

Is Combined Pulmonary Fibrosis and Emphysema (CPFE) a Distinct Entity?

Pro

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- CPFE, current
 - Definitions
 - Etiologies
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- CPFE, future
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CPFE, the current

- **Emphysema** is relatively common in ever-smokers with **fILDs**.

Cottin V, et al. Selman M, Inoue Y et al. Am J Respir Crit Care Med Vol 206, Iss 4, pp e7–e41, Aug 15, 2022

76세 남자
Smoking+ Ex
ANA-, ANCA-



Frequency Estimates of CPFE

Population

Reported Frequency (%)

General population	Unknown
Idiopathic pulmonary fibrosis	8–67
Idiopathic interstitial pneumonia	26–54
Lung cancer, with underlying idiopathic interstitial pneumonia or idiopathic pulmonary fibrosis	55–58
Rheumatoid arthritis–interstitial lung disease	8–58
Systemic sclerosis–interstitial lung disease	5–12
Lung cancer	3–10
Lung cancer screening cohort	0.04
Cohort undergoing chest computed tomography	3–7

CPFE, the current

- **Emphysema** is relatively common in ever-smokers with **fILDs**.
- Designated combined pulmonary fibrosis and emphysema (CPFE).

Eur Respir J 2005;26:586–593, Chest2009;136:1–2

- **CPFE** is characterized by the presence of emphysema and interstitial fibrosis, with a **wide variety** of appearances on chest HRCT



Imaging features of CPFE vary in both fILD and emphysema



Definitions Used by Studies

Definition for CPFE	Number of Studies
No clear definition	3
Definitions using radiologic features only	
Definition proposed by Cottin <i>et al.</i> (1) as outlined below:	52
i) Diffuse parenchymal lung disease with significant pulmonary fibrosis, defined as all of the following:	
• Reticulation with peripheral and basal predominance	
• Honeycombing	
• Architectural distortion	
• Minimal ground glass and/or consolidation	
ii) Areas of decreased attenuation with thin (<1 mm) or no walls that are upper-zone predominant	
Minimum disease extent for fibrosis or emphysema required	10
Presence of any fibrosis and emphysema that is different than criteria by Cottin <i>et al.</i>	22
Definitions using a combination of domains	
Clinical ILD diagnosis + emphysema on imaging	5
Clinical abnormalities (e.g., crackles on auscultation, abnormal gas exchange) + fibrosis and emphysema on imaging	2
Airflow obstruction confirmed by spirometry + fibrosis on imaging	2

CPFE, the current

- **Emphysema** is relatively common with **fILDs**.
- Designated combined pulmonary fibrosis and emphysema(**CPFE**).
- The **lack** of consensus over definitions and diagnostic criteria has limited CPFE research.
- **Poorly** understood
- The clinical **significance**
 - Concerns in drugs for fILD including IPF (antifibrotics), COPD (bronchodilators)
 - Prognosis

CPFE, the current

- **No** consensus exists on whether CPFE is a **syndrome** or a **distinct entity**

*Syndrome:

a cluster of clinical and radiologic manifestations with **clinically** relevant implications and/or major **pathogenetic** significance

*Distinct disease

a single biologically (clinical & pathologic) **unique entity** distinct from both IPF and emphysema

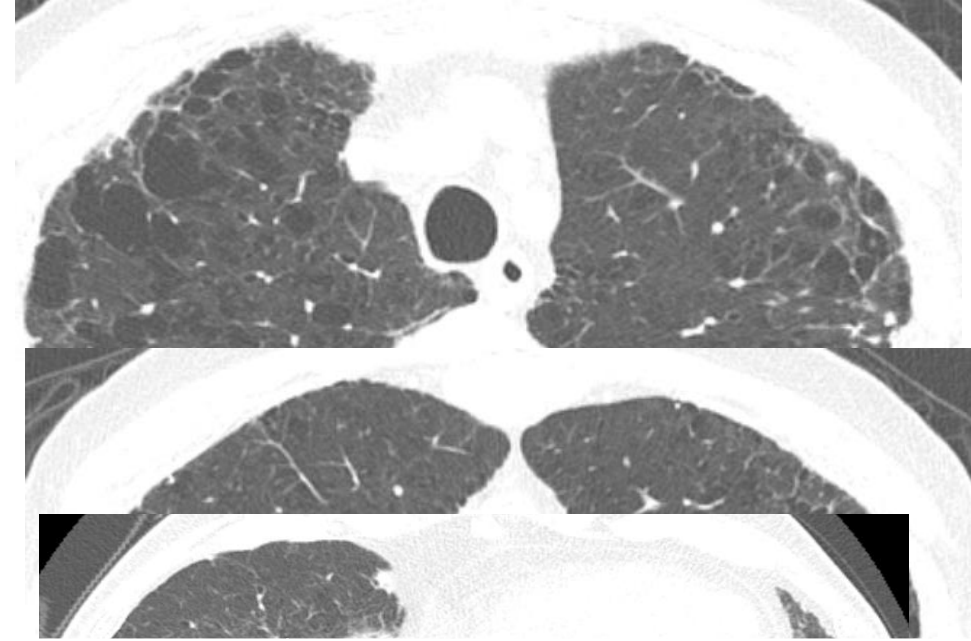
fILD+Emphysema

CPFE a syndrome or a disease

• Fasting plasma glucose (≥ 5.6 mmol/L, or ≥ 100 mg/dL).

78세 남자

- DOE MMRC II,
- 60갑년, EX, 섬유공장운영
- ANA-, ANCA-



	FEV ₁ /FVC	FVC, L	% pred	FEV ₁ , L	% pred	DLCO
2020.03	70	93	3.52	101	2.47	50
2020.09	71	109	4.05	118	2.88	70
2021.02	70	108	4.05	117	2.82	66
2021.08	72	101	3.77	113	2.72	56
2022.10	73	102	3.77	119	2.77	63
2023.04	75	100	3.68	118	2.75	55 ₁₁

Exposures and Etiologies assoc

Variables Associated with CPFE

Risk factors and demographics

Cigarette smoking
Male sex

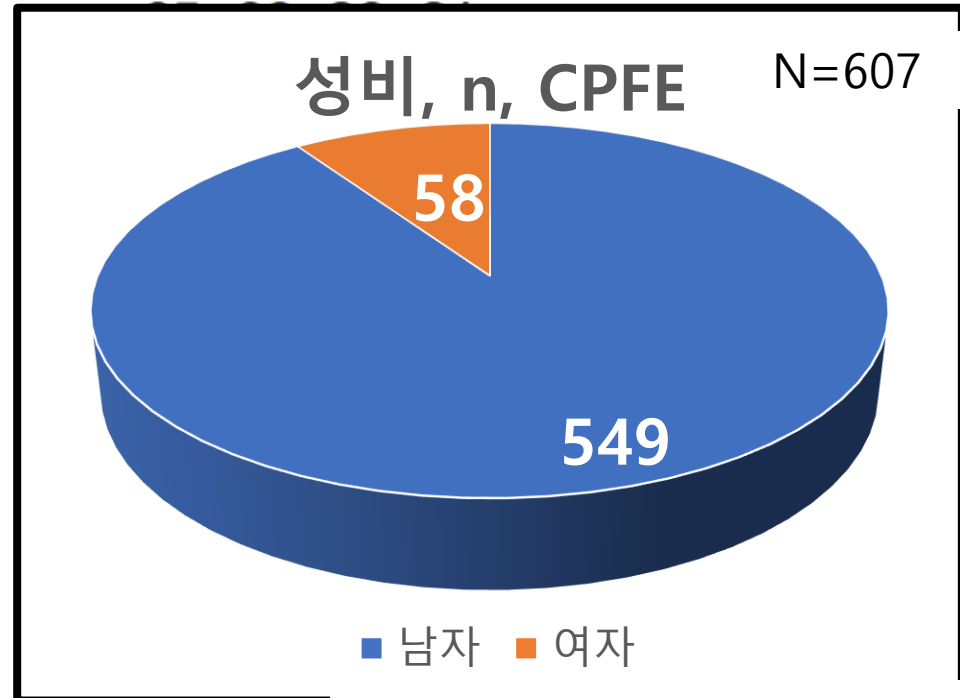
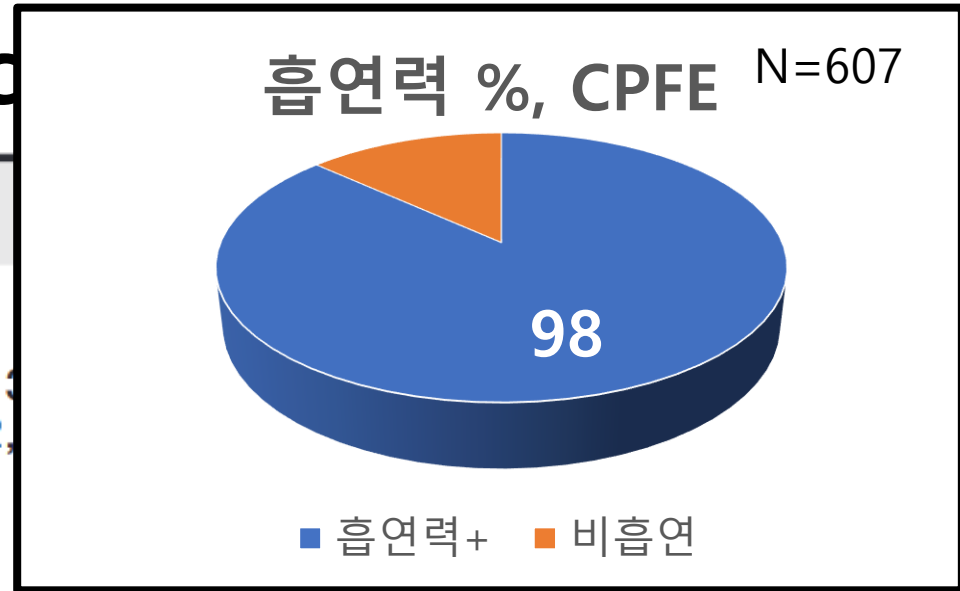
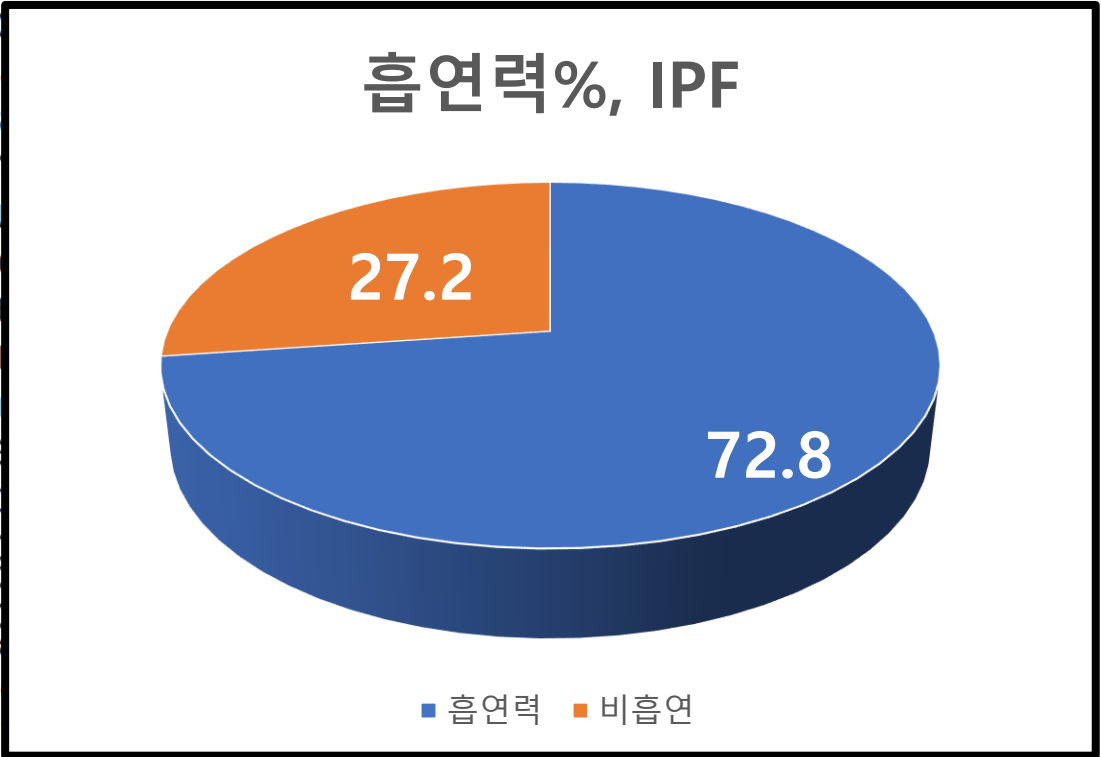
98%

73%~100%

24, 5
1, 32,

Diseases

- Idiopathic pulmonary fibrosis
- Connective tissue disease
- ANCA-associated
- Hypersensitivity pneumonitis
- Inhalation injury
- Coal dust
- Asbestos
- Silica and other inorganic dusts
- Rare genetic
- Telomerase
- Surfactant protein
- Other genetic
- Genetic polymorphisms
- MMP-9
- AGER
- rs2736



CHEST 2012; 141(1):222-231

Exposures and Etiologies associated with CPFE

Variables Associated with CPFE

Risk factors and demographics

Cigarette smoking

Male sex

Diseases

Idiopathic pulmonary fibrosis

Connective tissue disease

ANCA-associated vasculitis

Hypersensitivity pneumonitis

in nonsmokers,

Inhalational exposure

Coal dusts

Asbestos

Silica and mineral dust

Other inhalational exposures

Rare genetic variants

Telomerase-related genes (*TERT*, *RTEL1*)

Surfactant-related genes (*SFTPC*, *ABCA3*)

Other genes (*Naf1*, *PEPD*)

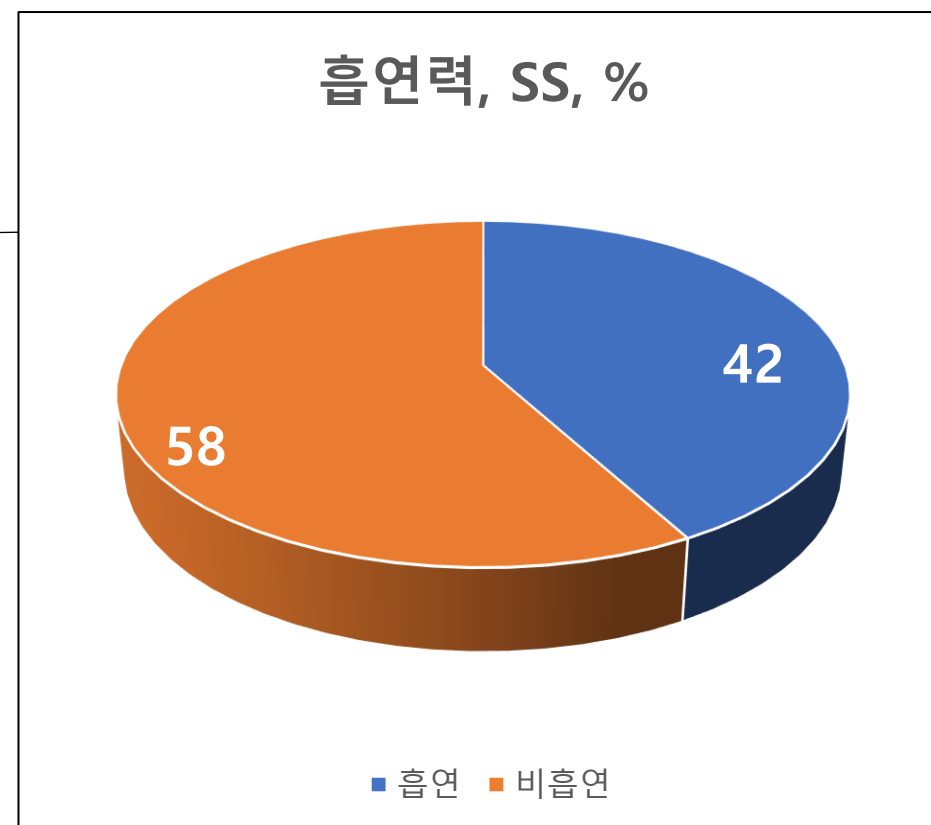
Genetic polymorphisms

MMP-9 and *TGF-β-1* genes

AGER gene

rs2736100 (*TERT*), rs2076295 GG (*DSP*)

References

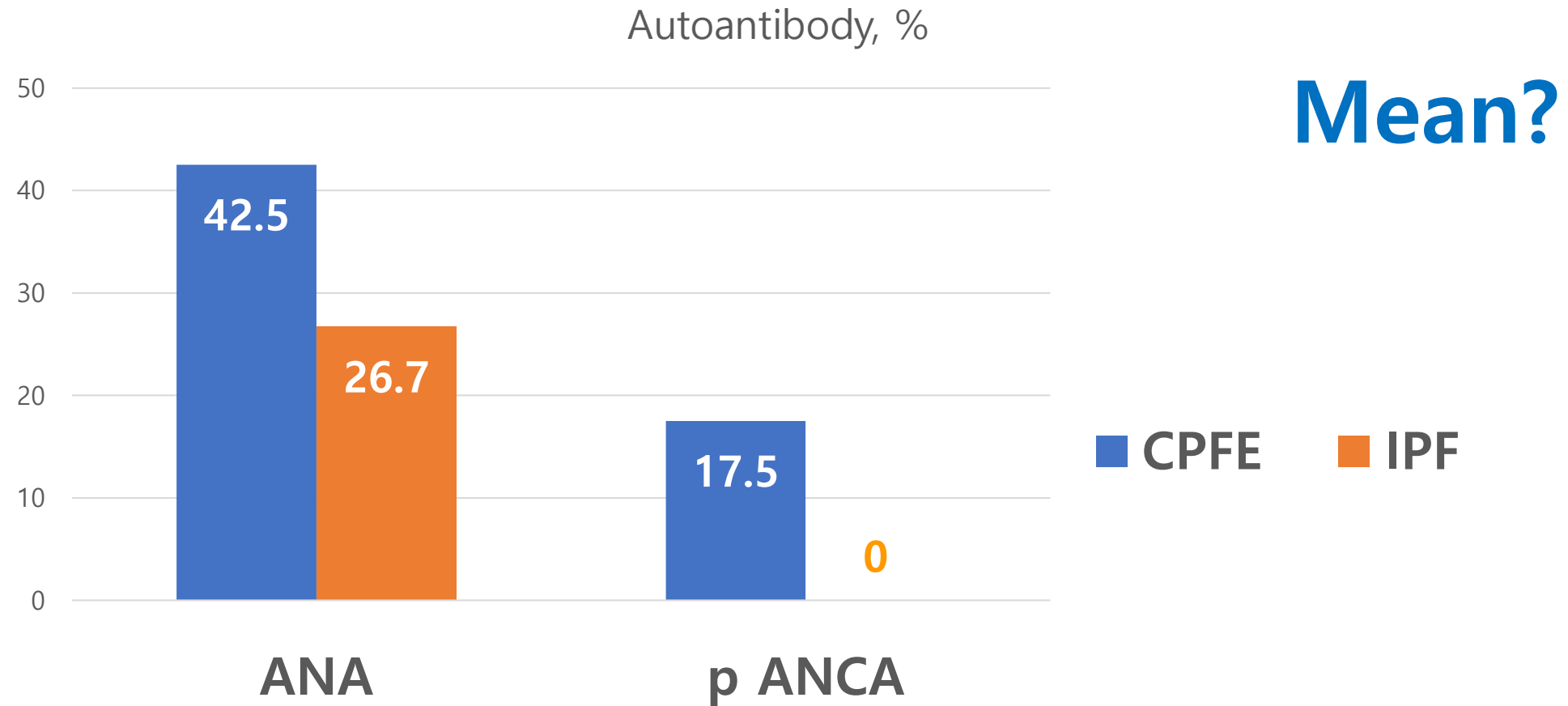


101–103

104

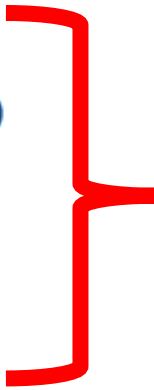
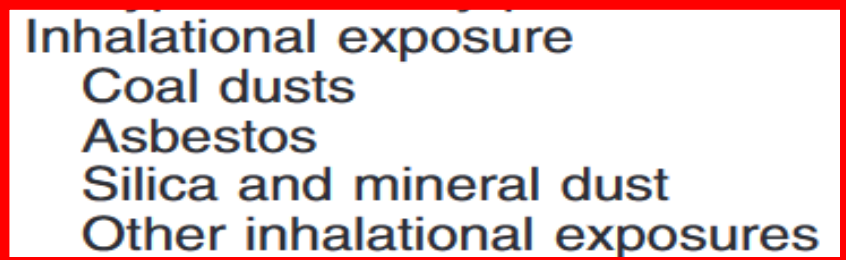
105

Autoantibodies in patients with CPFE



Exposures and Etiologies associated with CPFE

Variables Associated with CPFE	References
Risk factors and demographics	
Cigarette smoking	24, 32, 34, 38, 43, 45, 50, 54–58
Male sex	1, 32, 38, 43, 45, 46, 55–57, 60, 61
Diseases	
Idiopathic pulmonary fibrosis	24–33
Connective tissue disease	49–52, 62, 64, 79
ANCA-associated vasculitis	65, 66, 80, 81
Hypersensitivity pneumonitis	47, 78, 82, 83
Inhalational exposure	
Coal dusts	46, 70, 71
Asbestos	74–77
Silica and mineral dust	84
Other inhalational exposures	72, 73, 85–87
Rare genetic variants	
Telomerase-related genes (<i>TERT</i> , <i>RTEL1</i>)	88–92
Surfactant-related genes (<i>SFTPC</i> , <i>ABCA3</i>)	93–98
Other genes (<i>Naf1</i> , <i>PEPD</i>)	
Genetic polymorphisms	
<i>MMP-9</i> and <i>TGF-β-1</i> genes	101–103
<i>AGER</i> gene	104
rs2736100 (<i>TERT</i>), rs2076295 GG (<i>DSP</i>)	105



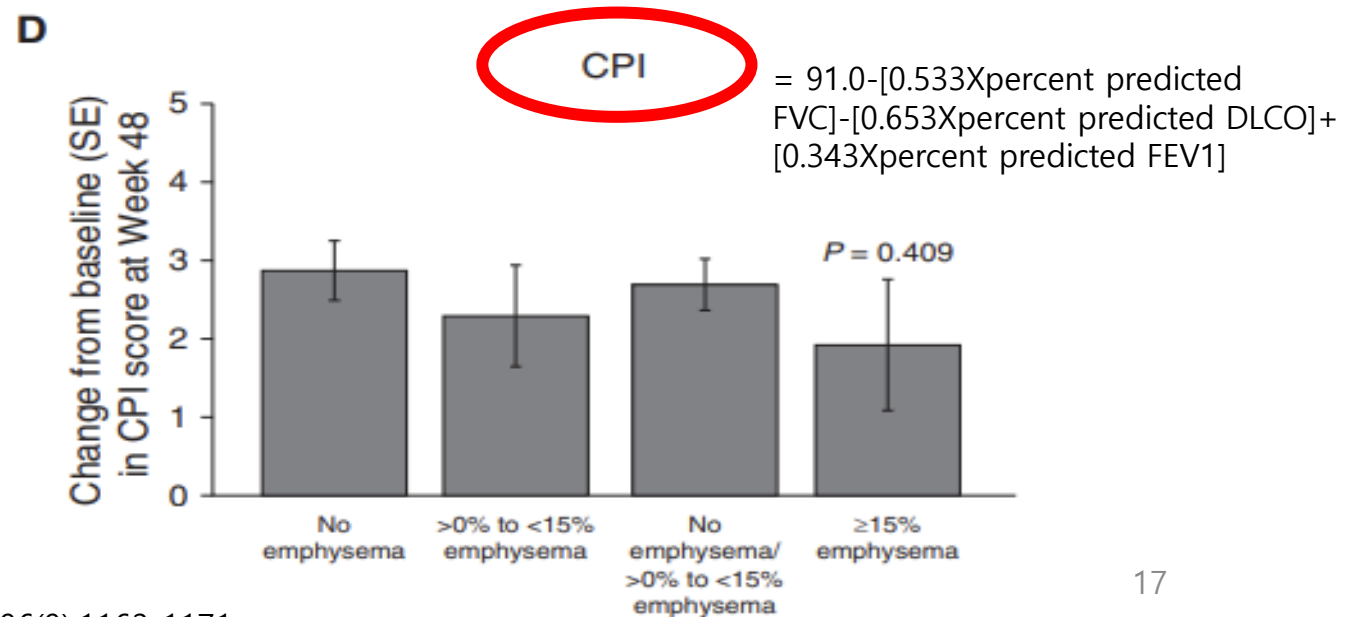
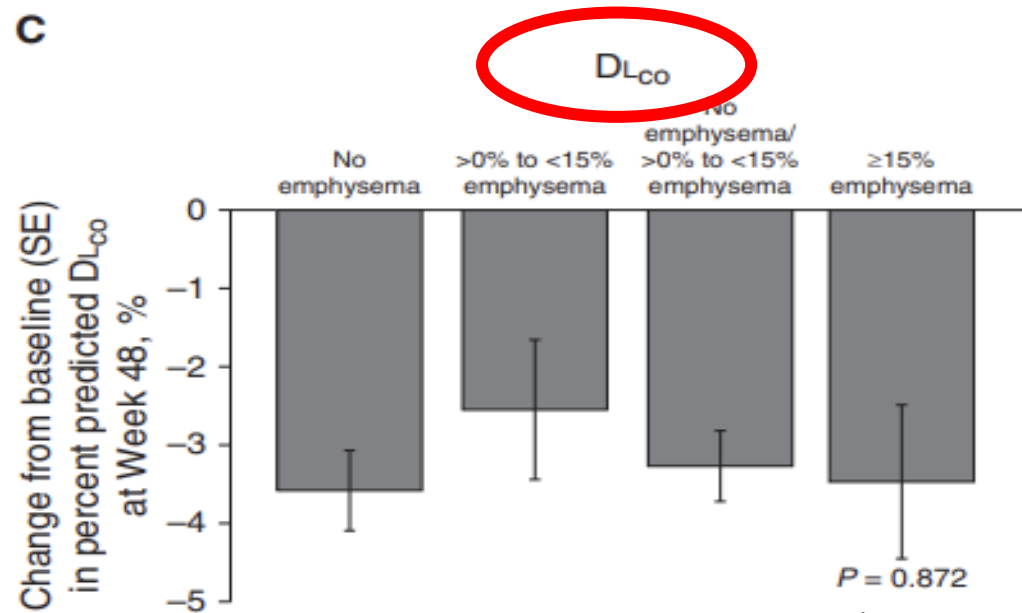
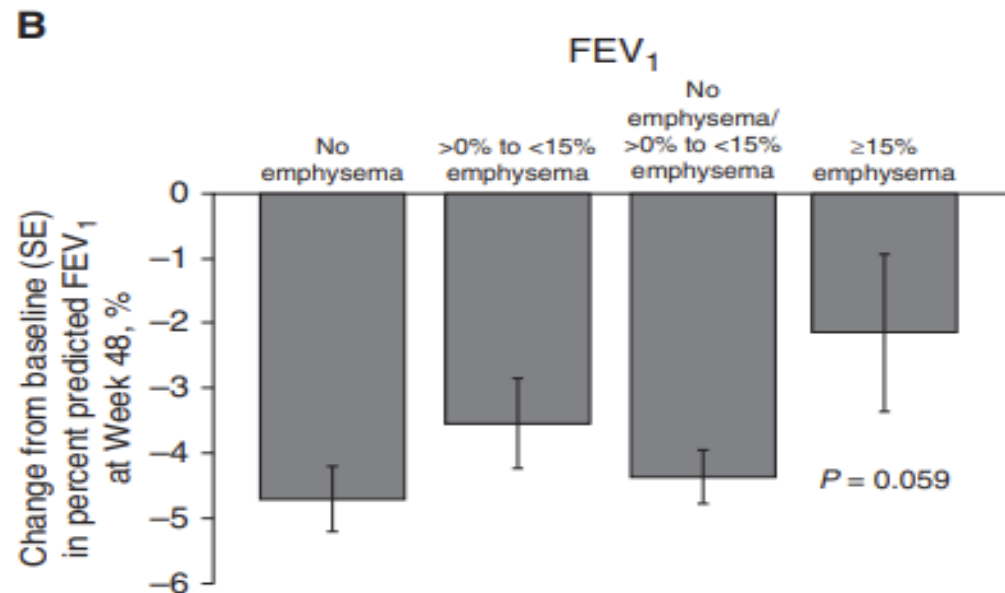
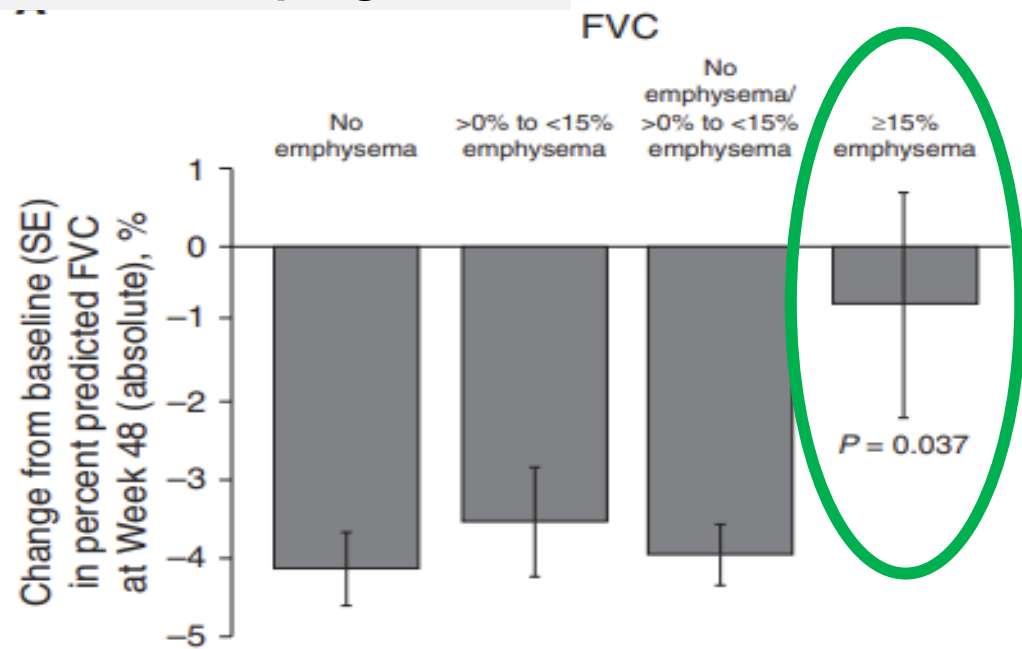
not well understood

Main Characteristics of Pulmonary Function of CPFE

Underdiagnosis of chronic lung disease

Pulmonary Function Test Measurement	Typical Abnormality Seen in CPFE	Typical Abnormality Seen in fILD without Emphysema
FVC	Decreased or <u>normal</u> (but preserved compared with idiopathic pulmonary fibrosis alone)	Decreased
FEV ₁	Decreased or normal	Decreased
FEV ₁ /FVC	Variable (<u>normal, decreased</u> , or increased)	Normal or increased
TLC	Variable (normal, decreased, or increased)	Decreased
FRC	Variable (normal, decreased, or <u>increased</u>)	Decreased
Residual volume	Variable (normal, decreased, or <u>increased</u>)	Decreased
DL _{CO}	Disproportionately decreased	Decreased
Transfer coefficient for carbon monoxide	Severely decreased	Normal or decreased
Saturation during exercise	Severe desaturation	Desaturation
Peak oxygen uptake	Decreased	Decreased

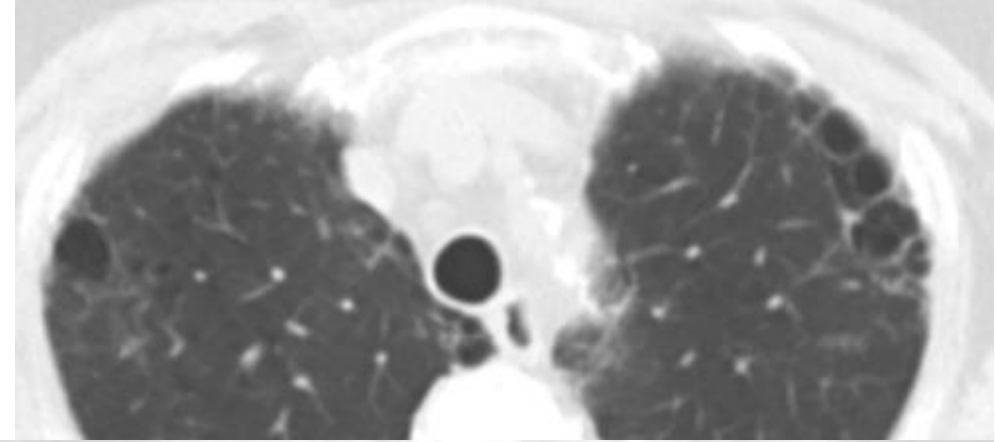
Marker of CPFE progression



75세, 여자

RF+, ANA+ 1:80
Smoking+ Ex.

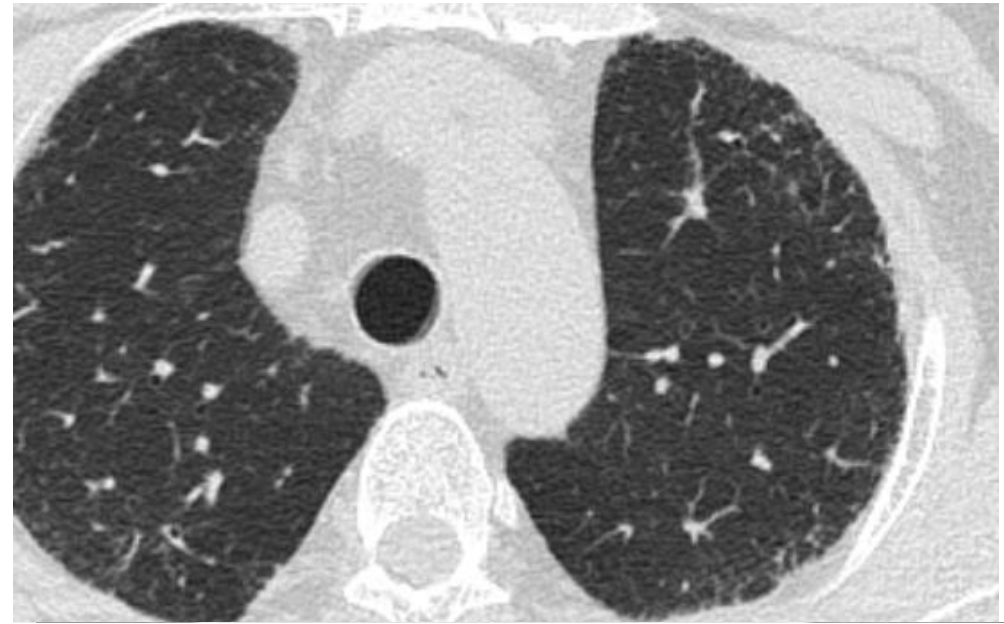
	FEV ₁ /FVC	FVC, L	% pred	FEV ₁ , L	% pred	DLCO
2022.06	83	69	1.73	82	1.44	54
2022.09	86	60	1.49	73	1.28	54



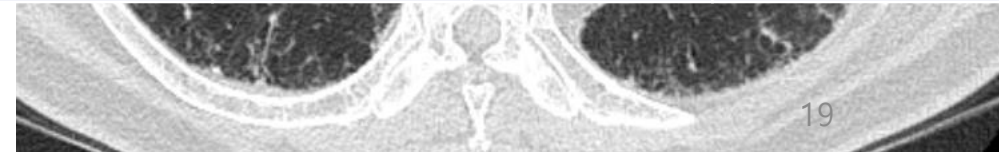
60세 남자

- Never smoker
- 지하철 지하 사무실 근무
- ANA-, ANCA-

pfNSIP



	DOE	FEV ₁ /FVC	FVC, L	% pred	FEV ₁ , L	% pred	DLCO
2021.08 LAMALABA 처방	III	80	42	2.12	44	1.70	50
2021.09	II	83	49	2.47	54	2.06	57
2022.03		80	50	2.50	52	1.99	60
2022.10		78	53	2.65	55	2.08	59



65세 남자

- Smoking+, current 90pyrs
- ANA+1:40, ANCA-



	DOE	FEV ₁ /FVC	FVC, L	% pred	FEV ₁ , L	% pred	DLCO
2020.12 LAMALABA처방	III	69	86	3.56	79	2.44	72
2021.10	I~II	71	87	3.58	82	2.54	61
2022.06		73	83	3.40	82	2.49	61

CPFE, monitoring

- CPFE should be monitored using a combination of **clinical**, **imaging**, and **multiple functional** parameters, with less emphasis on FVC trends than in the monitoring of ILD without concurrent emphysema

CPFE, Imaging Features

- 68세 남자
- Lower UIP
- Upper centrilobular emphysema
- Smoking+ ex

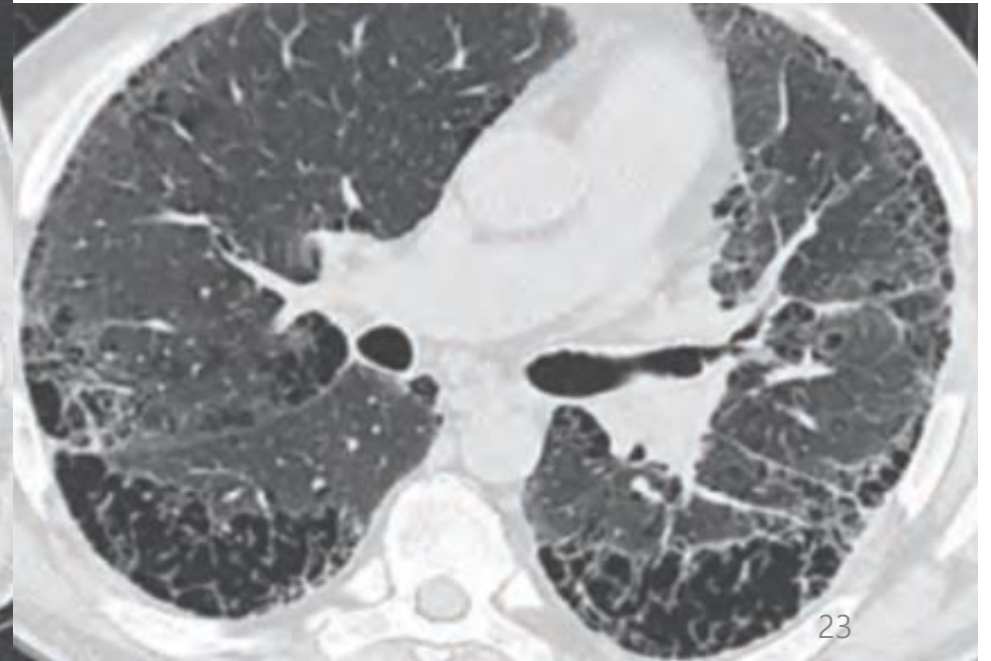
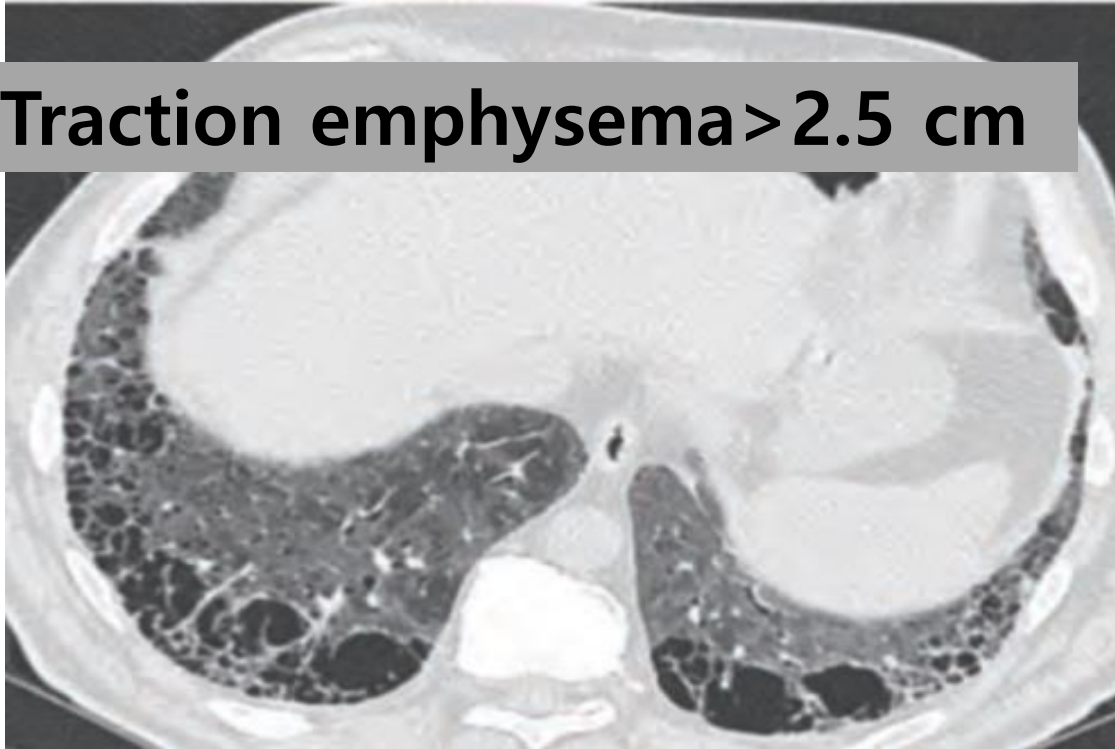
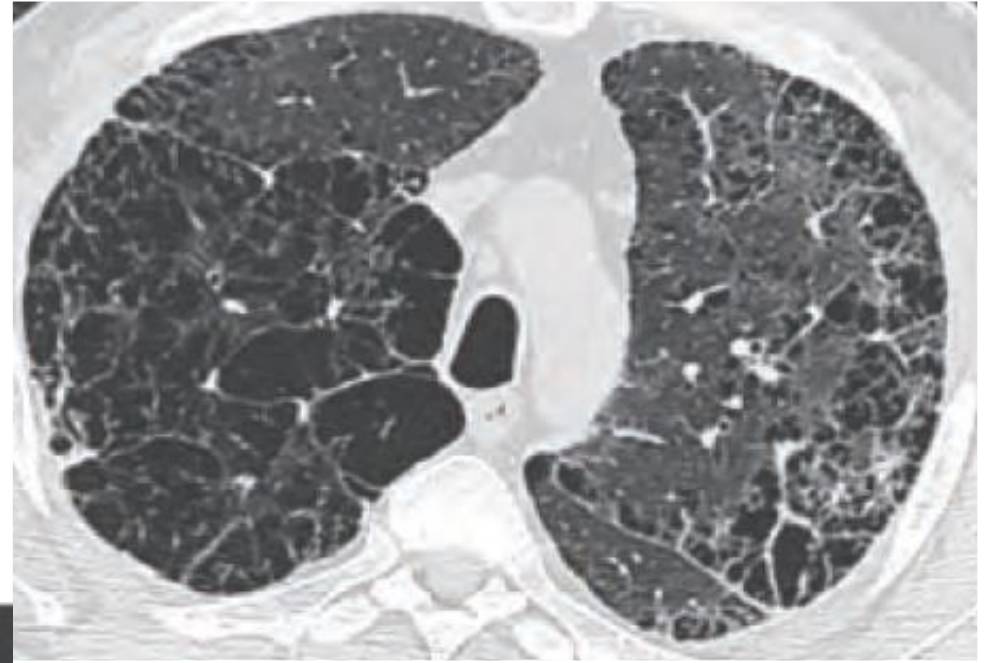
CPFE?
-Extent
-Quantification

	FEV ₁ /FVC	FVC, L	% pred	FEV ₁ , L	% pred	DLCO
2021.02	71	98	4.15	100	2.94	63
2021.07	66	95	4.02	91	2.65	52
2022.01	68	101	4.25	99	2.88	65
2022.07	64	92	3.87	86	2.49	66

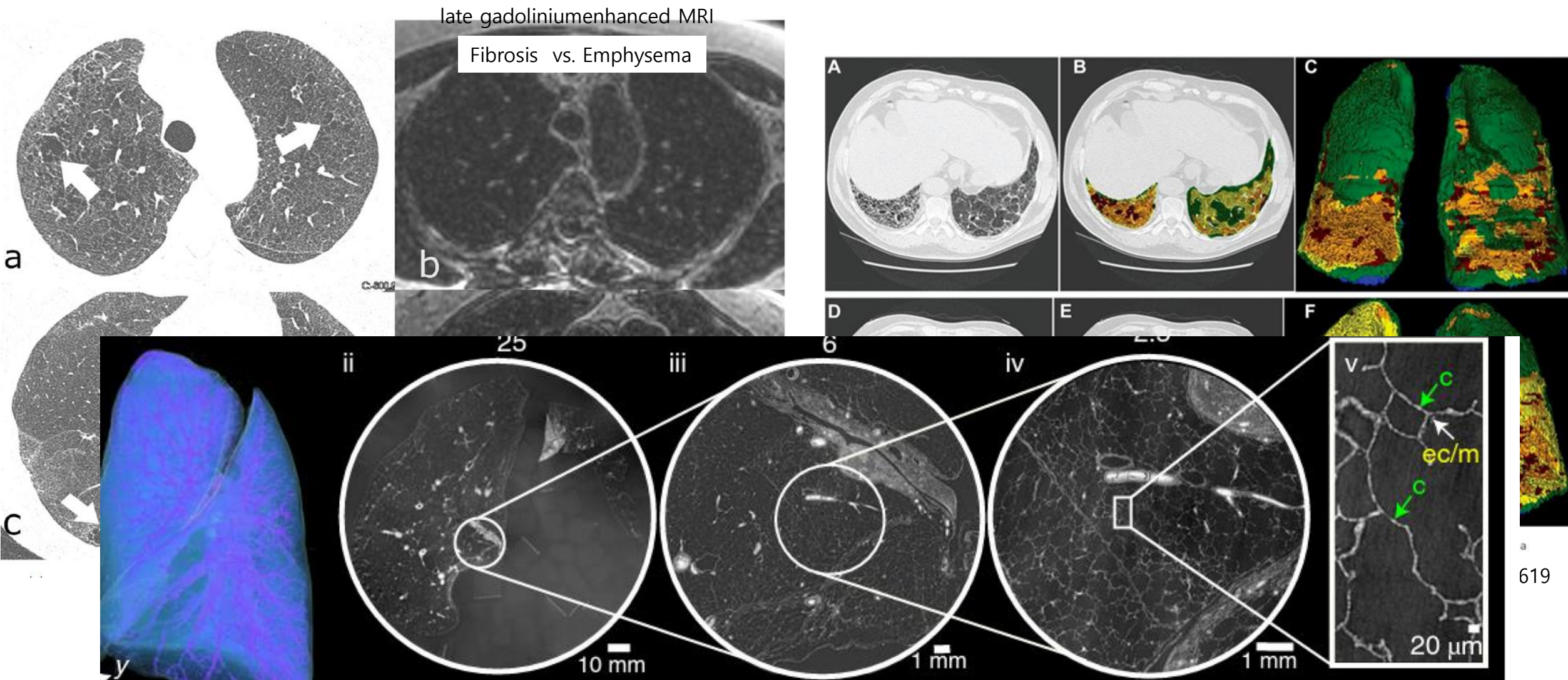
CPFE, Imaging Features

조직병리학적 정의의 부족

Traction emphysema > 2.5 cm



Distinguish IPF from CPFE



Hierarchical phase-contrast tomography (HiP-CT)

CPFE, Pathology Features

- **No criteria** for establishing a diagnosis of CPFE on the basis of histopathological findings alone.

Pattern of Fibrosis

SRIF (5, 23)

DIP (180)

UIP, probable UIP (144, 180)

F-NSIP (180)

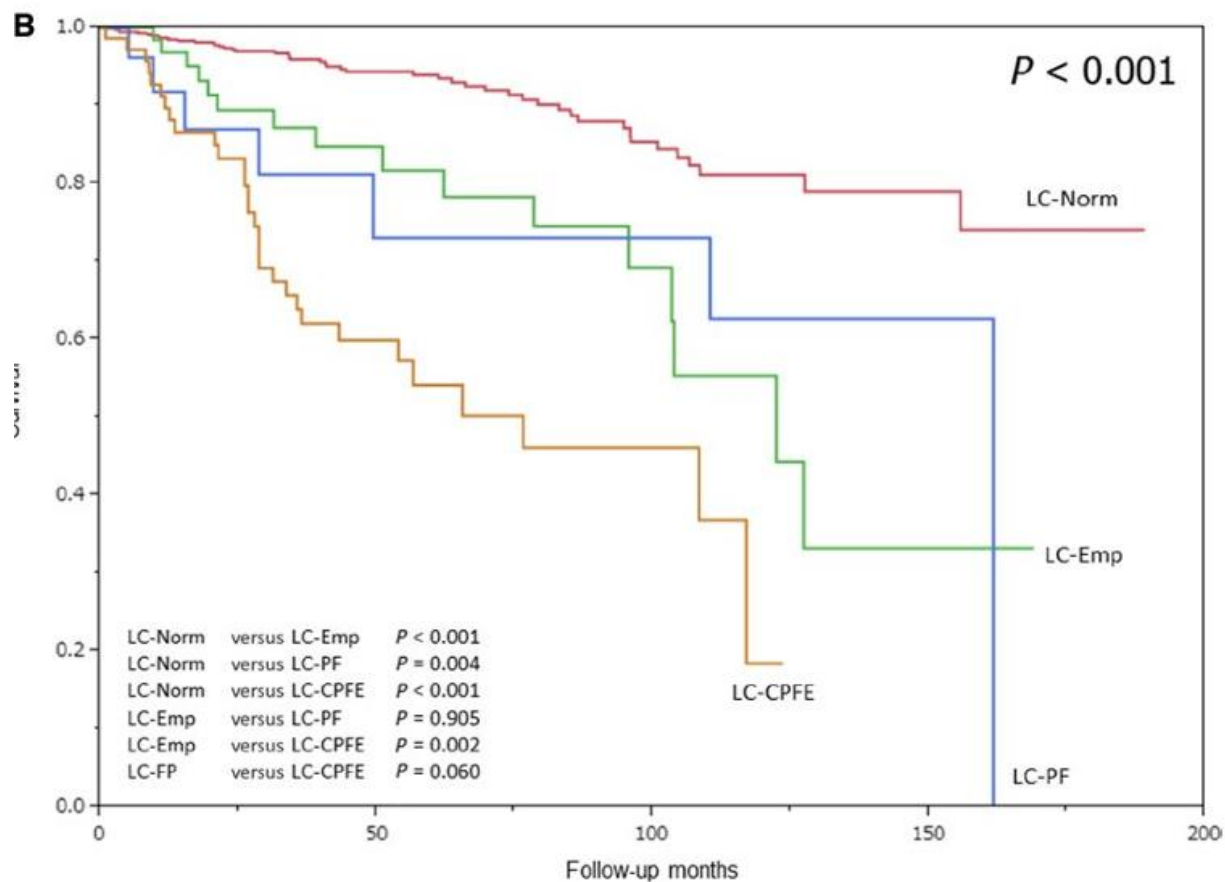
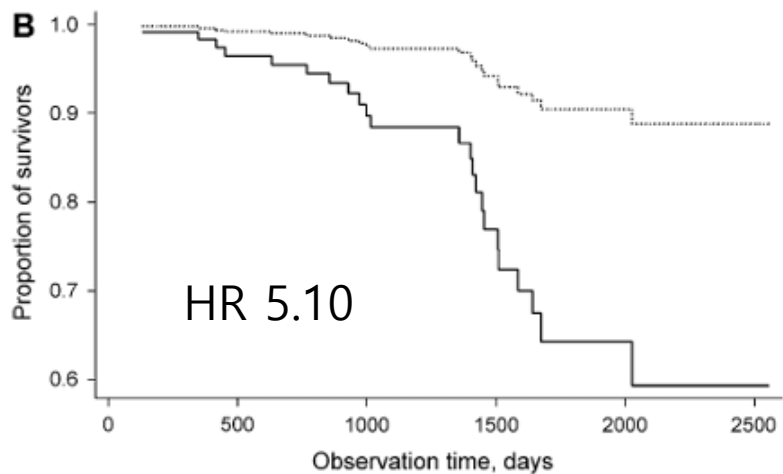
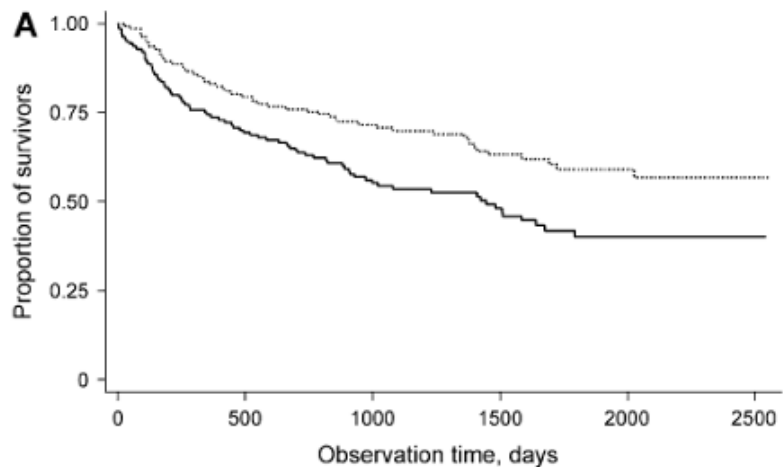
Indeterminate (180, 184)

CPFE, Comorbidity

- **PH** 15~55% severe than IPF or COPD
- **Lung Ca.** 2-52%, OR 2.37 than IPF

His. subtype	ADC	779	19	760	<0.001
	SqCC	152	46	106	
	SmCC	6	1	5	

CPFE, Mortality



Proposed definitions

“CPFE–IPF,” or “CPFE–radiologic UIP,” or
“CPFE–histologic NSIP,” or “CPFE–radiologic SRIF”) or
the underlying disease when known (e.g., “CPFE–fHP” or “CPFE–RA”)

- Lung fibrosis of any subtype¹¹

Classification criteria of CPFE *clinical syndrome*:
These additional criteria serve research
purposes and may be considered depending on
the objective of the study

Patients must have CPFE (see above) and one or more of the following:

- Emphysema extent $\geq 15\%$ of total lung volume⁵¹
- Relatively preserved lung volumes and airflow with very or disproportionately decreased D_{LCO} , especially in patients with limited extent of HRCT abnormalities, and in the absence of pulmonary hypertension
- Precapillary pulmonary hypertension considered not related to the sole presence of emphysema ($FEV_1 > 60\%$), fibrosis ($FVC > 70\%$), or the etiological context (e.g., absence of connective tissue disease)

Summary

- Current: It is reasonable that "CPFE is a syndrome"
 - Diagnosis, Management, and Researches can be definite
 - Comorbidities (PH, LC), Poor outcomes (>Fibrosis, Emphysema)
 - Cannot be monitored with FVC, FEV₁.....
- Future: Can be a disease entity?
- Management with antifibrotics and bronchodilators
- Future studies will be needed.

경청해주셔서 감사합니다.