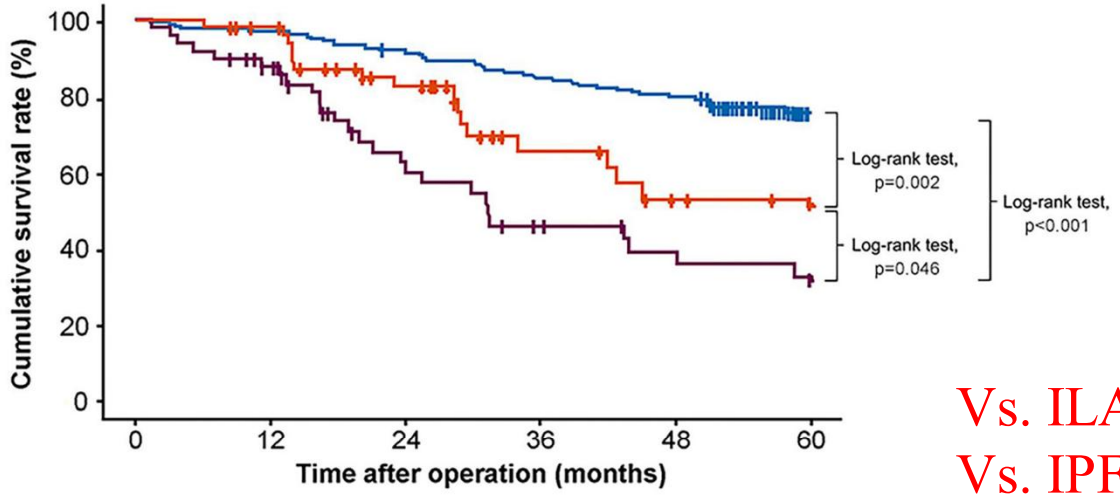
	Univariable		Multivariable	
Characteristics	**OR** (95% CI)	**P value**	**OR** (95% CI)	**P value**
Sex, male	5.50 (0.73 to 41.41)	0.098	9.83 (0.81 to 119.02)	0.073
Age, year	1.06 (1.01 to 1.12)	0.025	1.12 (1.04 to 1.20)	0.004
BMI, kg/m^2	0.96 (0.86 to 1.07)	0.427	0.98 (0.84 to 1.14)	0.781
Smoking history				
Never smoker	Reference		Reference	
Former or current smoker	1.03 (0.40 to 2.60)	0.959	0.38 (0.10 to 1.50)	0.166
Presence of ILA or IPF		(<0.001)		(<0.001)
Control	Reference		Reference	
ILA	8.56 (2.80 to 29.1)	<0.001	9.56 (2.85 to 32.10)	<0.001
IPF	39.0 (14.7 to 124)	<0.001	56.50 (17.92 to 178.14)	<0.001
Extent of surgery				
Segmentectomy or wedge resection	Reference		Reference	
Lobectomy	2.37 (0.81 to 10.1)	0.167	4.46 (1.11 to 17.90)	0.035

BMI, body mass index; ILA, interstitial lung abnormalities; IPF, idiopathic pulmonary fibrosis; PPCs, postoperative pulmonary complications.

*PPCs: postoperative pulmonary complications

Thorax . 2023 Feb;78(2):183-190.

Impact of ILA on postoperative pulmonary complications and survival of lung cancer



Number at risk						
Control	200	194	183	169	160	78
ILA	50	46	31	16	10	8
IPF	50	40	22	15	10	9

	1-yr survival rate (95% CI), %	2-yr survival rate (95% CI), %	3-yr survival rate (95% CI), %	5-yr survival rate (95% CI), %
Control	97(95-99)	91(87-95)	85(80-90)	76(71-83)
ILA	98(94-99)	82(71-94)	65(51-83)	52(37-74)
IPF	88(79-97)	60(46-77)	46(33-65)	32(19-53)

Vs. ILA HR 2.64 (1.47-4.74), P <0.001
Vs. IPF HR 4.68 (2.84-7.71), P <0.0001

Thorax . 2023 Feb;78(2):183-190.

COPD

SNUH, Retrospective, 2013-2018, COPD patients (n=363)

TABLE 3] Risk of Acute Exacerbation in Patients With COPD According to ILA Status

	Moderate		Severe		Moderate to Severe	
Parameter	β ± SD	*P* Value	β ± SD	*P* Value	β ± SD	*P* Value
ILA[a]	0.22 ± 0.08	.005	0.16 ± 0.08	.043	0.38 ± 0.12	.002
Age	−0.01 ± 0.01	.210	−0.00 ± 0.00	.586	−0.01 ± 0.01	.239
Male sex	0.02 ± 0.16	.884	0.34 ± 0.16	.034	0.36 ± 0.25	.142
Smoking intensity, pack-y	0.01 ± 0.00	< .001	0.00 ± 0.00	.456	0.01 ± 0.00	.005
Charlson Comorbidity Index	−0.03 ± 0.04	.431	0.05 ± 0.04	.146	0.02 ± 0.05	.672
Baseline FEV_1	−0.34 ± 0.08	< .001	−0.47 ± 0.08	< .001	−0.81 ± 0.12	< .001
Positive bronchodilator response	−0.21 ± 0.11	.045	−0.23 ± 0.10	.028	−0.44 ± 0.16	.006

Data are presented as mean ± SD unless otherwise indicated. See Table 1 legend for expansion of abbreviation.
[a]Includes both equivocal and definite ILA.

Chest . 2021 Jan;159(1):128-137.

Risk factors for progression of ILA

Clinical risk factors

- Cigarette smoking
- Other inhalational exposures
- Medications (eg, chemotherapy, immune checkpoint inhibitors)
- Radiation therapy
- Thoracic surgery
- Physiological or gas exchange findings at lower limits of normal

Lancet Respir Med . 2020 Jul;8(7):726-737.

Risk factors for progression of ILA

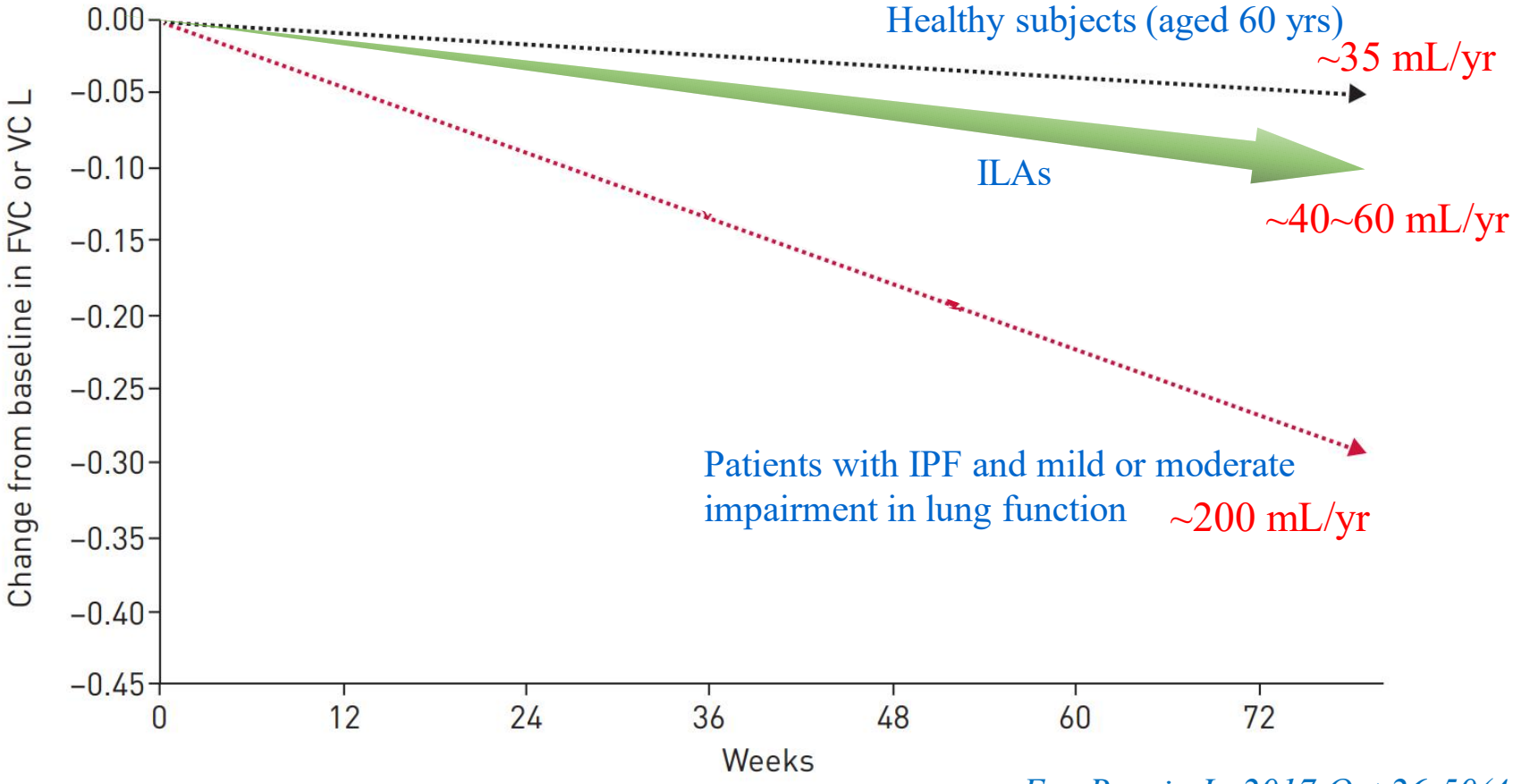
Subpleural predominant fibrotic ILAs are most likely to progress

Radiological risk factors

- Non-fibrotic interstitial lung abnormalities (ILAs) with basal and peripheral predominance
- Fibrotic ILAs with basal and peripheral predominance but without honeycombing (ILAs with probable usual interstitial pneumonia pattern)
- Fibrotic ILAs with basal and peripheral predominance and honeycombing (ILAs with usual interstitial pneumonia pattern)

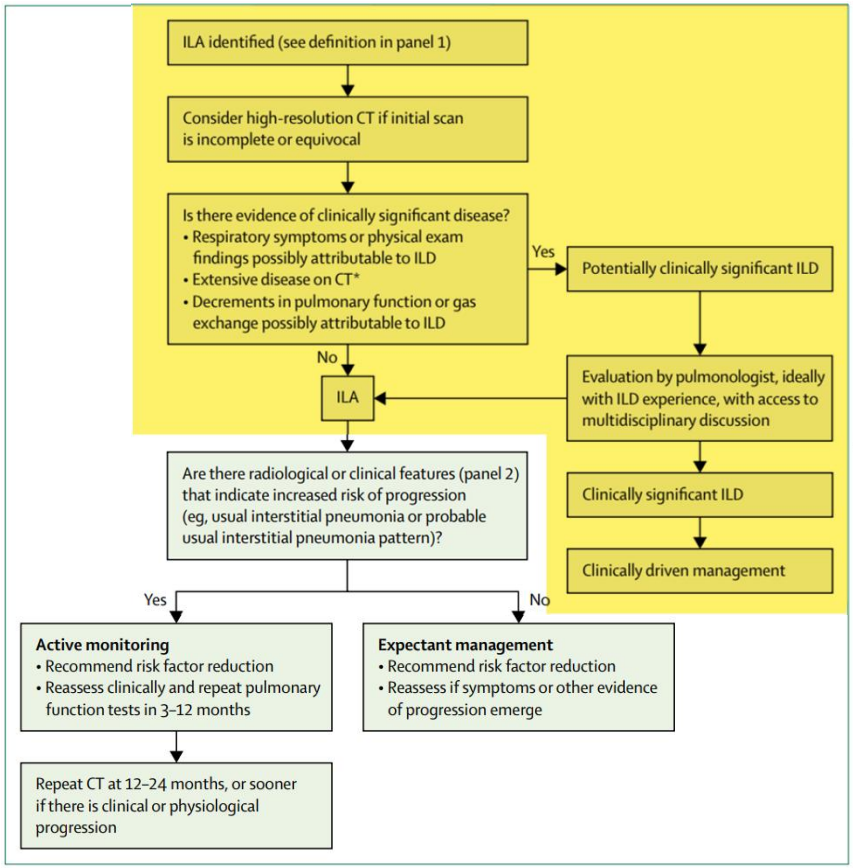
Lancet Respir Med . 2020 Jul;8(7):726-737.

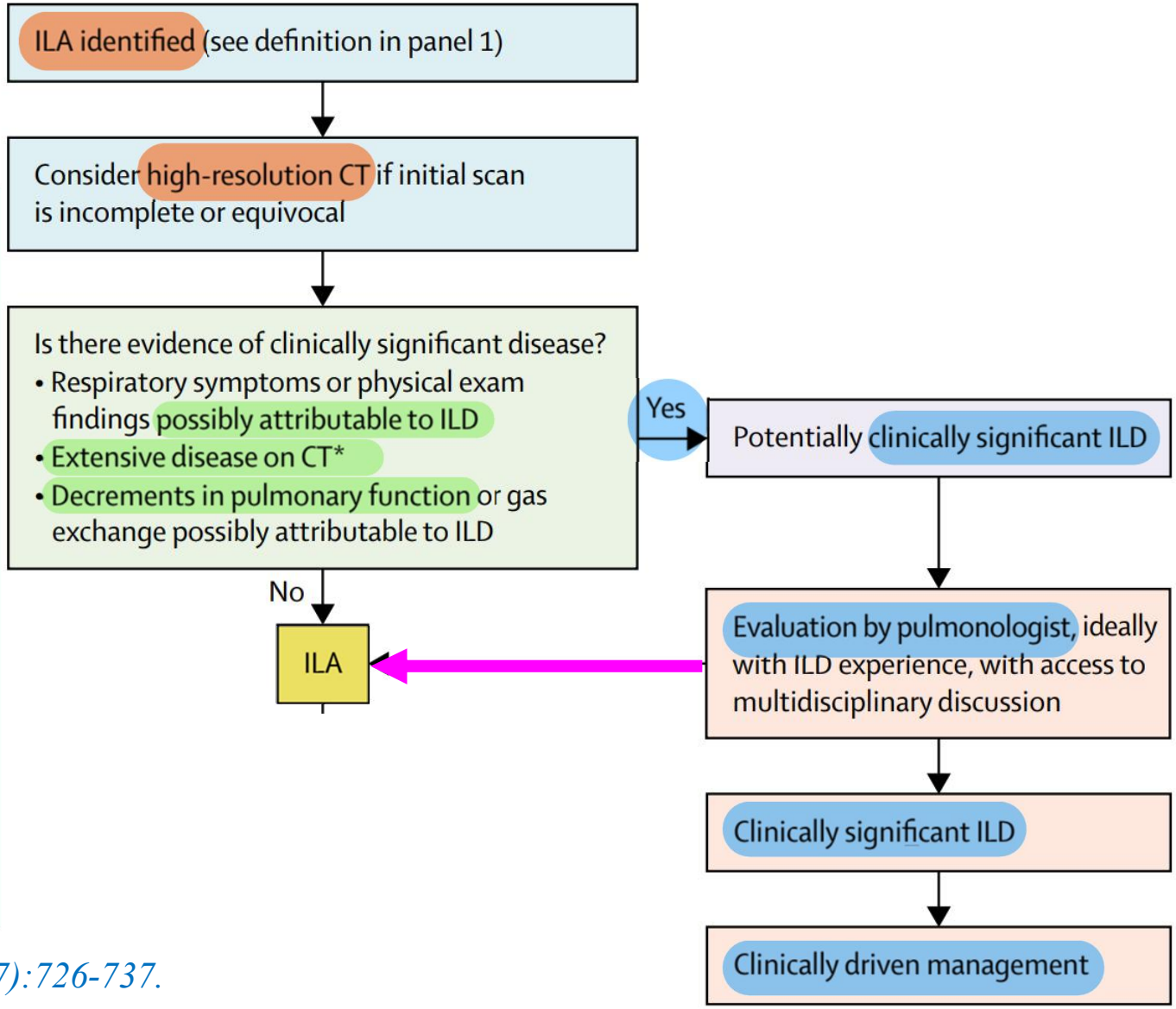
Natural course of lung function decline



Eur Respir J . 2017 Oct 26;50(4):1701209.

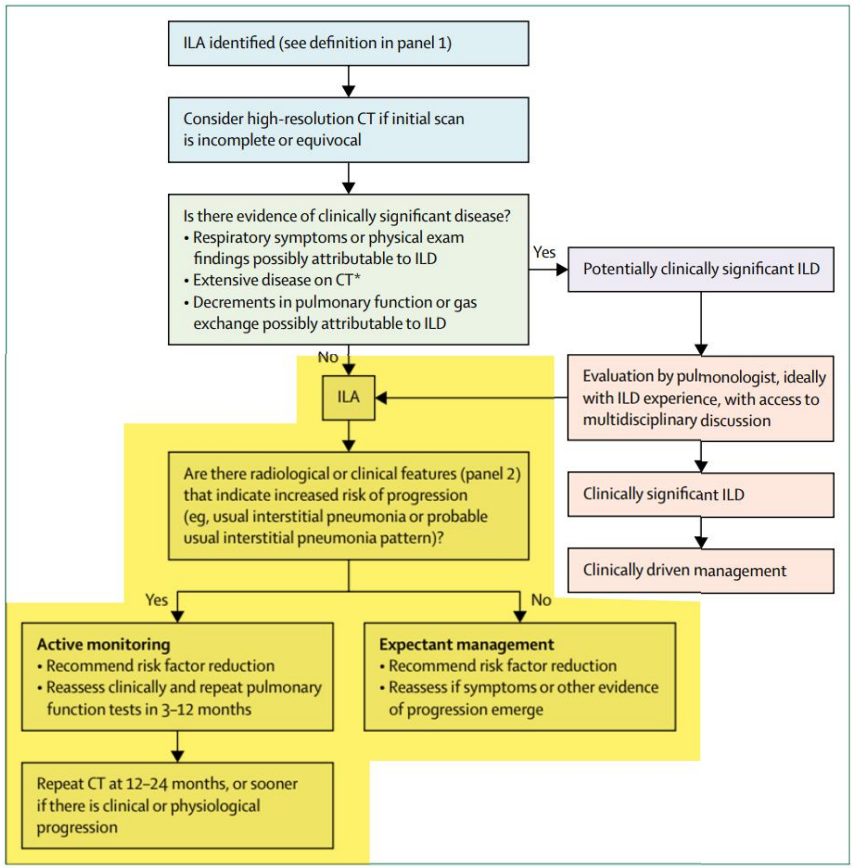
Management of ILA detected on chest CT

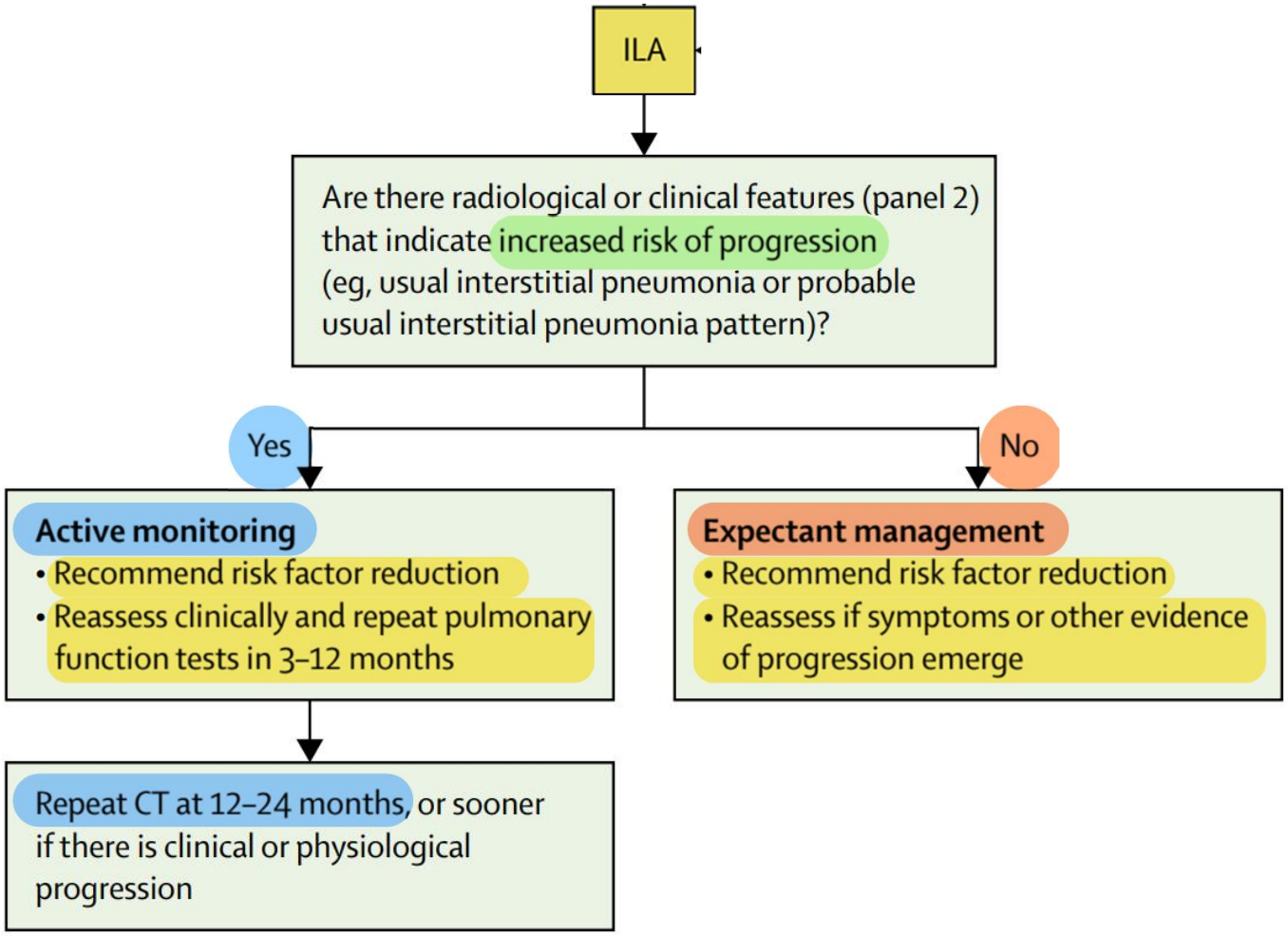




Lancet Respir Med . 2020 Jul;8(7):726-737.

Management of ILA detected on chest CT





Lancet Respir Med . 2020 Jul;8(7):726-737.

IPF 진단 전 CXR 평가, 409명의 IPF

Hoffman *et al. BMC Pulmonary Medicine* (2022) 22:329
https://doi.org/10.1186/s12890-022-02122-8

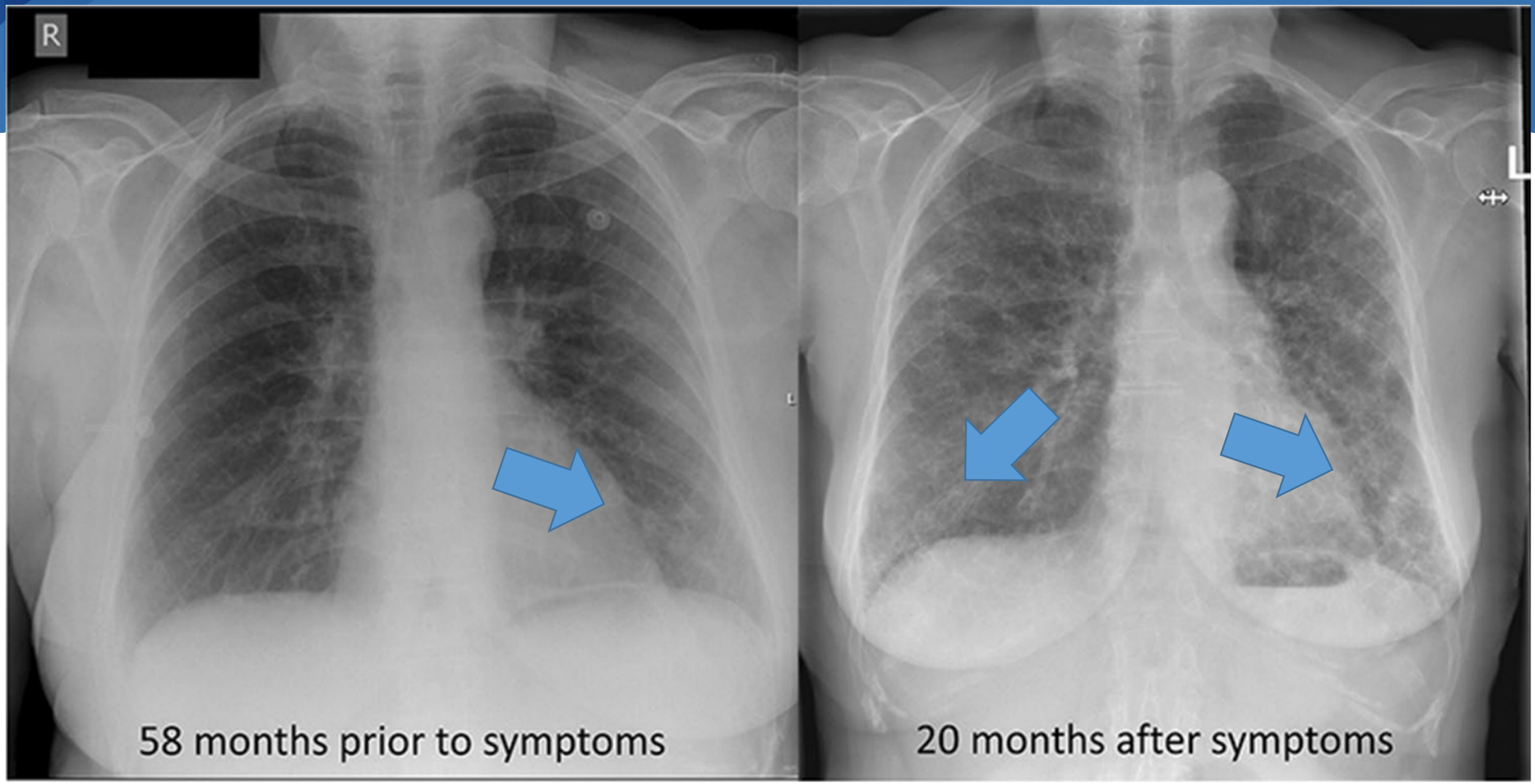
BMC Pulmonary Medicine

RESEARCH Open Access

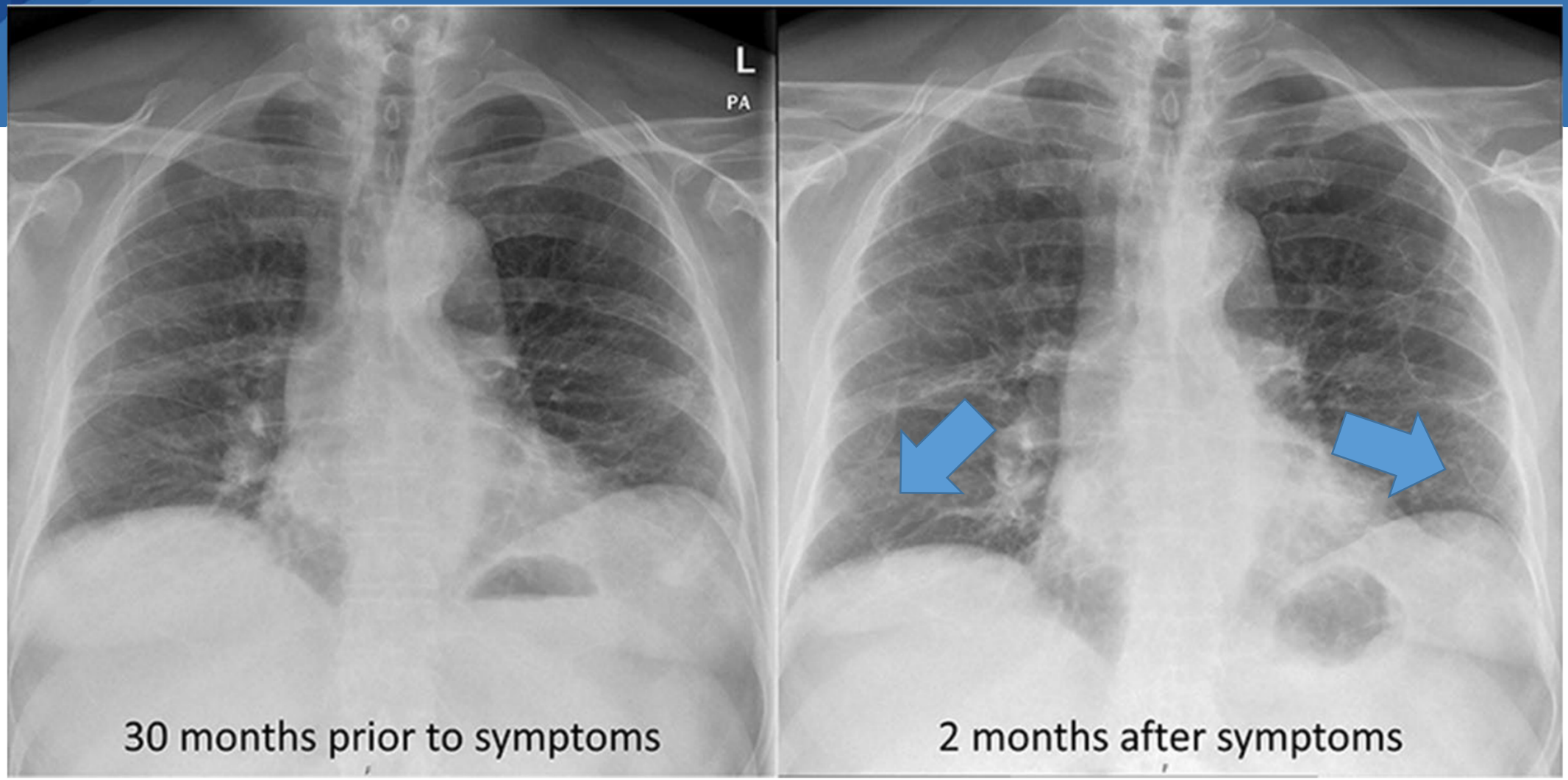
Potential interstitial lung abnormalities on chest X-rays prior to symptoms of idiopathic pulmonary fibrosis

T. W. Hoffman[1*], H. W. van Es[2], D. H. Biesma[3] and J. C. Grutters[1,4]

BMC Pulm Med . 2022 Aug 30;22(1):329.

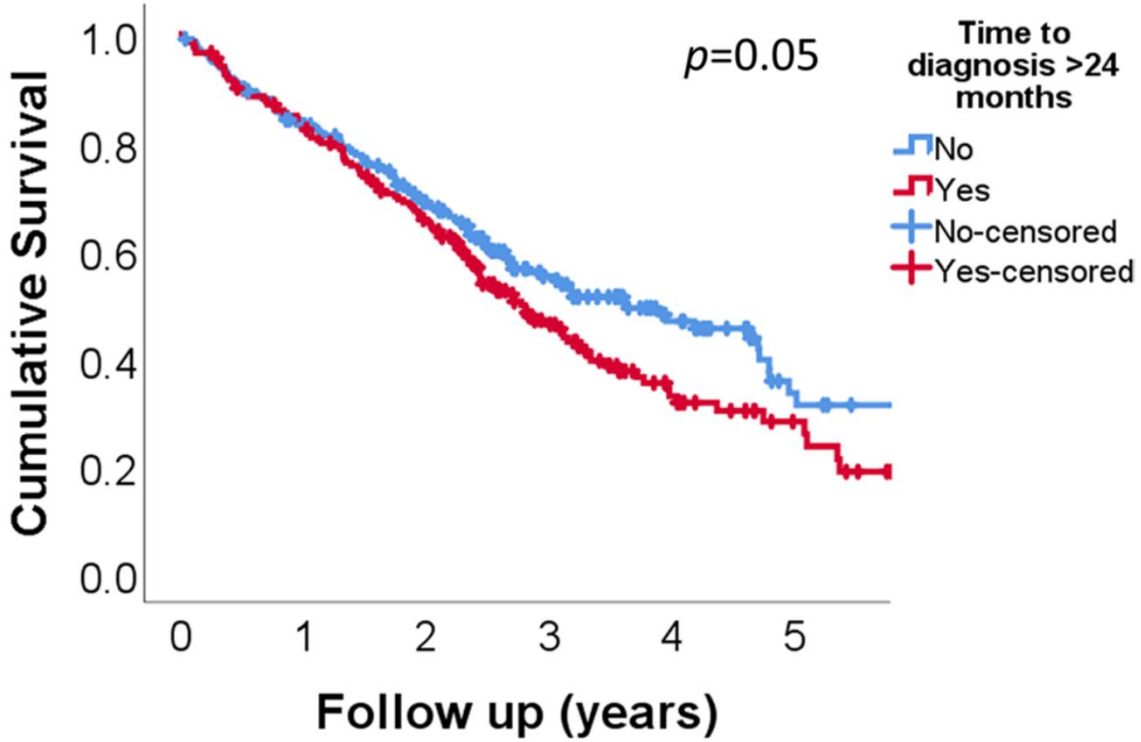


BMC Pulm Med . 2022 Aug 30;22(1):329.



BMC Pulm Med . 2022 Aug 30;22(1):329.

5 years survival



No	209	167	128	75	37	15
Yes	200	161	122	60	27	12

BMC Pulm Med . 2022 Aug 30;22(1):329.

Lung-RADS version 1.0 modified by Korean Lung Cancer Screening protocol

Solid nodule		
Size	**Timing/Change**	**Cat.**
<6 mm	Baseline	2
	No change	2
	Growing	4A
	New (<4 mm)	2
	New (4-6 mm)	3
6-8 mm	Baseline	3
	No change	2
	Growing	4A
	New	4A
8-15 mm	Baseline	4A
	No change	2
	Growing	4B
	New	4B
≥15 mm	Baseline	4B
	No change	2
	Growing	4B
	New	4B

Part solid nodule		
Size	**Timing/Change**	**Cat.**
<6 mm	Baseline	2
	No change	2
	Growing (solid <4 mm)	4A
	Growing(solid 4-6 mm)	4B
	New	3
≥6 mm (solid <6 mm)	Baseline	3
	No change	2
	Growing (solid <4 mm)	4A
	Growing (solid 4-6 mm)	4B
	New (solid <4 mm)	4A
	New (solid 4-6 mm)	4B
≥6 mm (solid 6-8 mm)	Baseline	4A
	No change	2
	Growing	4B
	New	4B
≥8 mm (solid ≥8 mm)	Baseline	4B
	No change	2
	Growing	4B
	New	4B

Ground glass nodule		
Size	**Timing/Change**	**Cat.**
<20 mm	Baseline	2
	No change	2
	Growing	2
	New	2
≥20 mm	Baseline	3
	No change	2
	Growing	2
	New	3

Other	Cat.
Endobronchial nodule	4A
Cat. 3,4+additional finding ; Consolidation, atelectasis, lymph node enlargement, other (spiculation, etc.)	4X
Other clinically significant findings	S
Prior lung cancer	C

Category	Description	Prob.cancer	Manage
0	Incomplete	Not evaluable	Additional LDCT images and/or comparison to prior chest CT images
1	Negative	< 1%	Continue annual screening with LDCT in 12 months
2, 2b[a]	Benign	< 1%	Continue annual screening with LDCT in 12 months
3	Probably benign	1-2%	Follow up LDCT in 6 months
4A	Suspicious	5-15%	Follow up LDCT in 3 months, PET-CT may be used when there is a solid ≥8mm
4B, X	Very suspicious	> 15%	Immediate chest CT, consider biopsy, PET-CT may be used

대한내과학회지: 제 95 권 제 2 호 2020

Significant Abnormalities Other than Lung Cancer in the Korean Lung Cancer CT Screening

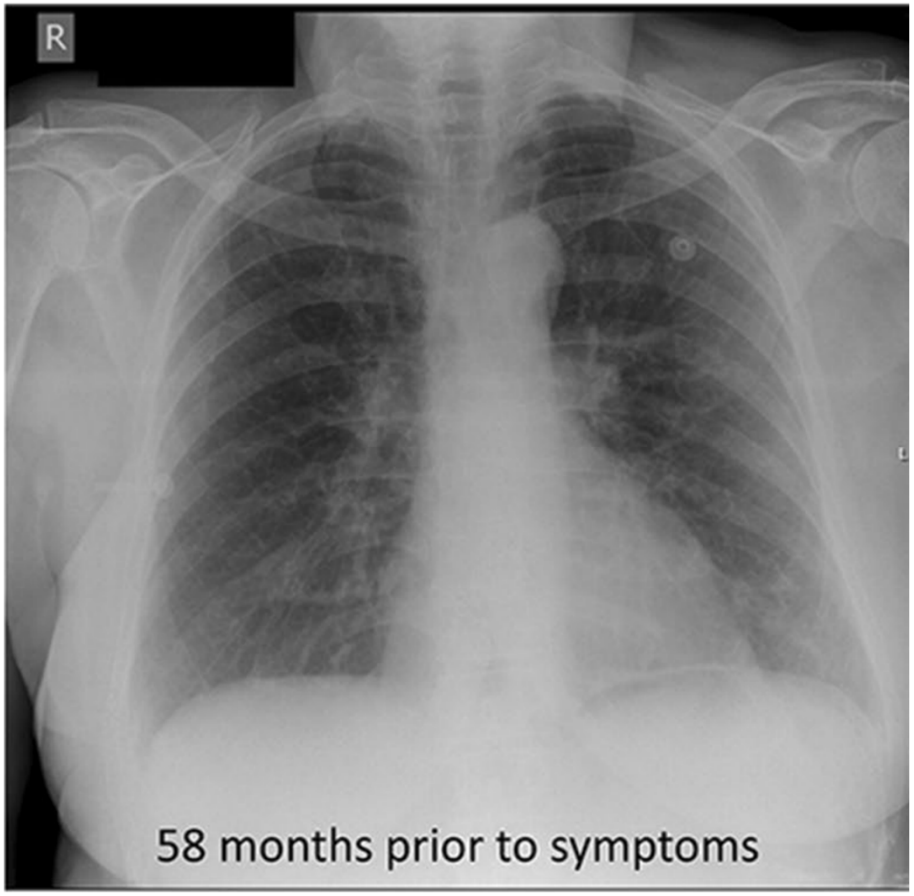
Moderate to heavy coronary artery calcification (visual assessment)
Moderate or higher-degree emphysema (visual assessment)
Interstitial lung abnormalities
Pneumonia and active pulmonary tuberculosis
Extrapulmonary malignancy
Thoracic aortic aneurysm ≥ 5.5 cm
Large amount of pleural or pericardial effusion

J Korean Soc Radiol 2019;80(5):837-848

To understand the prevalence and natural course of ILAs in the lung cancer screening population, ILAs should be considered as a specific subcategory under the significant other findings modifier in the LungRADS scoring system, as used in the USA; the Korean Society of Radiology has already implemented a similar change .

Lancet Respir Med . 2020 Jul;8(7):726-737.

CXR 의심되면 HRCT



HRCT

Interstitial lung abnormality 란?

Incidental
Involving > 5%
Non-dependent, GGO, reticulation, traction BE, HC
ILD is not suspected

문제점

Increased mortality rate
COPD 급성악화
Lung cancer 발생, 치료, 예후에 영향
ARDS 발생 및 사망률 영향

Progression Risk는?

Smoking
CTx, RTx, ICI, Op
Fibrotic ILA

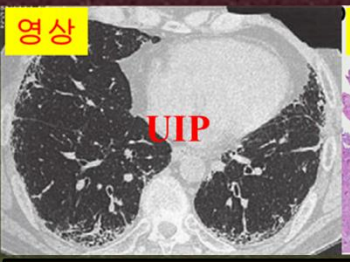
Management 는?

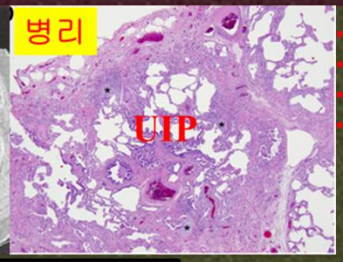
주기적인 PFT 및 HRCT f/u

ILA

PPF

IPF



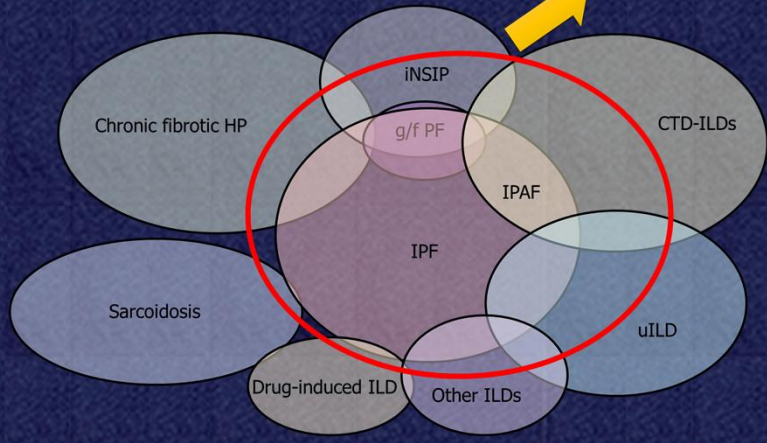


- Rheumatoid factor
- Anti-CCP Antibody
- ANA (titer)
- ANCA

① FVC ≤ 90%, or
② DLco ≤ 80%, or
③ 다음 중 2개 이상 만족
- FVC ≥10% 감소/year
- FVC ≥ 200 mL 감소/year
- 임상증상 악화
- 흉부영상 악화

Standard dose (1800mg) → Dose reduction !!!

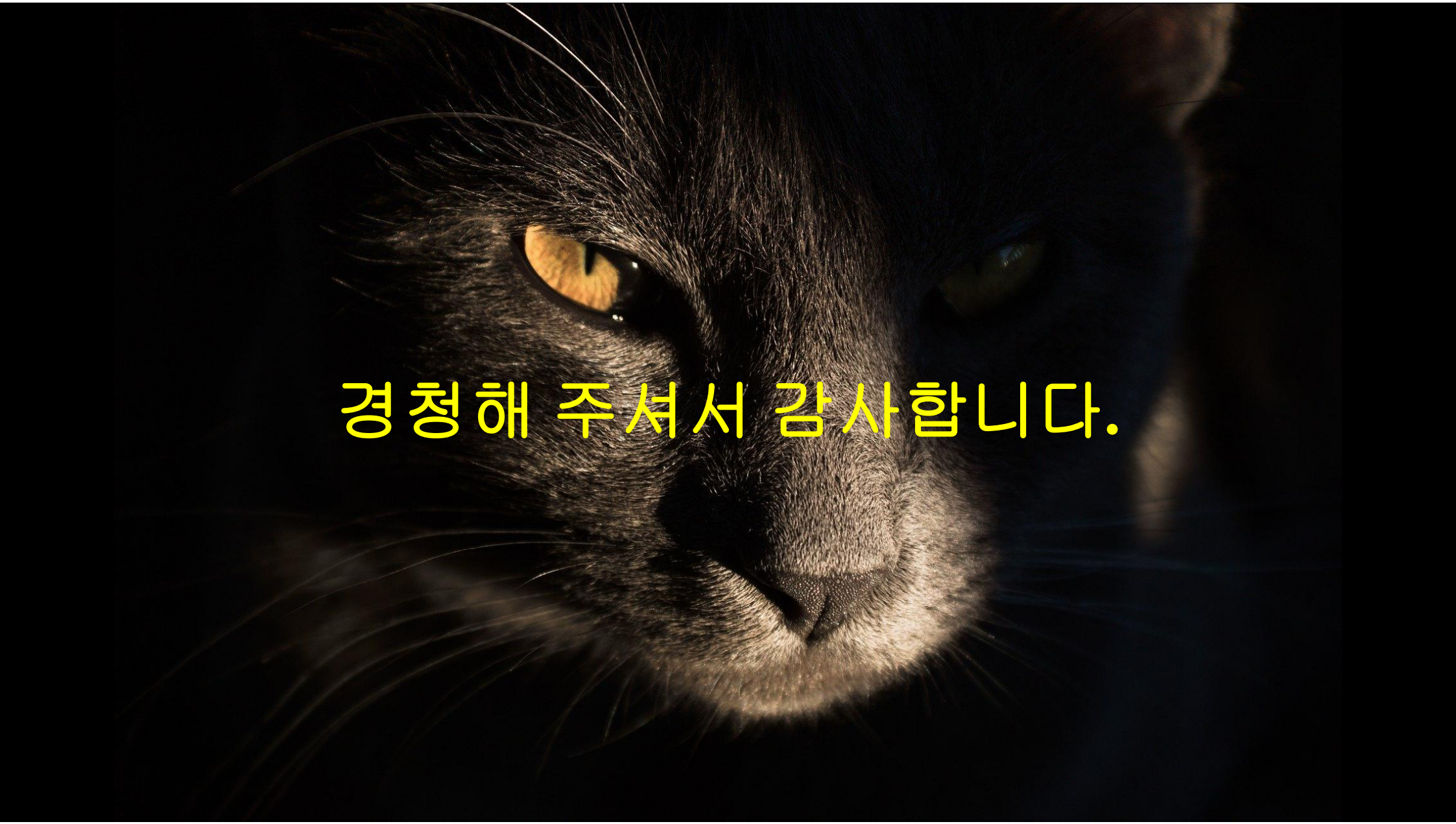
IPF를 제외하고 만성적으로 섬유화가 진행되는 ILD **PPF**



PPF의 진단기준

증상 | 폐기능 | HRCT

- IPF가 아니면서, 다음 중 2가지 이상
① **증상의 악화**
② **FVC ≥5% 이상 감소/1년 또는 DLco ≥10% 이상 감소/1년**
③ **영상소견상 진행**


경청해 주셔서 감사합니다.