

Post-ATS

Combined Pulmonary Fibrosis and Emphysema (CPFE): Bad and Ugly All The Same?

2019-06-15

長庚醫院 胸腔內科 林鴻銓

Lin, Horng-Chyuan

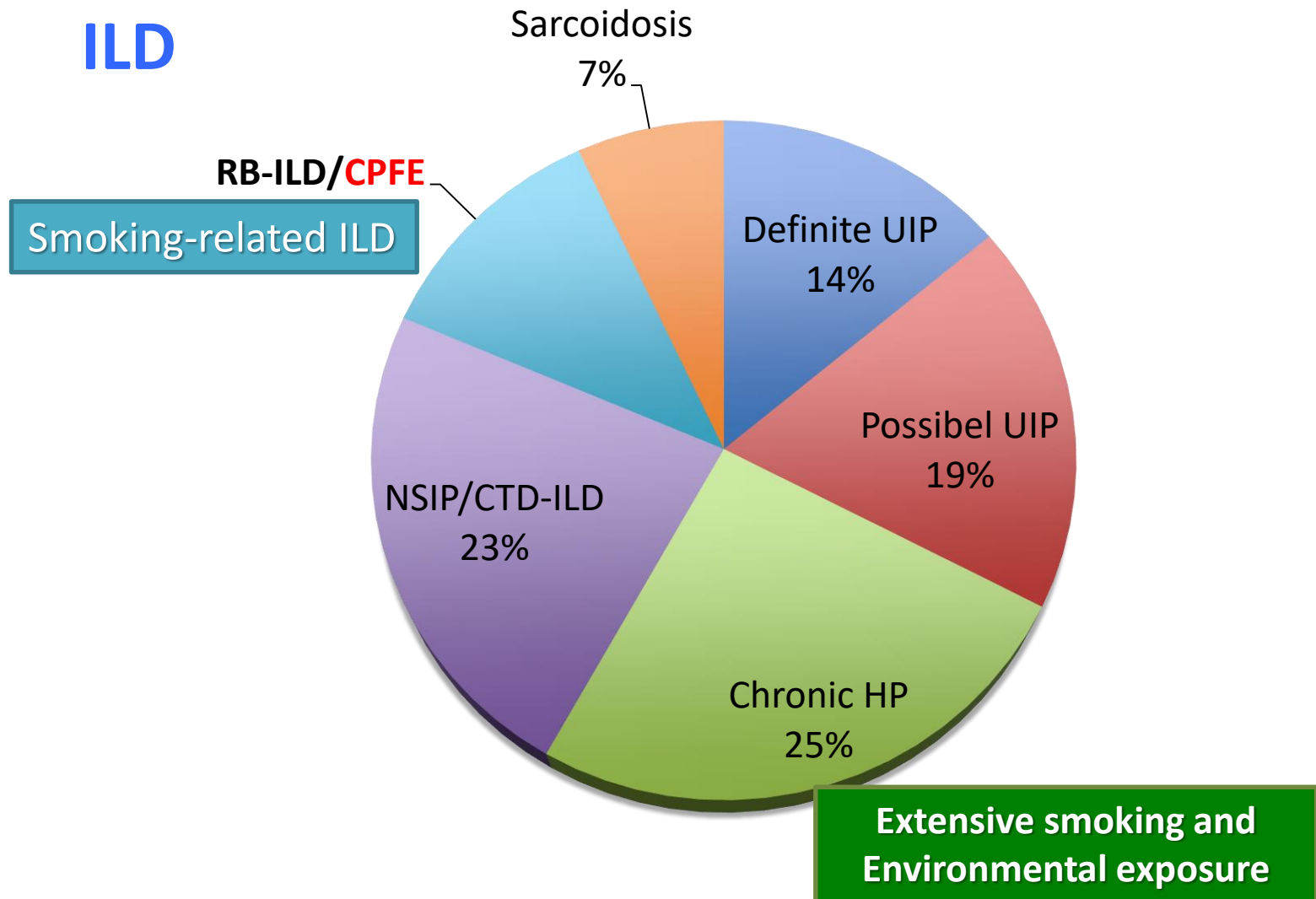
Department of Thoracic Medicine

Chang Gung Memorial Hospital

Chang Gung University, Taiwan



Interstitial Lung Disease Among US Veterans: Pilot Study of a Prospective Registry



CPFE 2005

Subnormal
spirometry



EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Heavy smoking
history

Exercise
hypoxemia

Upper lobe
emphysema and
lower lobe fibrosis

Unexpected
subnormal lung
volumes

Unexpected severe
reduction of carbon
monoxide transfer

Poor survival

Severe impairment
of gas exchange

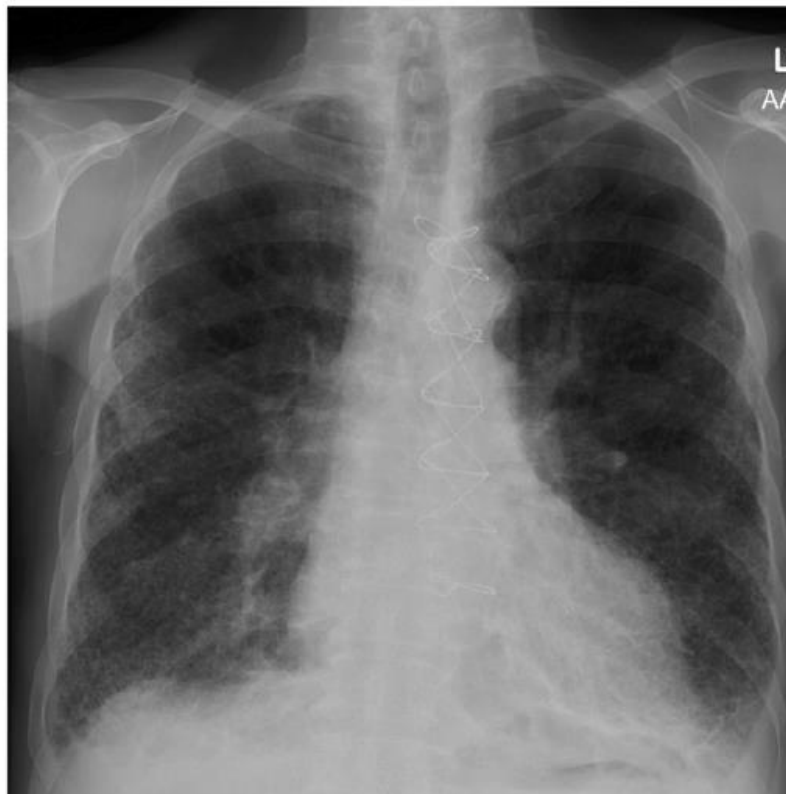
High prevalence of
pulmonary
hypertension

2005

Prof. Vincent Cottin
Head of the Department of Respiratory Medicine
University of Lyon

**Prevalence of CPFE is still
not specifically known**
Emphysema: **8~51%** in IPF
PF: **4.4~8%** in Emphysema

A



Emphysema

- Centrilobular emphysema
- Paraseptal emphysema
- Bullae

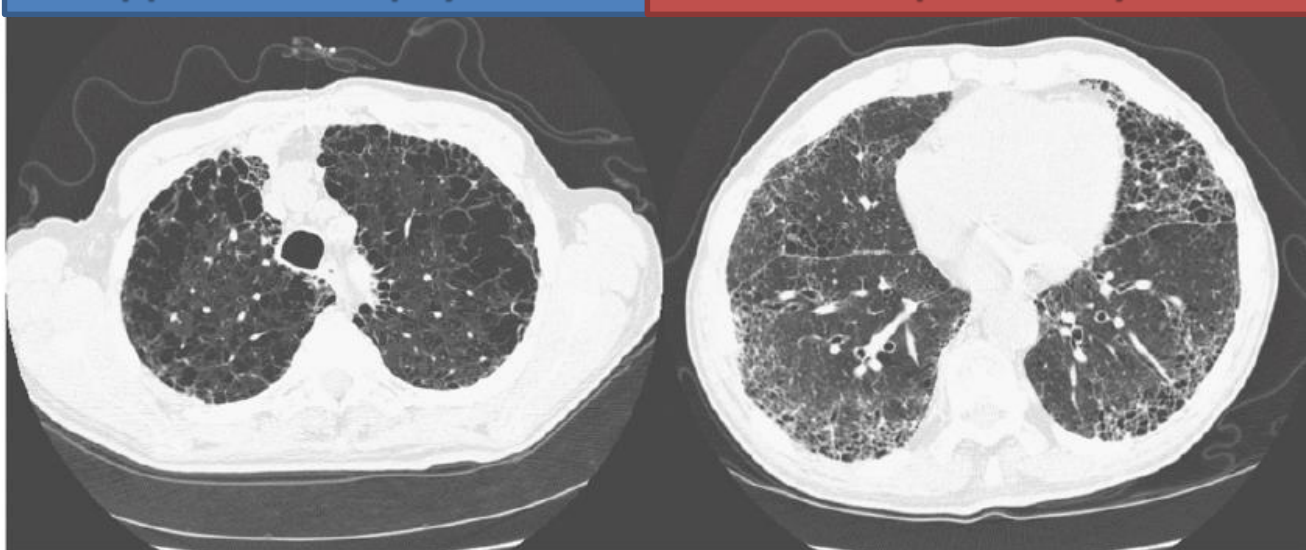
Fibrotic changes

- Honeycombing
- Reticular opacities
- Traction bronchiectasis
- Ground-glass opacities
- Architectural or bronchial distortion

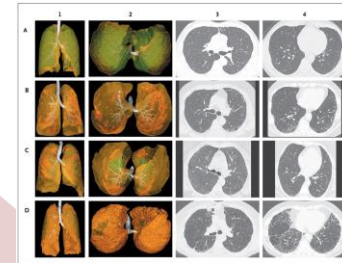
Upper-lobe emphysema

Lower-lobe pulmonary fibrosis

B



Pathogenesis



8%

N Engl J Med. 2011, 10;364(10):897-906

Cigarette smoking

Idiopathic CPFE

Genetic susceptibility

Mutations in the essential **telomerase genes** (*hTERT* or *hTR*)

Connective tissue disease (CTD)

CTD-associated CPFE

1. lower prevalence of pulmonary hypertension
2. better survival

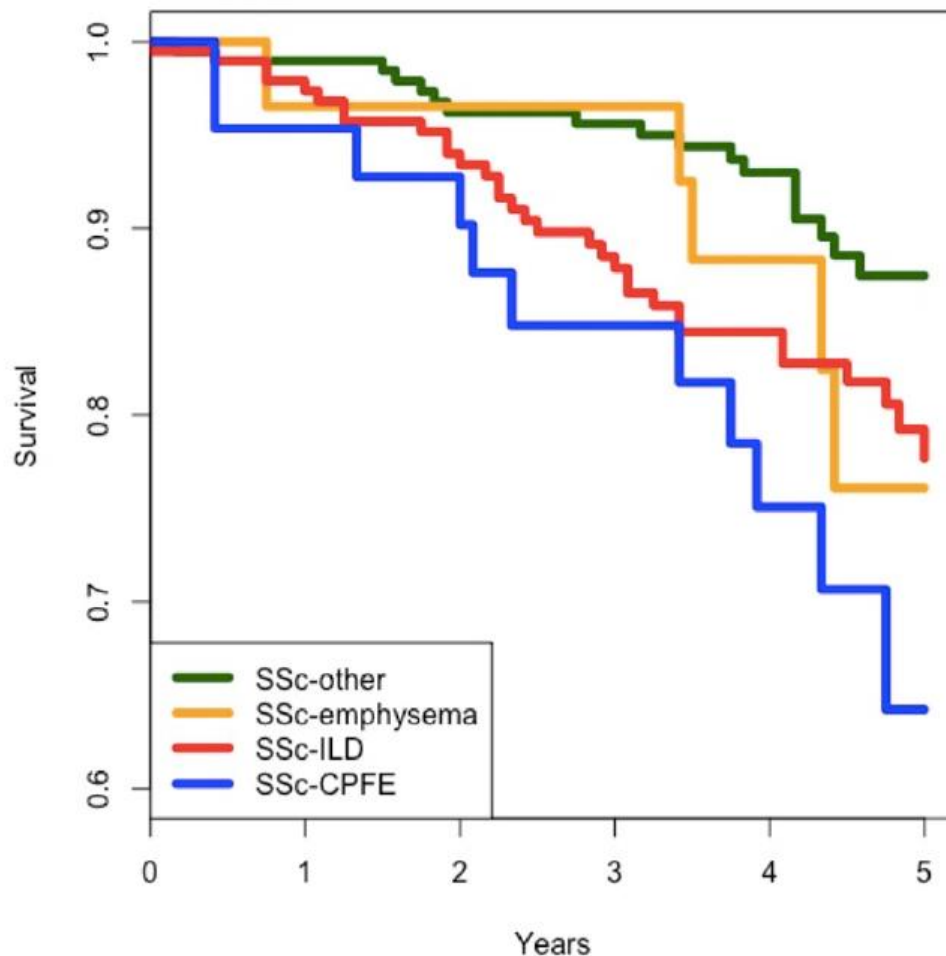
Mineral dust exposure
Agrochemical compounds
Tyre industry worker
Welder

礦物粉塵暴露
農用化學品
輪胎行業工人
焊機

Occupational exposures

J Thorac Dis 2015;7(4):767-779

CPFE Related to Systemic Sclerosis



SSc-Other	202	184	170	147	116	64
SSc-emphysema	29	28	26	25	17	8
SSc-ILD	196	180	158	133	100	50
SSc-CPFE	43	39	35	29	18	9

Complications

19.8% in CPFE+lung cancer
27.3% during surgery
20% during chemotherapy
16.7% during radiation

47-90% in CPFE
50% in COPD
31-46% in advanced IPF

Acute lung injury

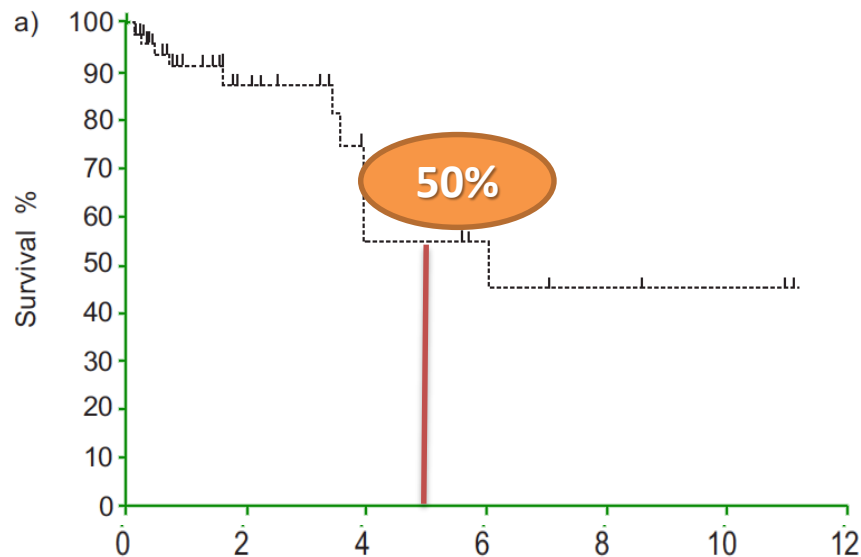
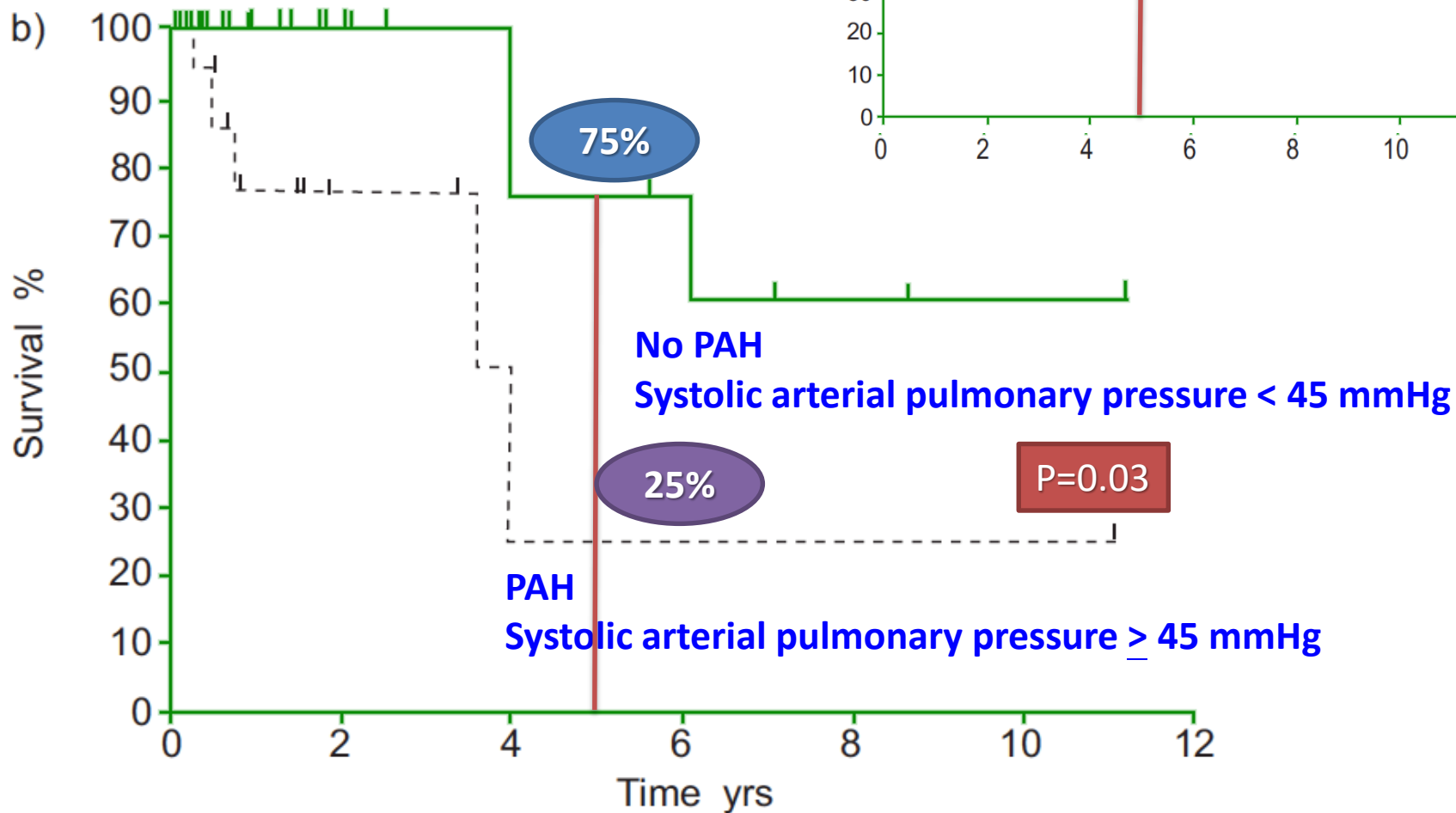
Pulmonary arterial hypertension (PAH)

The mortality rate and median survival time from onset of ALI: **75%** and **22 days**

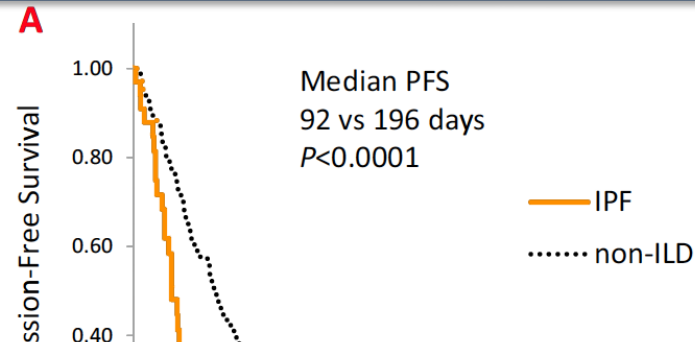
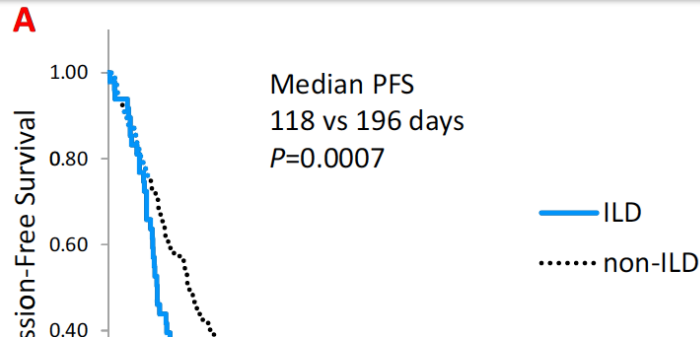
Lung cancer

35.8-46.8% in CPFE
6.8-10.8% in COPD
22.4-31.3% in IPF

CPFE with Pulmonary arterial hypertension (PAH)



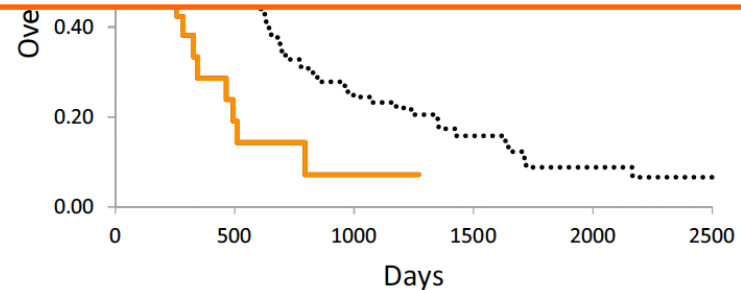
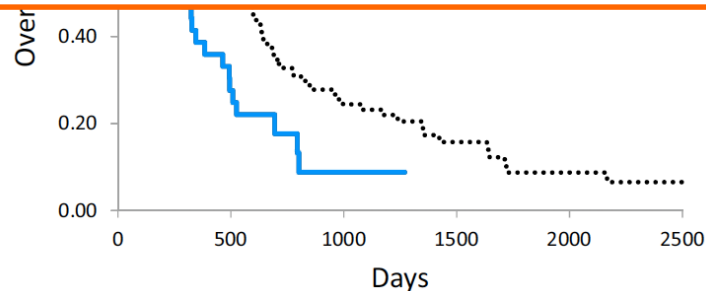
IPF and Lung Cancer



Lung cancer in IPF

1. Most commonly SQCC
2. Presents in elderly heavy smokers with a male
3. Locating in peripheral regions and the lower part of lung predominance

PLoS ONE 13(8): e0202360.2018



CPFE Syndrome and Lung Cancer

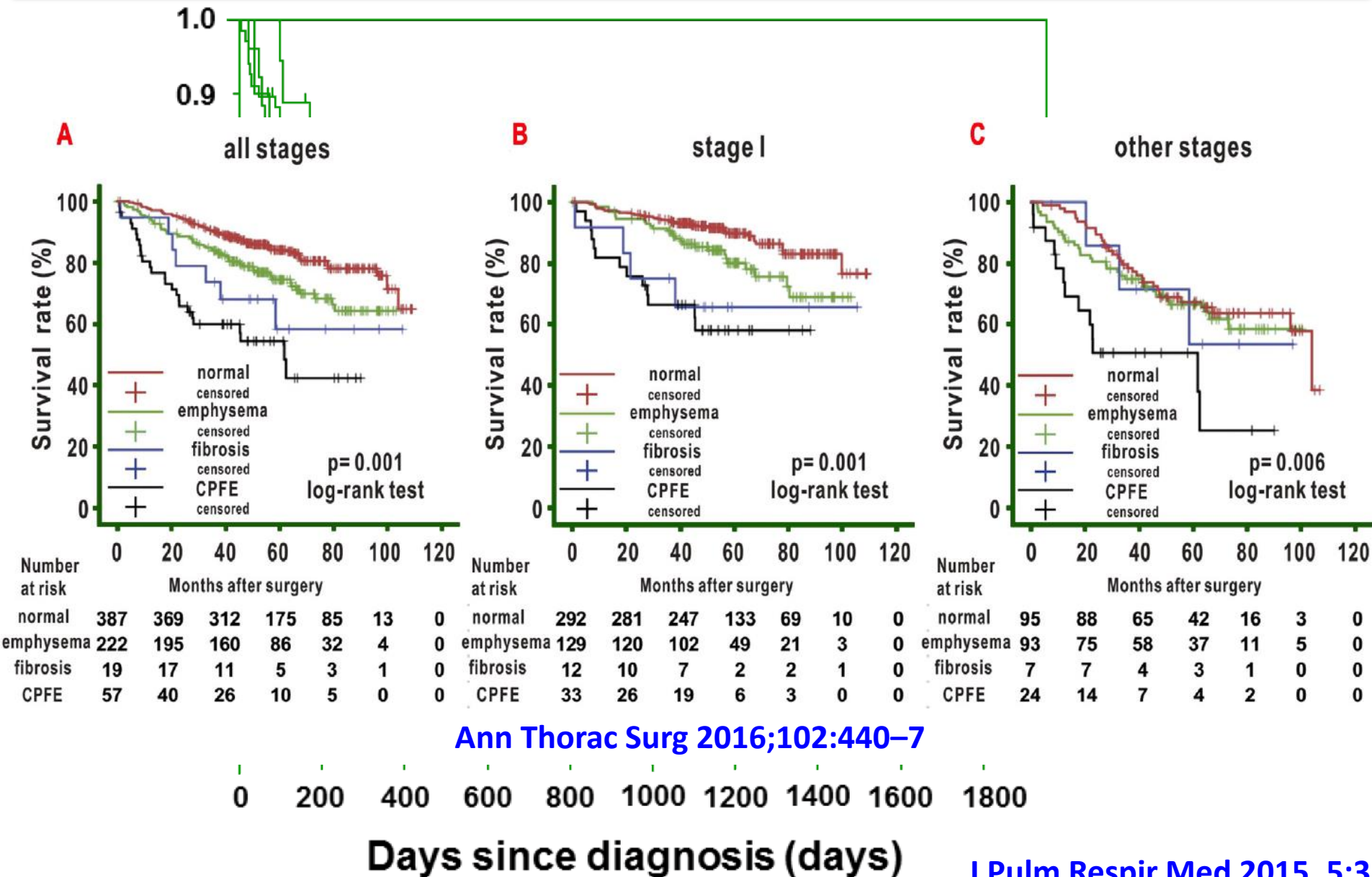
Operative Outcomes

Operative Outcomes	All Cases (n = 685)	Normal (n = 387)	Emphysema (n = 222)	Fibrosis (n = 19)	CPFE (n = 57)	p Value
Surgical procedure						0.294
Lobectomy	90.2 (618)	89.7 (347)	89.6 (199)	89.5 (17)	96.5 (55)	
Operation time, minutes	234.1 (31–873)	214.1 (31–583)	265.0 (61–873)	241.4 (116–519)	250.6 (137–505)	0.001
Blood transfusion	3.2 (22)	1.8 (7)	5.4 (12)	10.5 (2)	1.8 (1)	0.031
Postoperative outcomes						
Prolonged oxygen therapy	27.0 (185)	17.1 (66)	40.1 (89)	26.3 (5)	43.9 (25)	0.001
Complications ^a	21.0 (144)	14.7 (57)	26.6 (59)	31.6 (6)	38.6 (22)	0.001
Arrhythmia	10.1 (69)	7.5 (29)	12.2 (27)	15.8 (3)	17.5 (10)	0.043
Minitracheostomy	2.9 (20)	1.8 (7)	4.5 (10)	5.3 (1)	3.5 (2)	0.132
Reoperation ^b	2.6 (25)	2.1 (8)	4.1 (9)	10.5 (2)	10.5 (6)	0.009

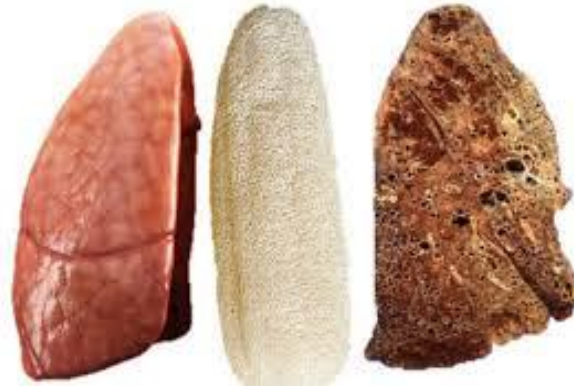
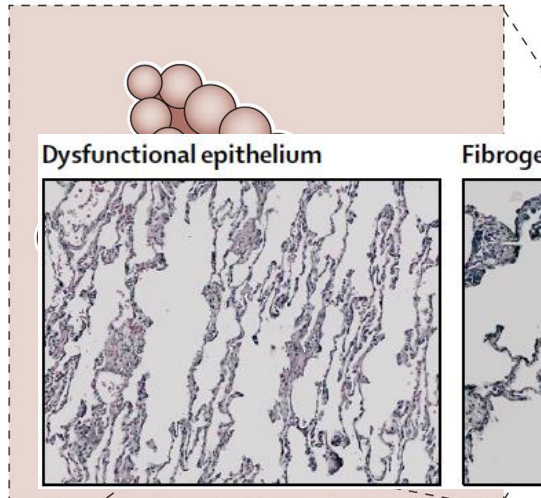
Acute Lung Injury

Case No.	Age	Sex	Procedure	pStage	TSCT Findings	Fibrosis Grade	Emphysema Grade	Onset of ALI Within 30 Days	Outcomes	Death Due to ALI	Death Due to Lung Cancer
1	76	Male	Lobectomy	I	CPFE	1	1	Yes	Dead	Yes	No
2	81	Male	Lobectomy	II	CPFE	2	1	Yes	Dead	Yes	No
3	83	Male	Lobectomy	III	CPFE	1	1	Yes	Alive	NA	NA
4	77	Male	Lobectomy	III	CPFE	2	1	No	Dead	No	Yes
5	72	Male	Lobectomy	III	CPFE	1	1	No	Dead	Yes	No
6	76	Male	Lobectomy	II	CPFE	1	1	No	Alive	NA	NA

CPFE Syndrome and Lung Cancer

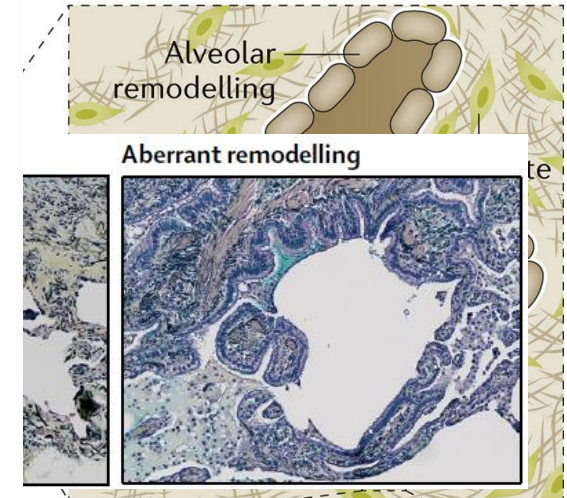


Healthy



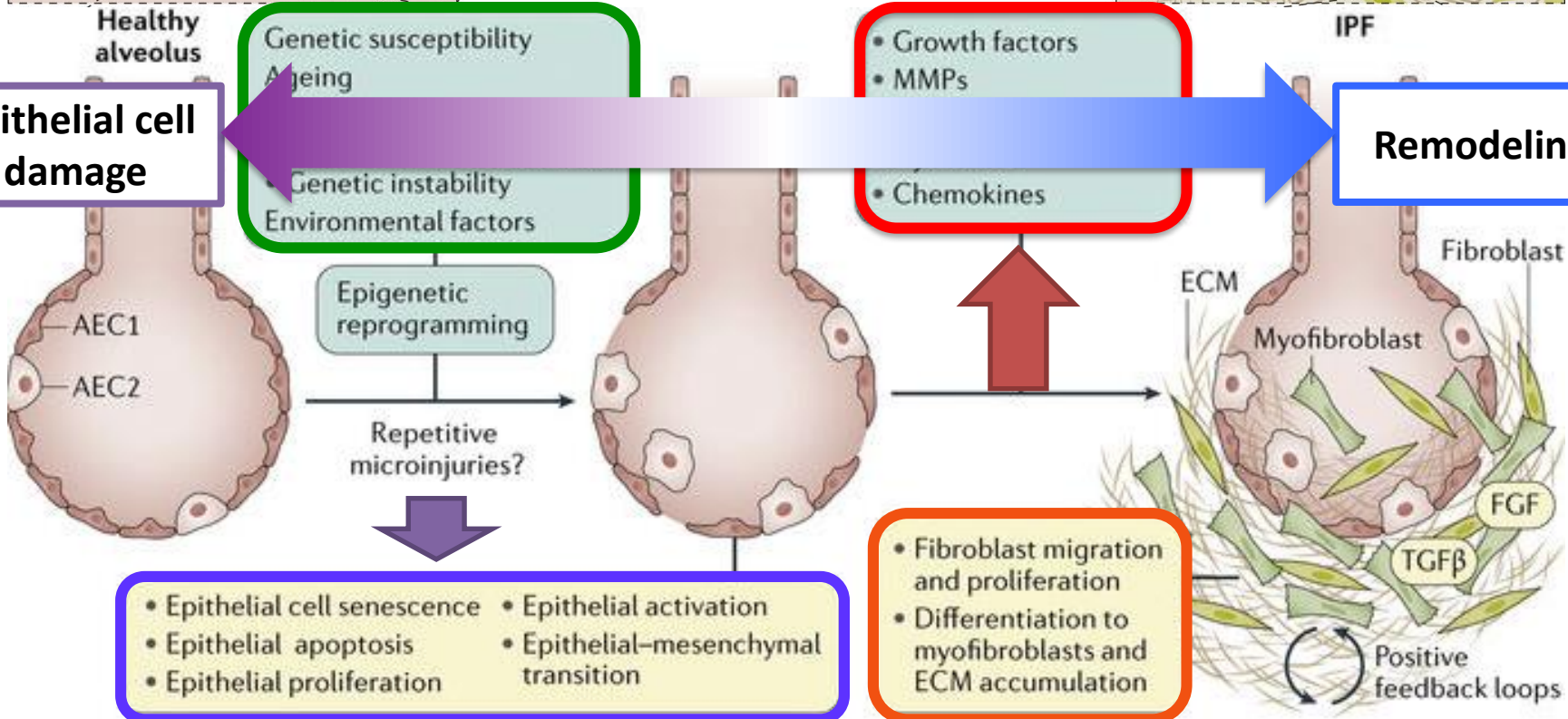
菜瓜布肺

Idiopathic pulmonary fibrosis



Epithelial cell damage

Remodeling



Radiographic characteristic

Emphysema in the upper zones and fibrosis in the bases

Progressive transition between emphysema and fibrosis

Paraseptal emphysematous lesions at the bases of the lungs within the fibrotic lesions

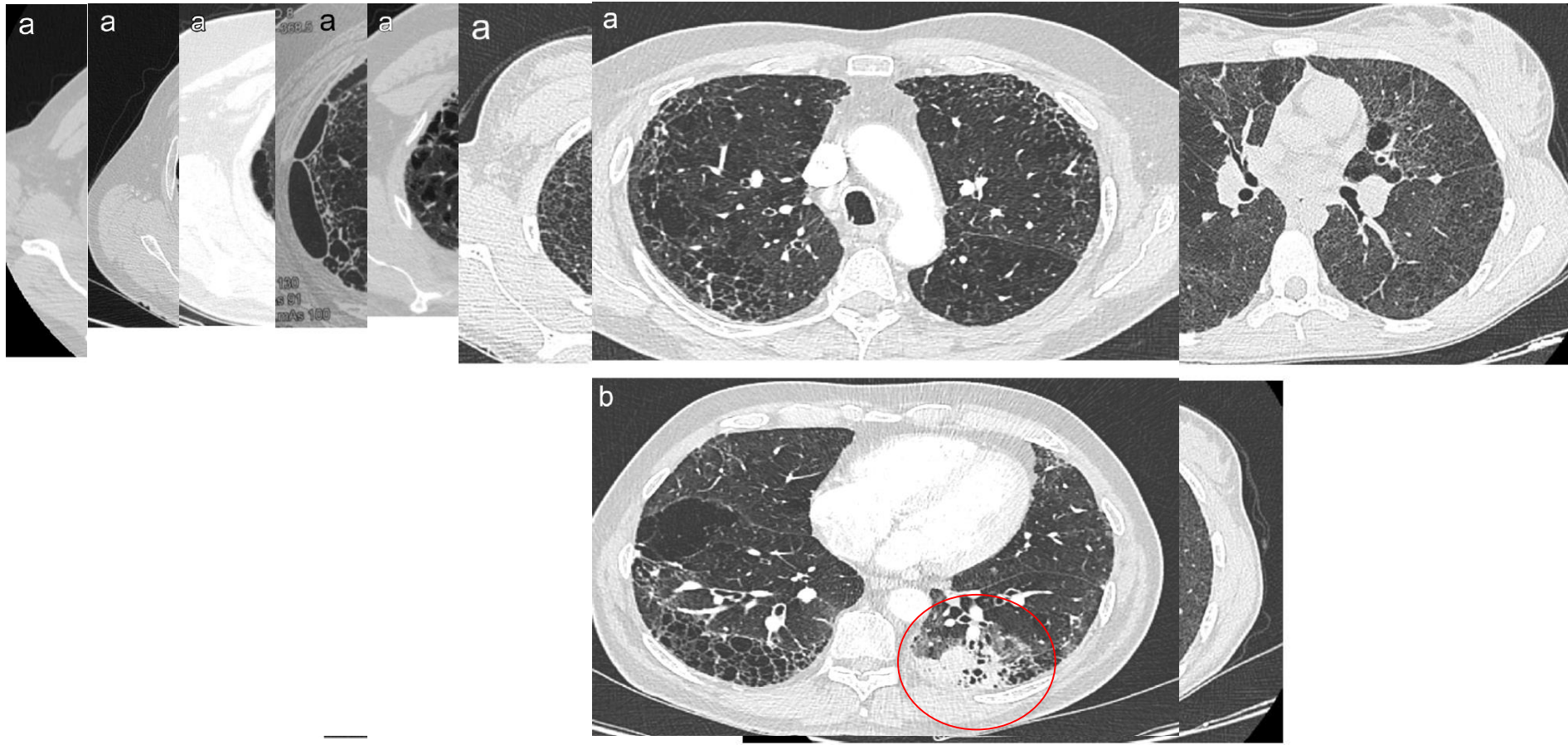
Large thick-walled cystic lesions (diameter ≥ 1 cm) delineated by a 1-mm-thick wall. These cysts can be situated either in the upper lungs just beneath the chest wall or grow within the areas of reticulation and/or honeycombing

Centrilobular nodules which correspond to airway-centered fibrosis, (i.e. fibrotic changes along the respiratory bronchioles)

Subpleural curvilinear opacities

Ground Glass opacities

Findings suggestive of pulmonary hypertension (i.e. dilatation of the central pulmonary arteries, enlargement of the right heart, reduction of peripheral branches of the pulmonary arteries and mosaic appearance of the pulmonary parenchyma)



CPFE

Radiographic characteristic

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SRIF

CPFE

Pathological findings

Diffuse form of smoking-related interstitial lung disease: Overlap of pulmonary emphysema and fibrotic interstitial pneumonia (UIP or f-NSIP)

Localized form of smoking-related interstitial lung disease: Presence of emphysema with fibrosis, air space enlargement with fibrosis, or occult fibrosis of smokers

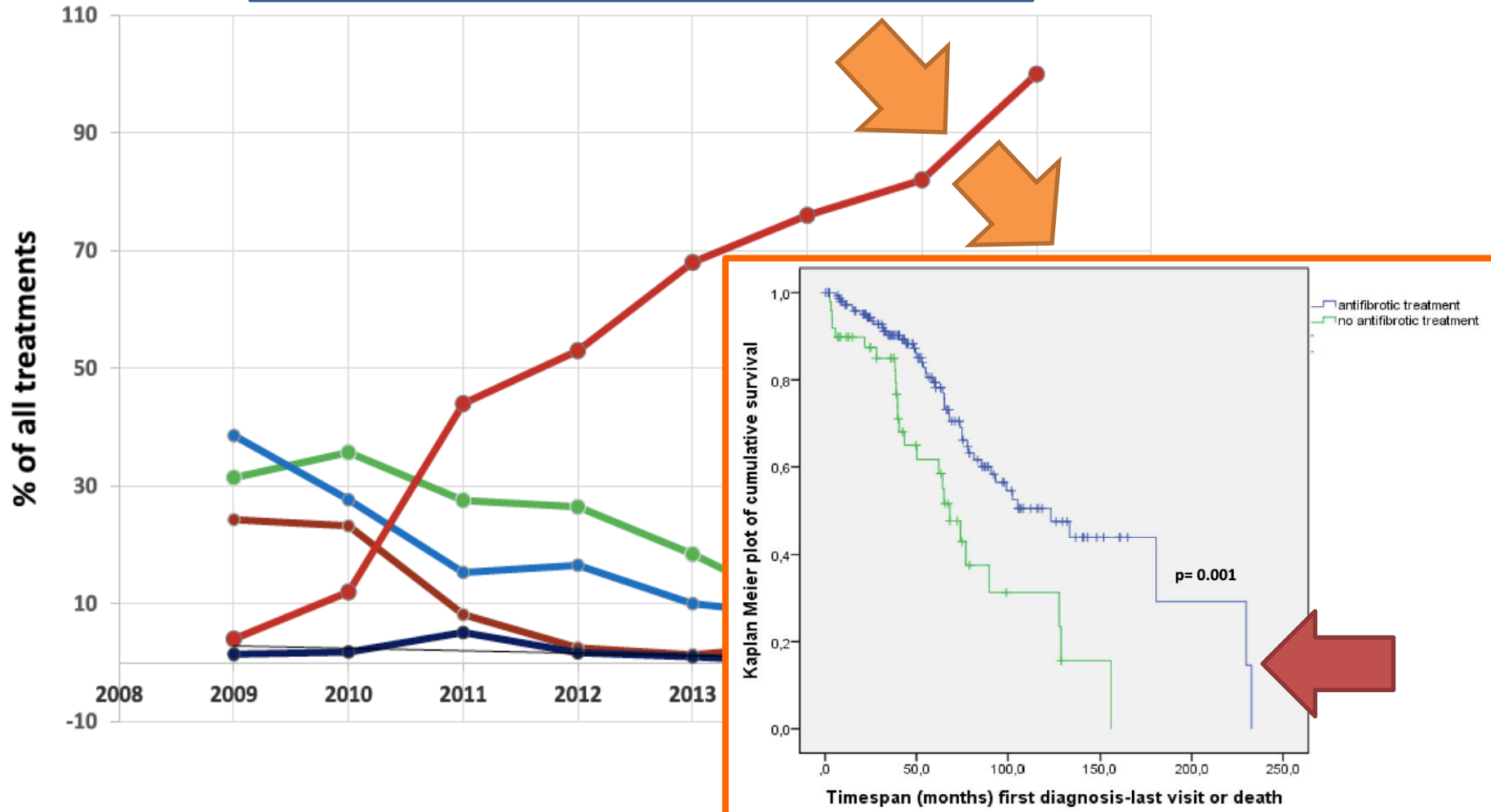
Fibrotic lesions along bronchioles around the emphysematous areas

Thick-walled cystic lesions involving one or more acini characterized by dense wall fibrosis, and occasional fibroblastic foci, surrounded by honeycombing and normal alveoli

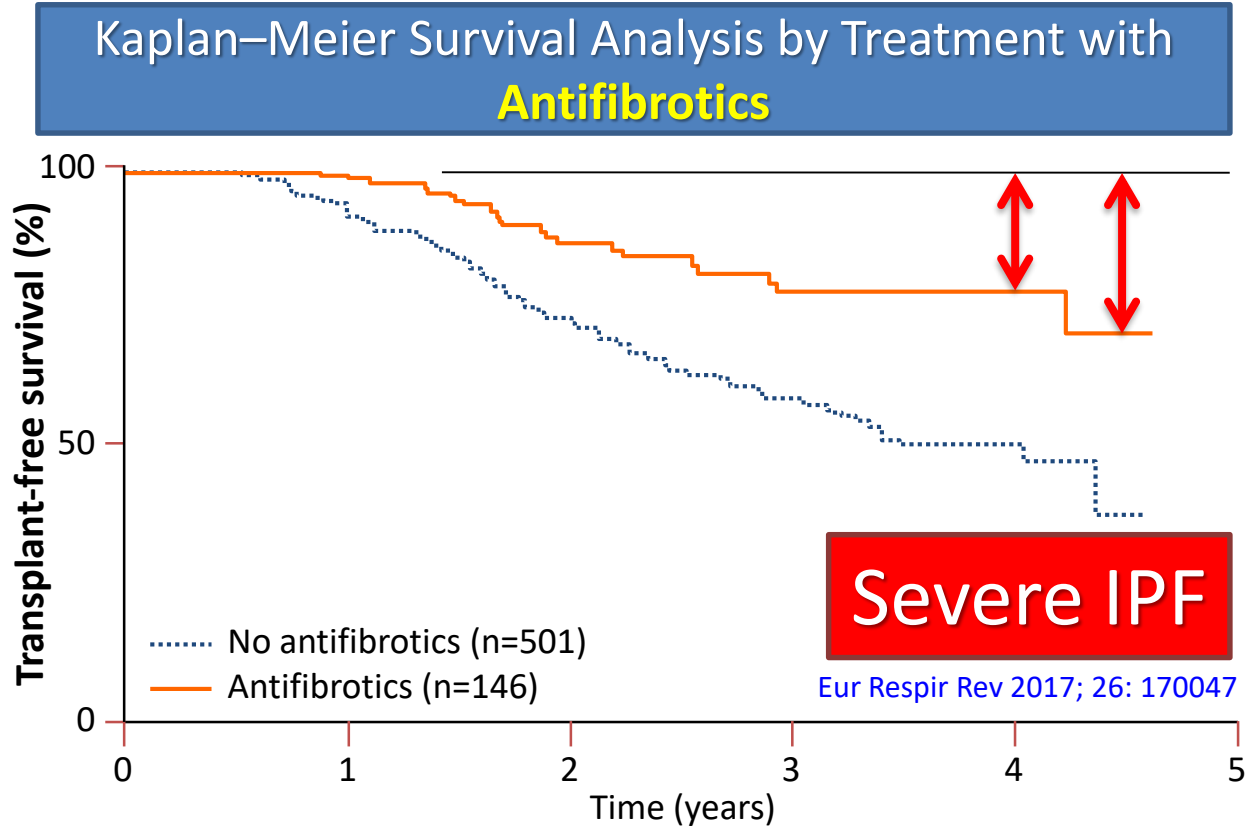
Occult fibrosis of smokers or smoking related interstitial fibrosis (SRIF): Alveolar septal widening by collagen deposition along with emphysema and respiratory bronchiolitis both in subpleural areas and in deeper parenchyma, surrounded or not by emphysematous lesions

The European IPF Registry (eurIPFreg)

Change in IPF treatment over time



Australian IPF Registry - Antifibrotic Therapy May Improve Survival, Regardless of Disease Severity

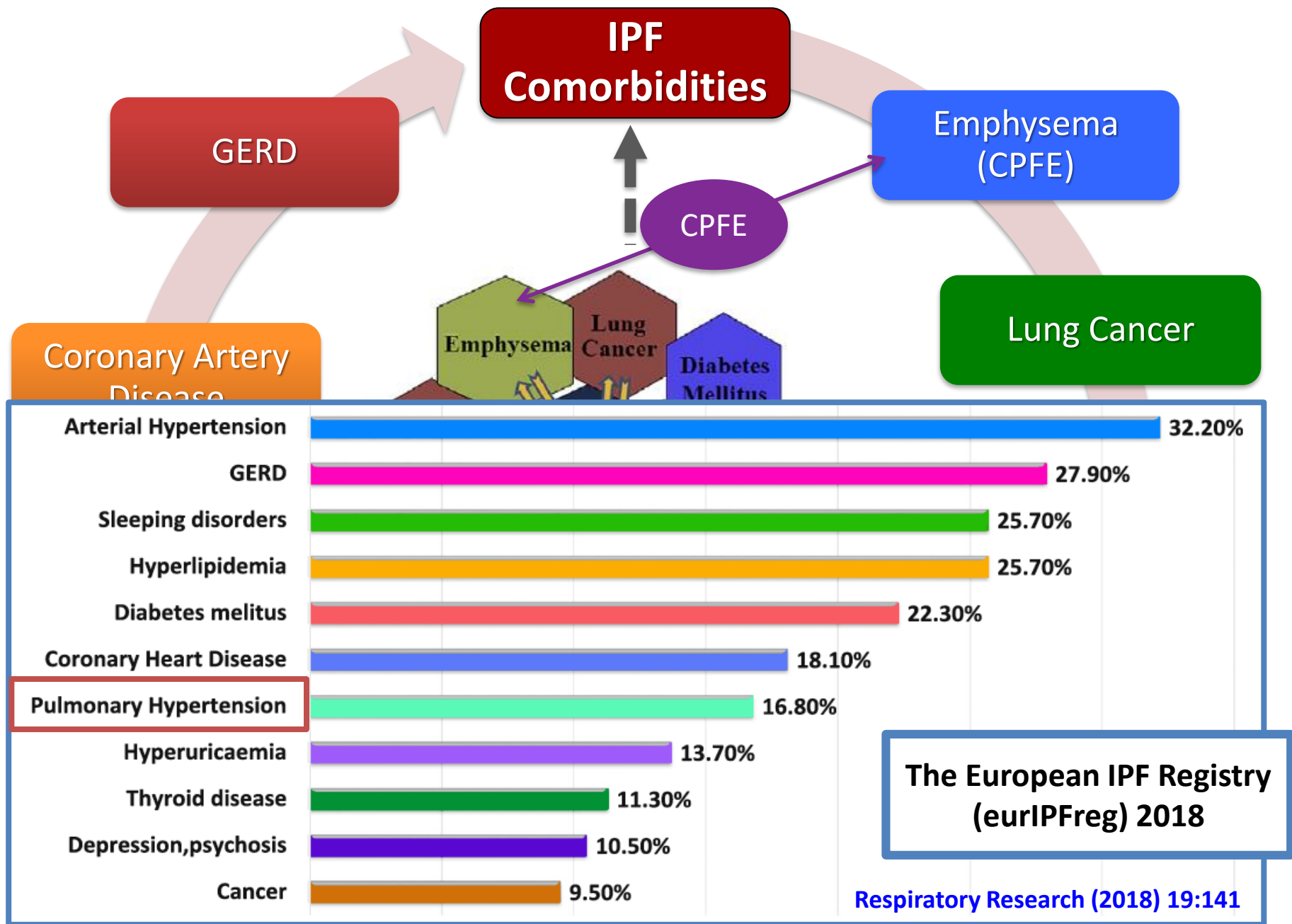


Australian IPF Registry:

- The mortality rate across all patients after 4 years was **44%**
- GAP stage was a strong predictor of mortality

Patients receiving antifibrotics had better survival (**HR 0.56, 95% CI 0.34–0.92, $P=0.02$**), irrespective of underlying disease severity

CI, confidence interval; HR, hazard ratio



FVC less reliable in CPFE

Eur Respir J 2011; 38: 176–183

Pulmonary
Fibrosis

CPFE

Pulmonary
Emphysema

Respiratory
Medicine 117
(2016) 14-26

	IPF	CPFE	Emphysema
Pulmonary function tests		Higher lung volumes by 5–10%	
FEV ₁	↓	↓ or N	↓
FVC	↓	↓ or N	↓
FEV ₁ /FVC	↑	↓ or ↑ or N	↓
TLC	↓	↓ or ↑ or N	↑
FRC	↓	↓ or ↑ or N	↑
RV	↓	↓ or ↑ or N	↑
DLCO	↓	↓↓	↓
Desaturation during exercise	+	++	+
CT findings			
Emphysema	–	+	+
Fibrosis	+	+	–
Pathological findings	UIP	UIP or f-NSIP + Emphysema	Emphysema
Pulmonary Hypertension	+	++	+
Lung cancer risk	++	++	+

Lower DLCO by ~15%

> 50%

Eur Respir J 2010; 35: 105–111.

Prognosis of IPF

FVC Decline and Mortality

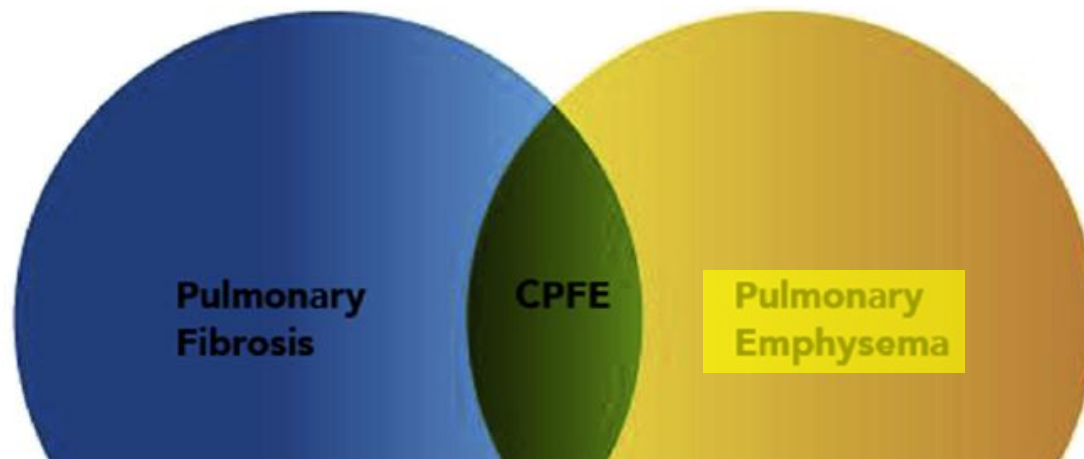
Decline in %FVC in the preceding 24 weeks	Mortality in the subsequent 48 weeks
0 – 4.9 %	5 %
5 – 9.9 %	12 %
> 10 %	24 %

du Bois et al, AJRCCM 2011



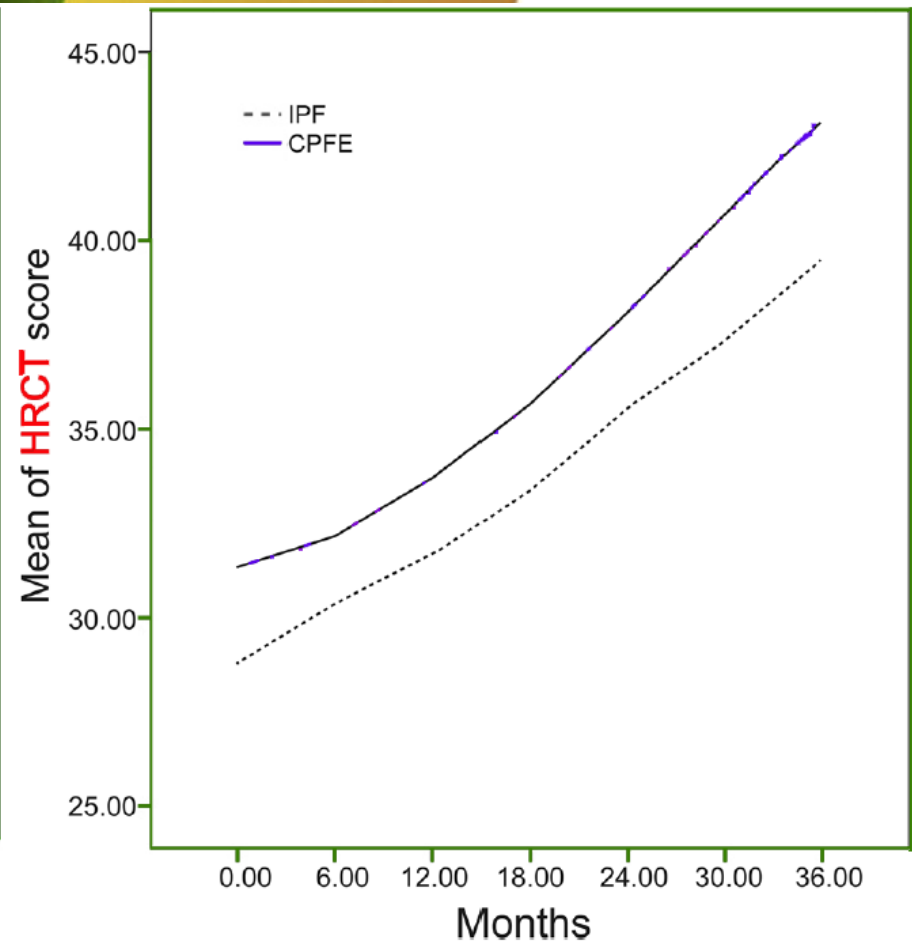
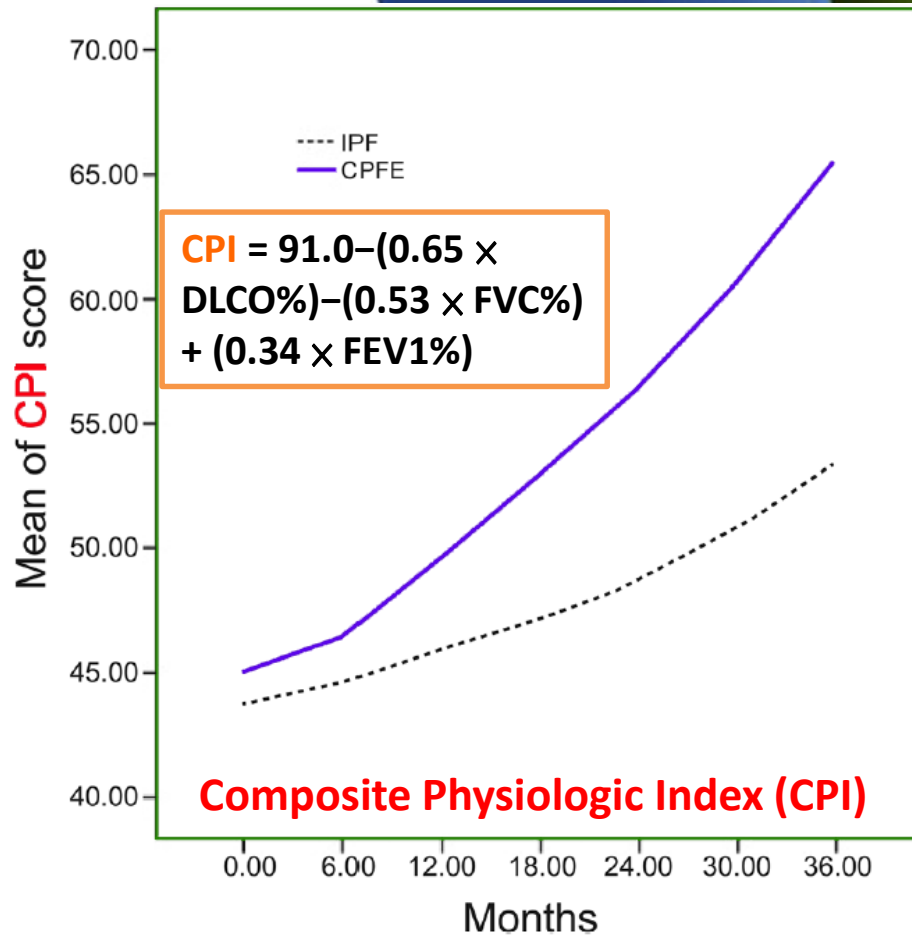
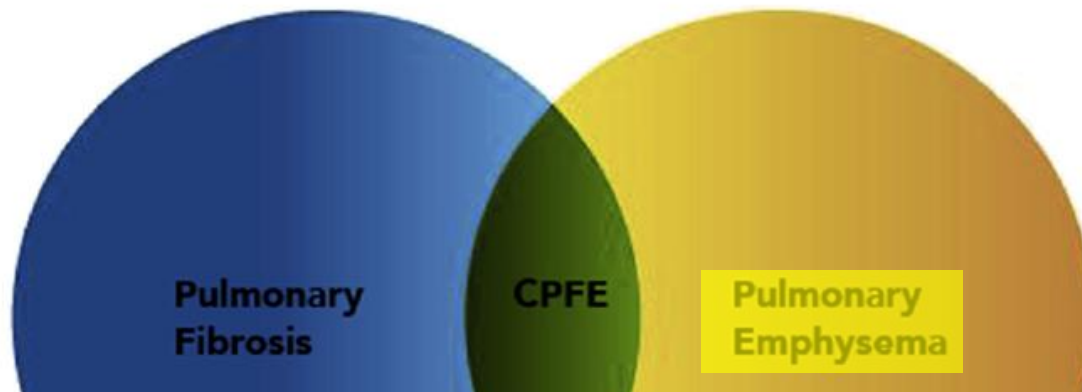
Less Reliable in CPFE

Eur Respir J 2011; 38: 176–183



Group	CPFE (N = 87)	IPF (N = 105)	Chi-square value	P
Age, years	66 ± 8.5	60 ± 4.3	0.63	<0.0001*
Male	76	66	14.83	0.0001
BMI < 18 kg/m ²	37	39	0.58	0.4475
Smokers	75	44	39.63	<0.0001
History of viral infection	13	37	10.18	0.0014
Diabetes	16	10	3.19	0.0739
Cardiovascular and cerebrovascular diseases	67	63	6.29	0.0121
Cancer	8	8	0.15	0.694
Cor pulmonale	21	25	0.01	0.9577
PAH	39	45	0.08	0.7841

Group	CPFE (N = 87)	IPF (N = 105)	Chi-square value	P
Finger clubbing	13	11	0.87	0.3516
Wheeze	55	12	56.17	<0.0001
Basal crackles	47	97	37.34	<0.0001
CEA increasing	21	6	49.11	<0.0001
5-year survival, %	43.42 (33/76)	65.56 (59/90)	9.37	0.023
All-cause mortality, %	56.58 (43/76)	34.44 (31/90)	14.33	<0.001
Direct-cause mortality, %	39.47 (30/76)	23.33 (21/90)	22.14	<0.001



	CPFE (n=17)	COPD (n=49)	p Value
Age, years	76.5±7.1	73.4±9.0	0.209
Males, n (%)	15 (88.2)	36 (73.5)	0.318
Smoking index	989.7±574.1	1304.2±745.4	0.119
Former smokers, n (%)	16 (94.1)	41 (83.7)	0.428
Current smokers, n (%)	1 (5.9)	8 (16.3)	
Body mass index, kg/m ²	21.0±2.9	20.0±4.0	0.324
MRC grade (1/2/3/4/5)	0/0/8/8/1	0/2/25/18/4	0.613
Home oxygen therapy, n (%)	10 (58.8)	26 (53.1)	0.898
Emphysema score	9.1±3.2	13.1±5.0	<0.005
Pulmonary function			
FVC, litres	2.1±0.5	1.8±0.7	0.136
FVC, %predicted	67.2±15.9	59.3±18.7	0.124
FEV ₁ , litres	1.7±0.4	0.8±0.5	<0.0001
FEV ₁ , %predicted	70.6±14.2	33.8±16.6	<0.0001
FEV ₁ /FVC, %	82.8±10.1	44.4±13.9	<0.0001
PASP, mm Hg	54.2±26.1	42.7±10.2 (n=45)	0.016
6 min walk test	n=15	n=44	
Distance, m	270.5±59.4	216.0±99.1	0.054
SpO ₂ nadir, %	85.1±8.6	87.8±6.5	0.221
Borg scale	3.9±1.5	5.2±2.1	0.035
Short Form-36	n=16	n=45	
Physical function	38.3±23.7	31.9±19.6	0.299
Role-physical	36.8±27.9	31.1±25.2	0.451
Body pain	60.1±29.0	51.4±26.9	0.280
General health	40.4±18.1	32.6±18.3	0.143
Vitality	42.2±24.8	29.3±19.8	0.041
Social functioning	57.8±33.8	56.1±30.3	0.852
Role-emotional	37.0±27.0	31.7±28.7	0.521
Mental health	56.3±19.4	43.6±22.8	0.053

Patterns of Exacerbations

Emphysema (COPD)

CPFE

IPF

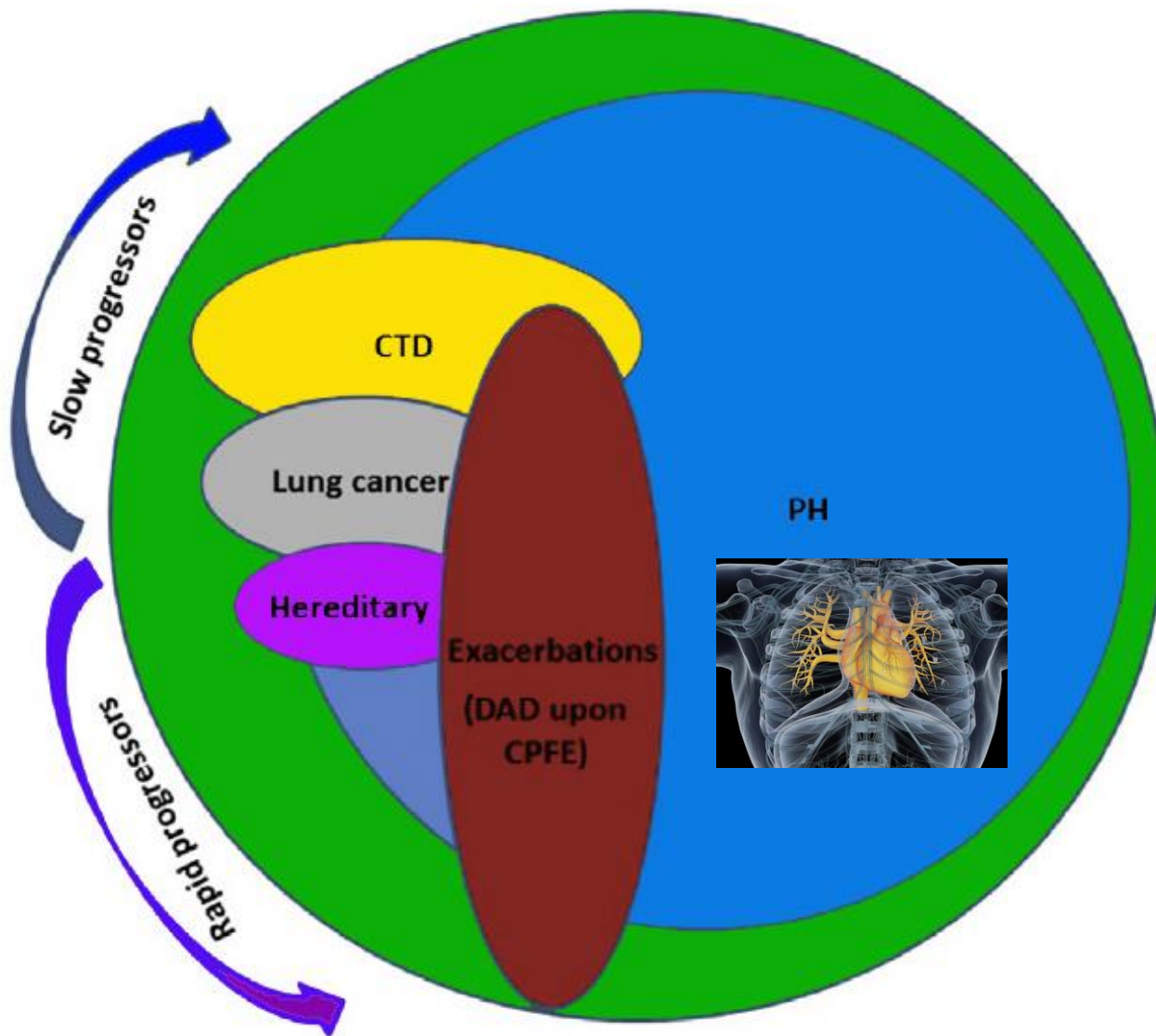
AE-COPD

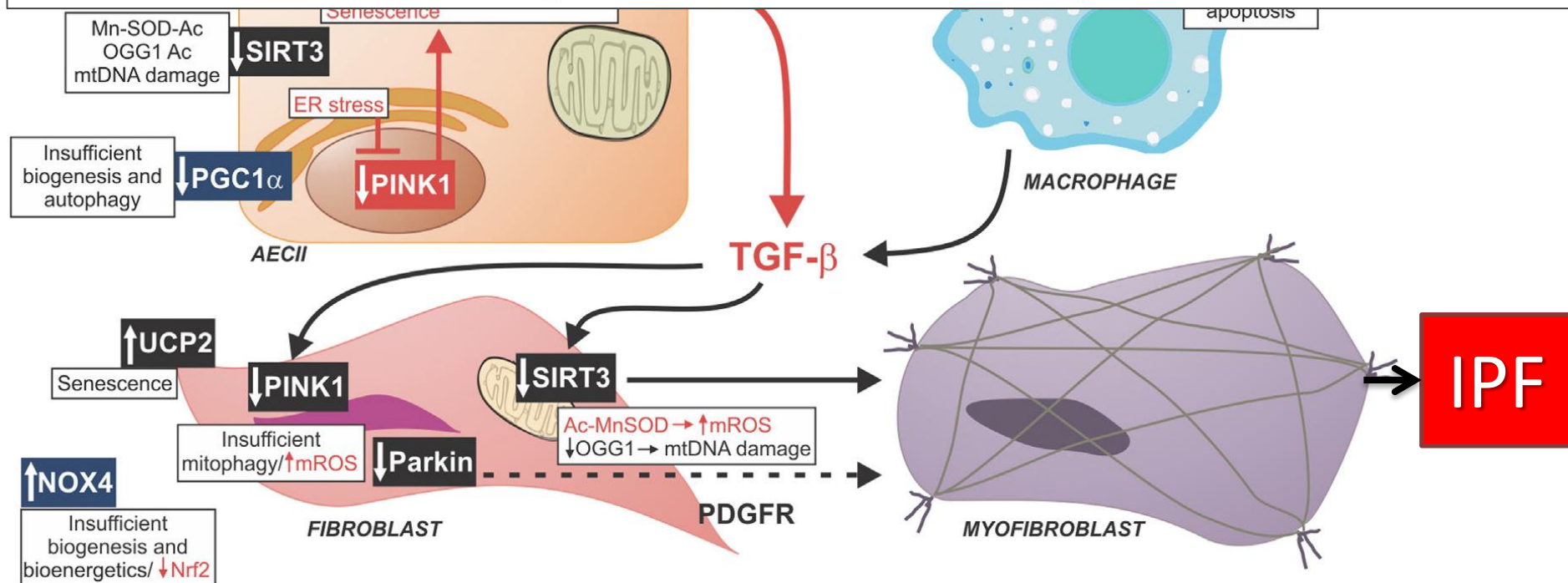
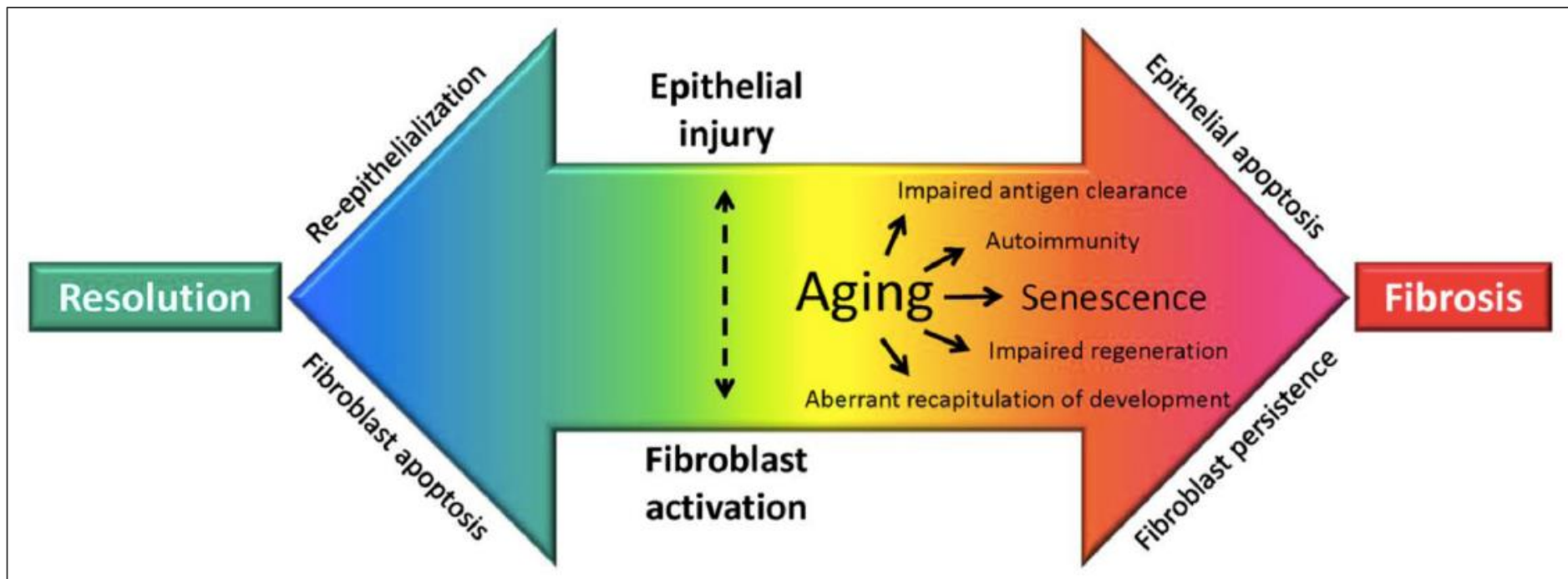
AE-IPF

	CPFE (n=83)		IPF (n=112)	P value
	AE-COPD	AE-IPF	AE-IPF	
Acute Exacerbation pre transplant	22/83 (26.15%)		45 (40.18%)	0.047
	10/83 (12%)	12/83 (14.4%)		* <0.05
Rate of exacerbation per year	0.33 (+/- 0.9)		0.43 (+/- 1.2)	0.5
Need for mechanical ventilation	10/22 (45%)		20/45 (44.44%)	0.938
	2/22 (9%)	8/22 (36%)		* 0.004
Need for mechanical ventilation and ECMO	3/22 (13.6%)		17/45 (37.8%)	0.043
	0/22 (0%)	3/22 (13.6%)		* <0.05

* P value comparing AE-COPD in the CPFE group vs AE-IPF in the IPF group.

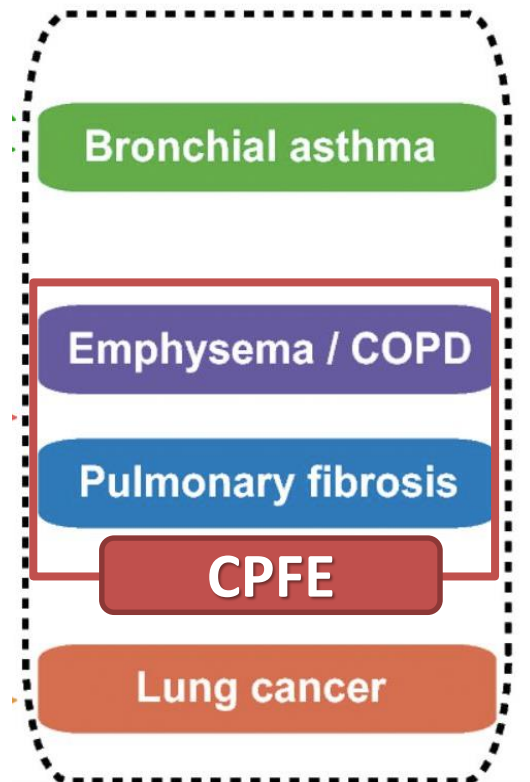
CPFE Phenotypes

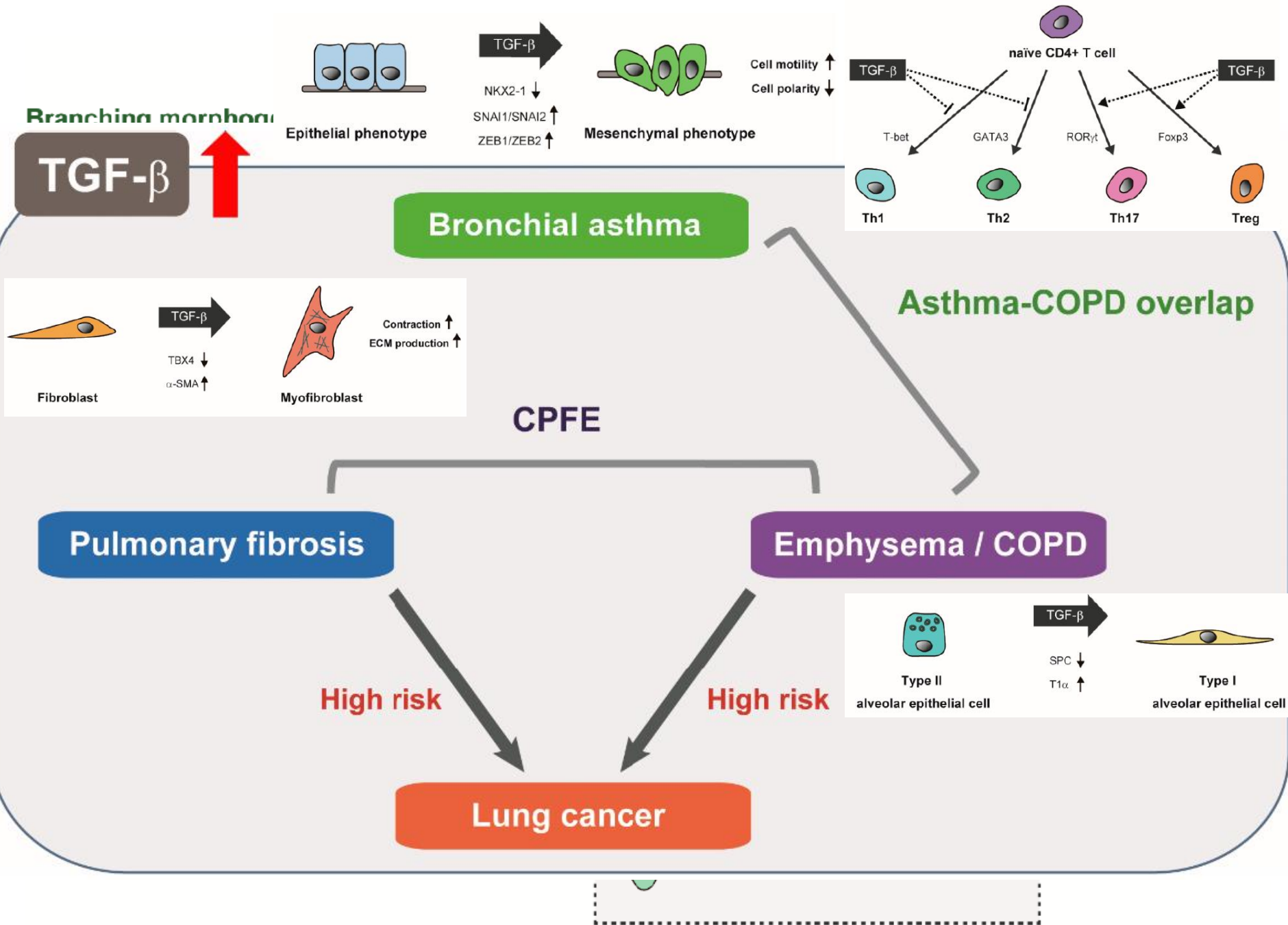




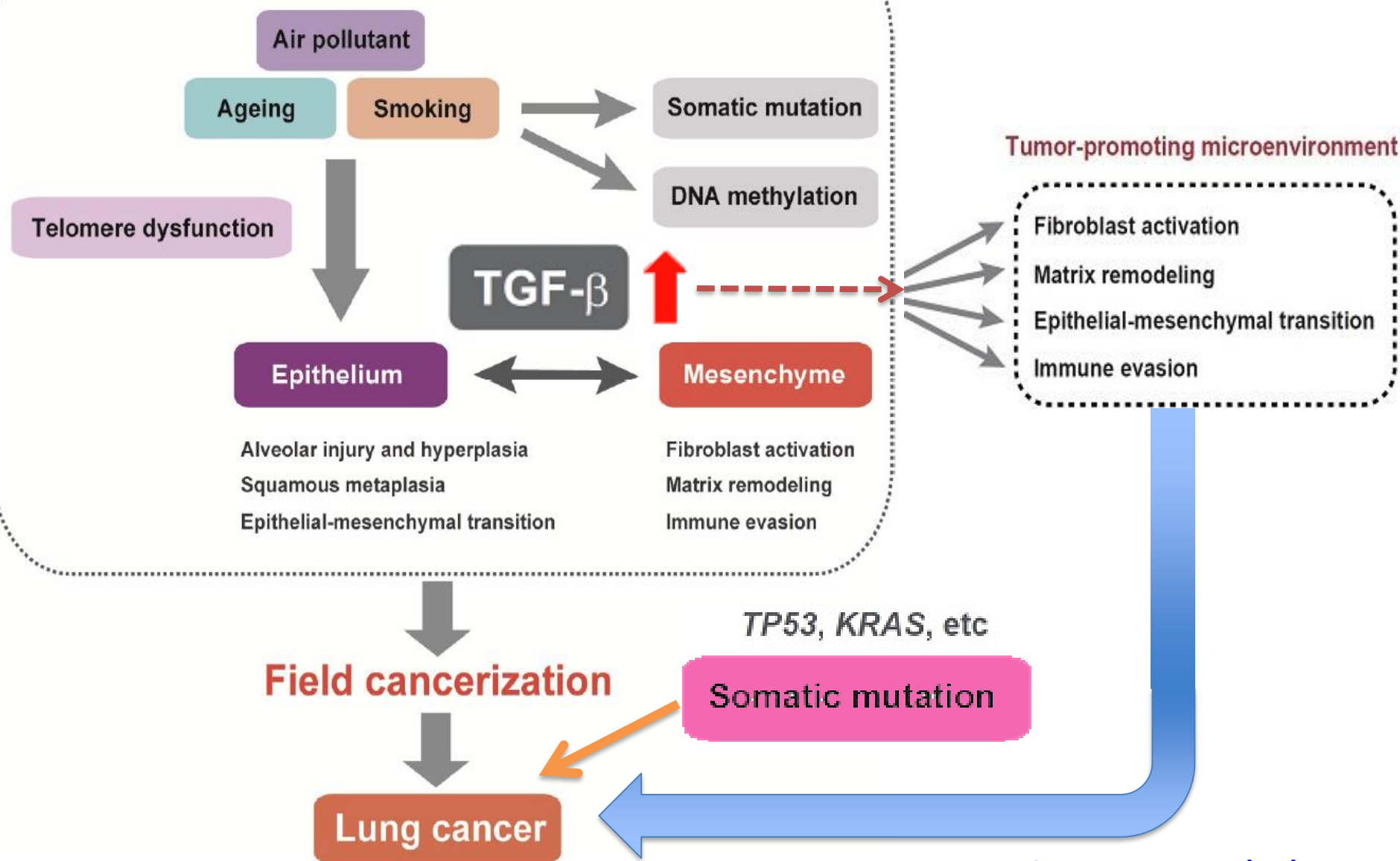
TGF- β Signaling in Lung Health and Disease

Pulmonary diseases

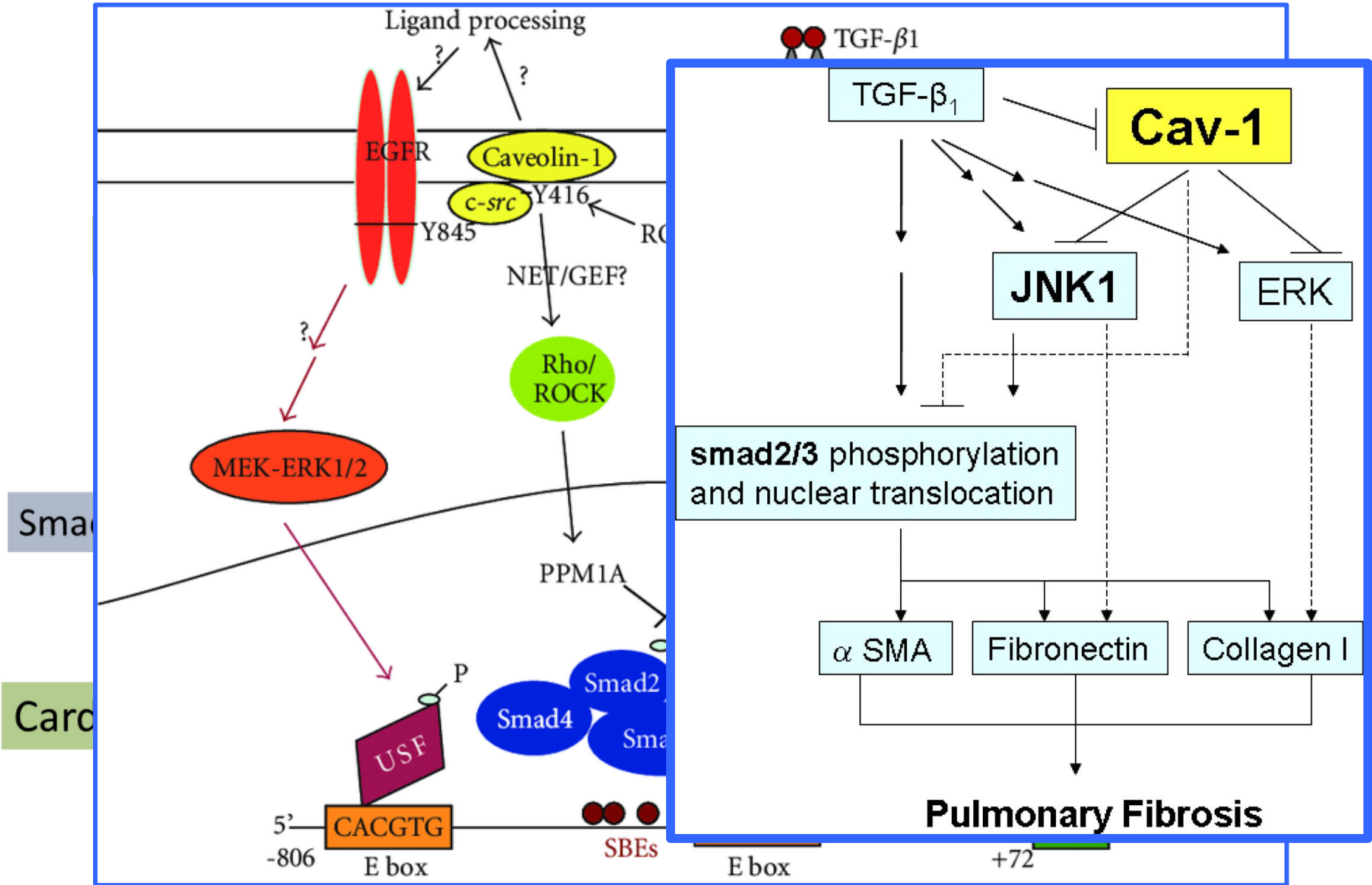




Pulmonary fibrosis



Caveolin-1 in Fibrosis



Sildenafil therapy



CPFE

Caveolin-1

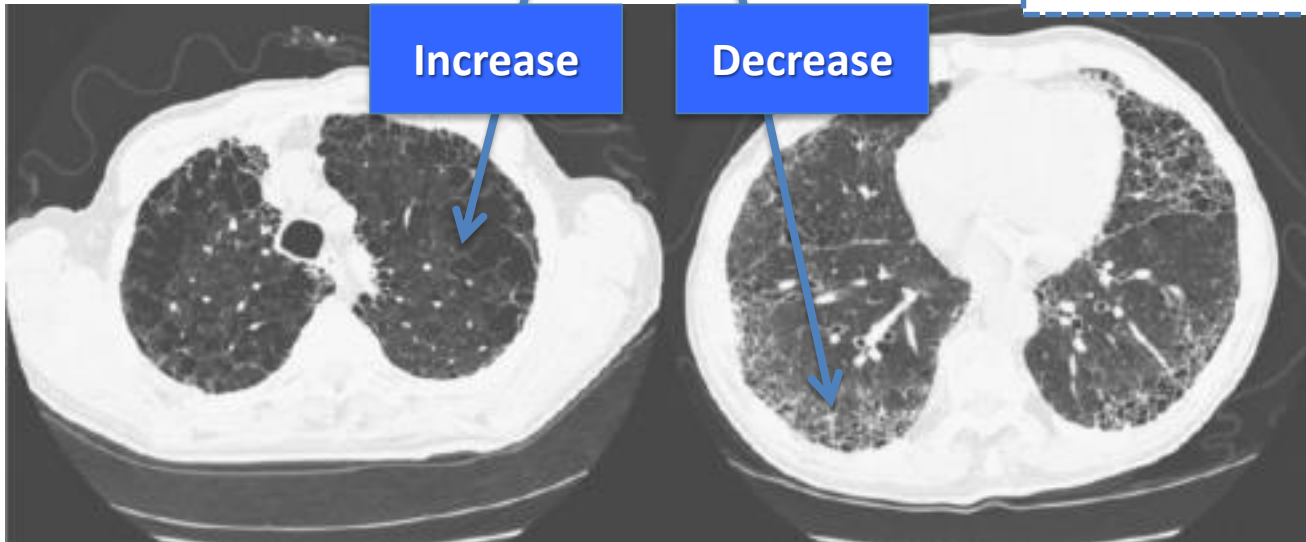
窖蛋白-1

Attenuated the **parenchymal caveolin-1** expression and remodeling in emphysematous areas,

Not effective in reducing **endothelial cell caveolin-1** expression as well as VSMC hypertrophy

Increase

Decrease



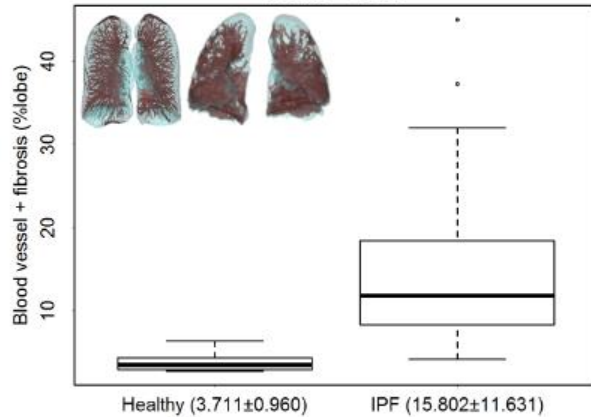
Premature senescence of lung fibroblasts and emphysema formation alternating

Propagation of EMT and collagen deposition

Early Diagnosis of IPF

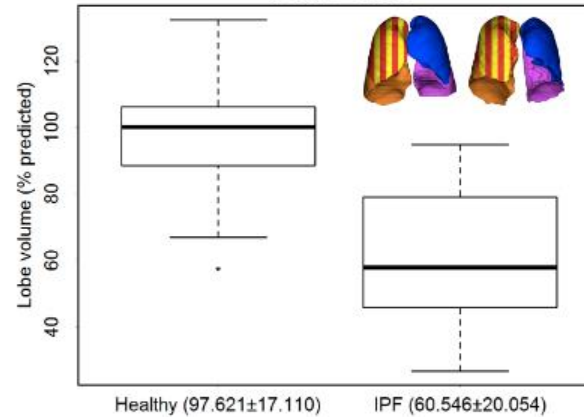
Functional Respiratory Imaging (FRI)

p-value = 0.037



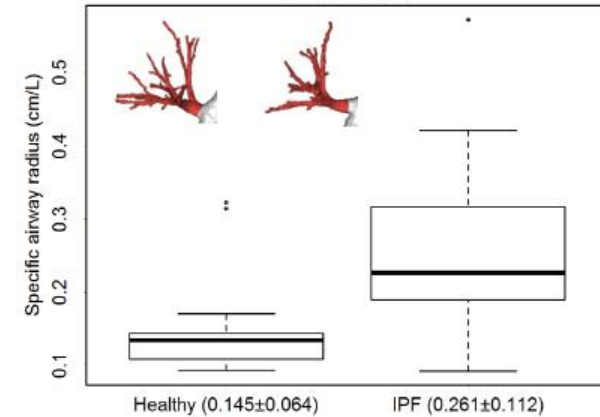
More fibrosis

p-value = 0.002



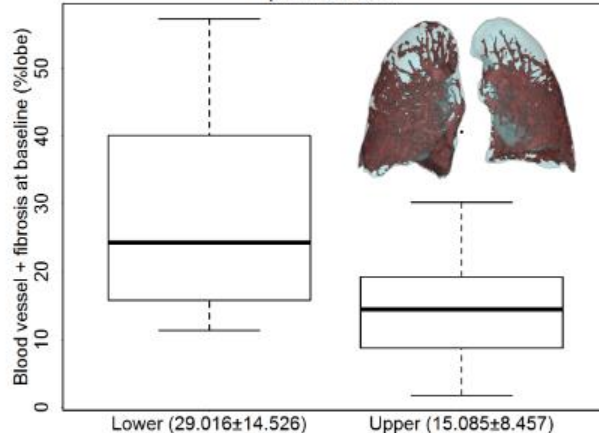
Smaller lung lobes

p-value = 0.013

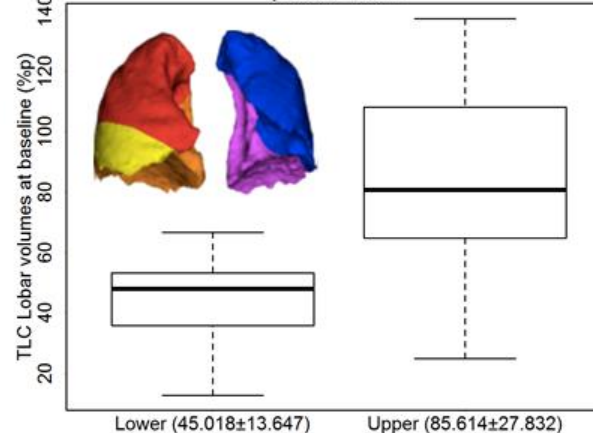


Larger airways

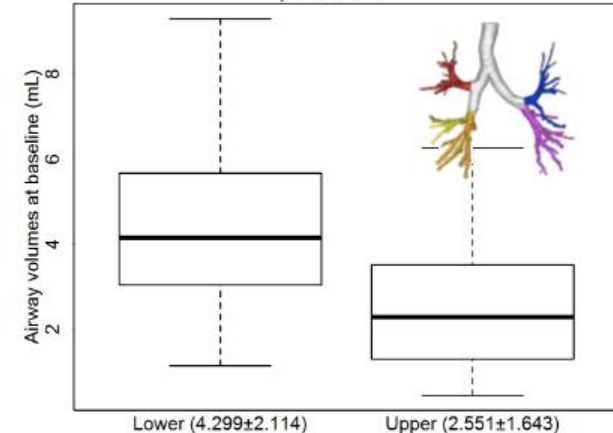
p-value < 0.001



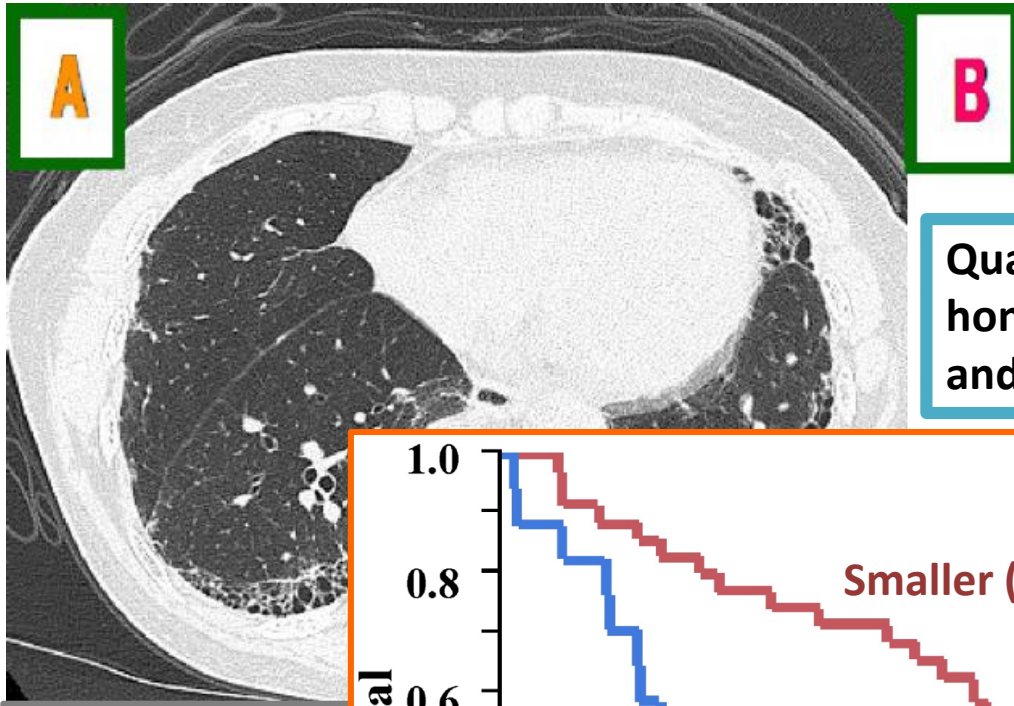
p-value < 0.001



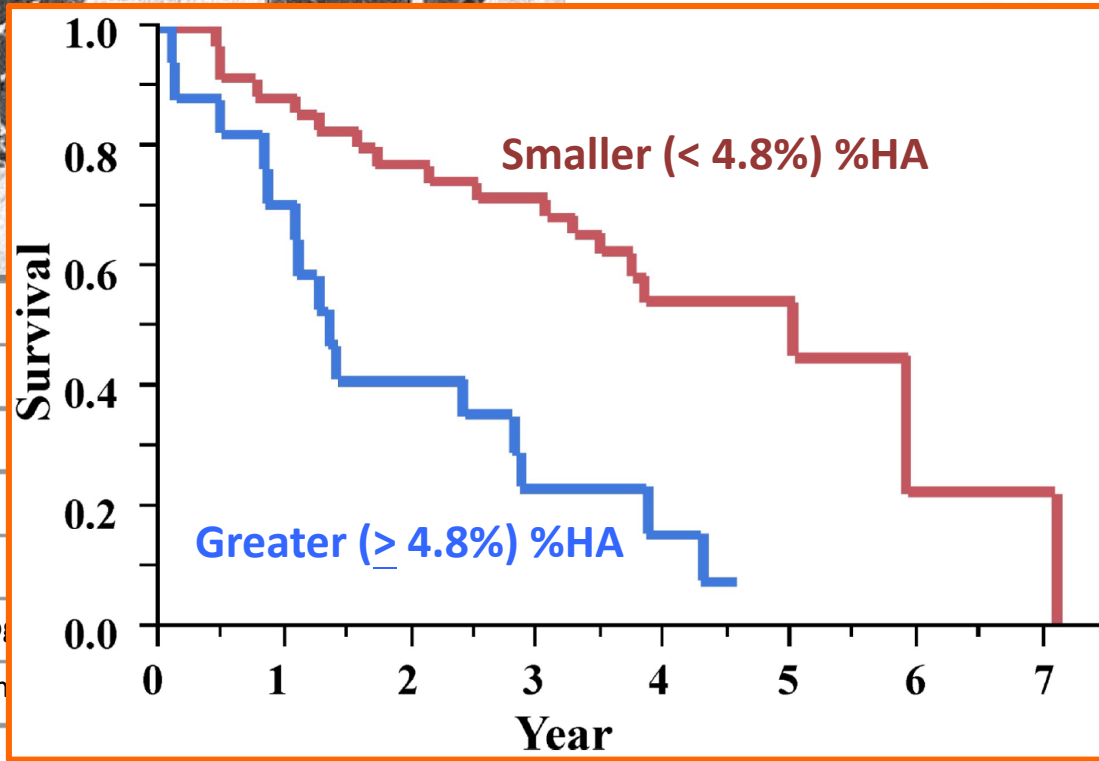
p-value < 0.001



Quantitative CT Analysis



Quantitative CT-derived
honeycombing area (HA)
and percentage of HA (%HA)

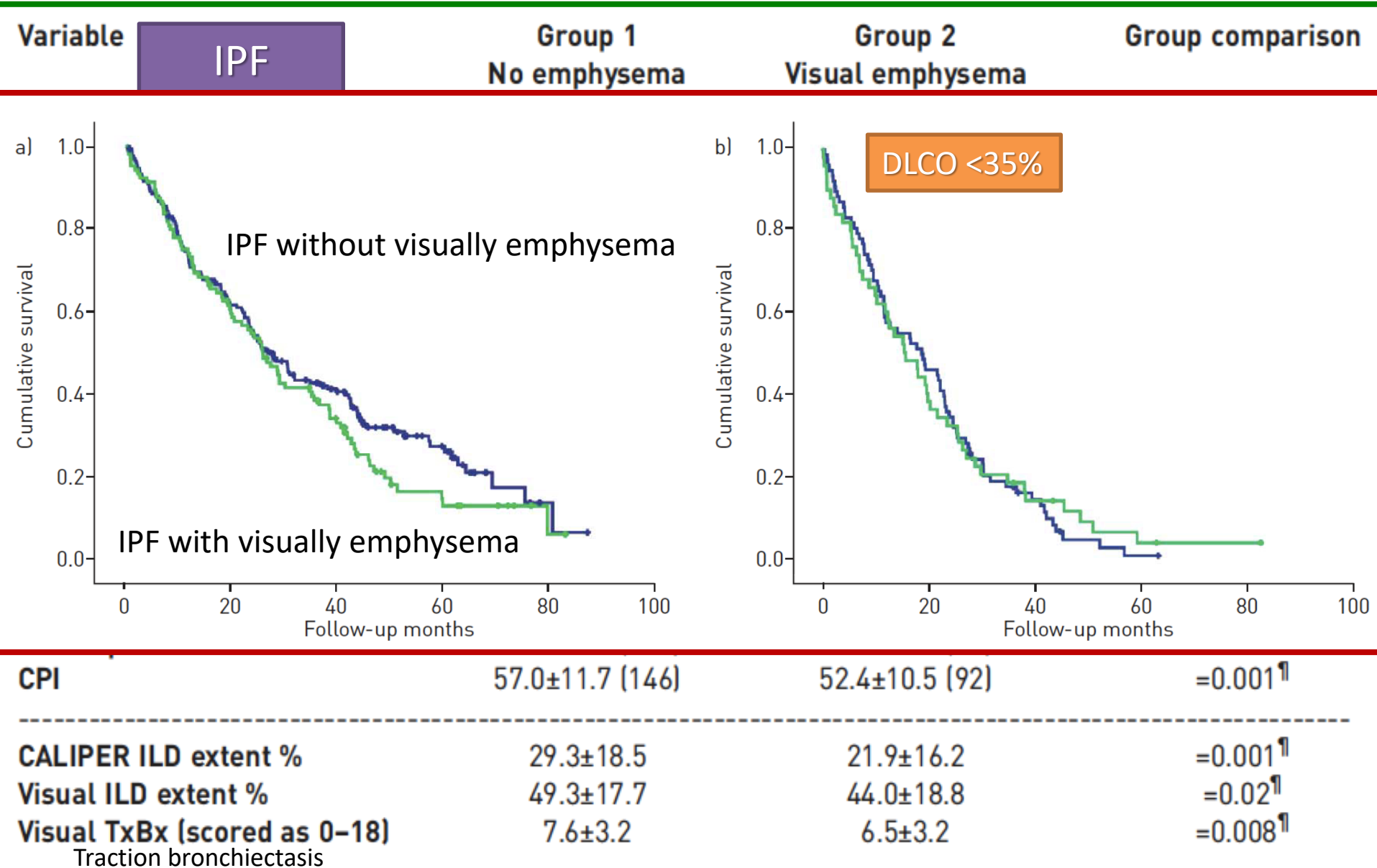


%HA, %
FVC %pred., %
FEV ₁ %pred., %
DL _{CO} %pred., %
CPI composite physiolog
KL-6, U/ml Krebs von
GAP stage

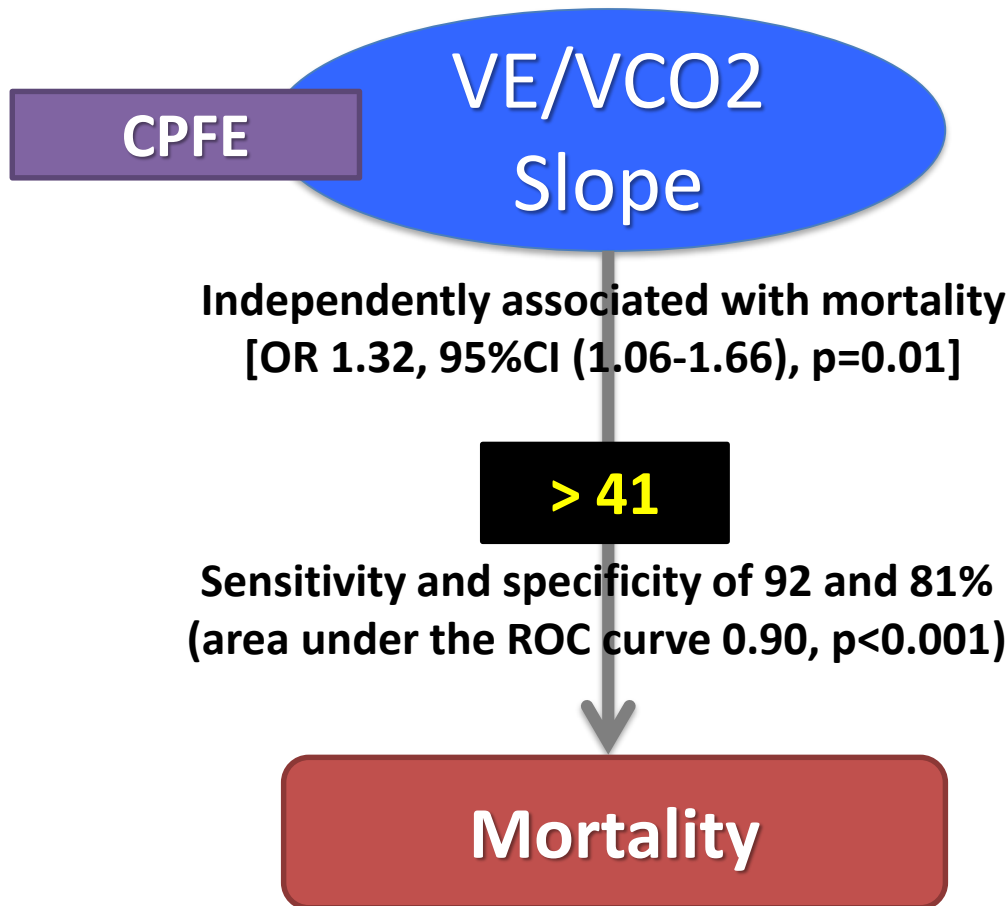
<i>p</i> value
0.011
0.009
0.076
0.079
0.004
0.104
0.005

Visual CT analysis

Computer-based (CALIPER) CT analysis

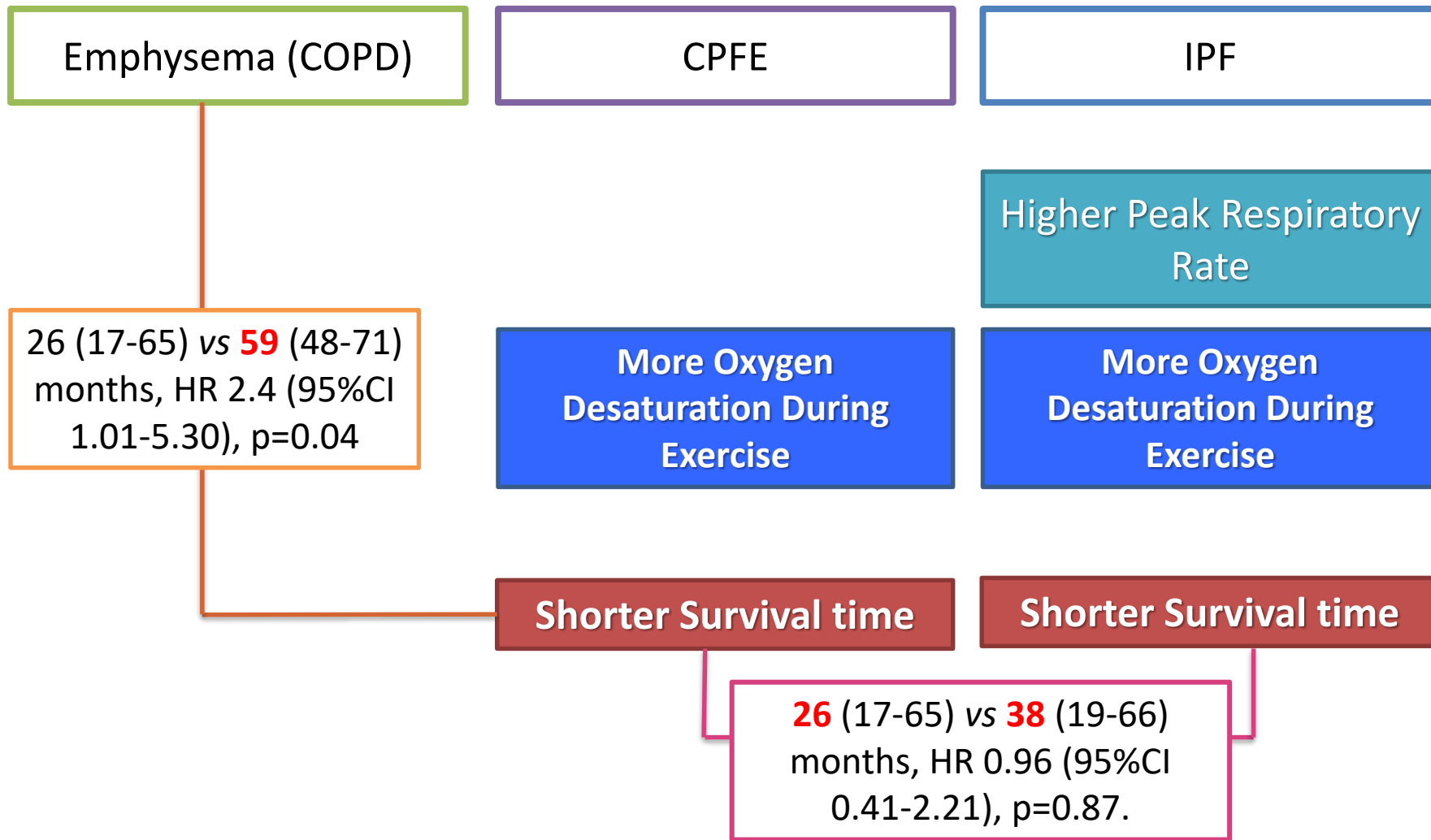


Cardiopulmonary Exercise Testing (CPET) in CPFE



Median survival in VE/VCO₂ slope >41 was **44** (34-54) months
, compared to 83 (75-91) months in others (p<0.001)

Physiological Response to Exercise and Vital Prognosis in CPFE



Similar regarding peak values of oxygen uptake, workrate, heart rate, oxygen pulse, ventilation, ventilatory threshold, dyspnea and ventilation/CO₂ production slope

Treatment

Inhaled
bronchodilators

Smoking cessation

Systemic corticosteroids
Immunosuppressants

Keep Away
occupational
exposures

CTD-associated CPFE

N-acetylcysteine

Oxygen therapy

Nintedanib
Pirfenidone

**No Specific
Effective
Treatments**

Vaccination against
influenza and
pneumococcus

Specific pulmonary
hypertension therapies

**May be the only reasonable
and effective measure to
improve survival**

Pulmonary
rehabilitation

Lung transplantation

Prof. Vincent Cottin
Head of the Department of Respiratory Medicine
University of Lyon



Treatment of IPF

Antifibrotic Activity



Anti-inflammatory



Nintedanib

Pirfenidone

Endothelin receptor
antagonists

Sildenafil

Etanercept

ACEIs

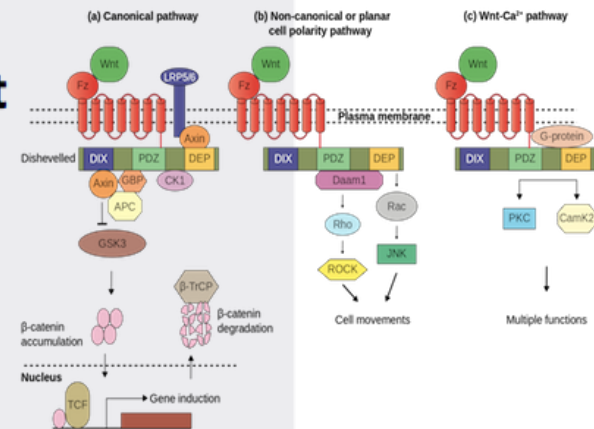
Statins

NAC

Immunosuppressants

Corticosteroids

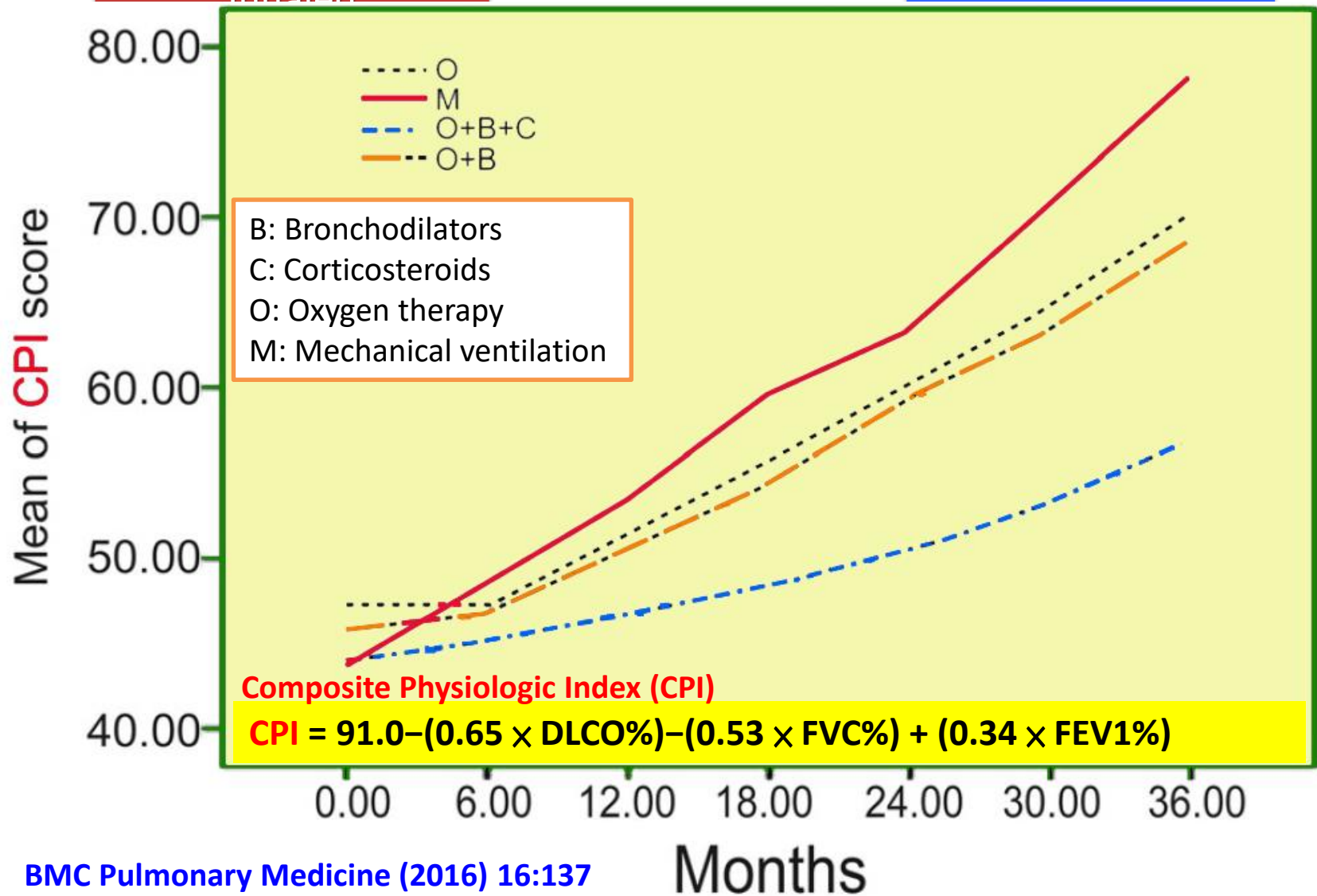
Treatment of PAH



Treatment of Emphysema

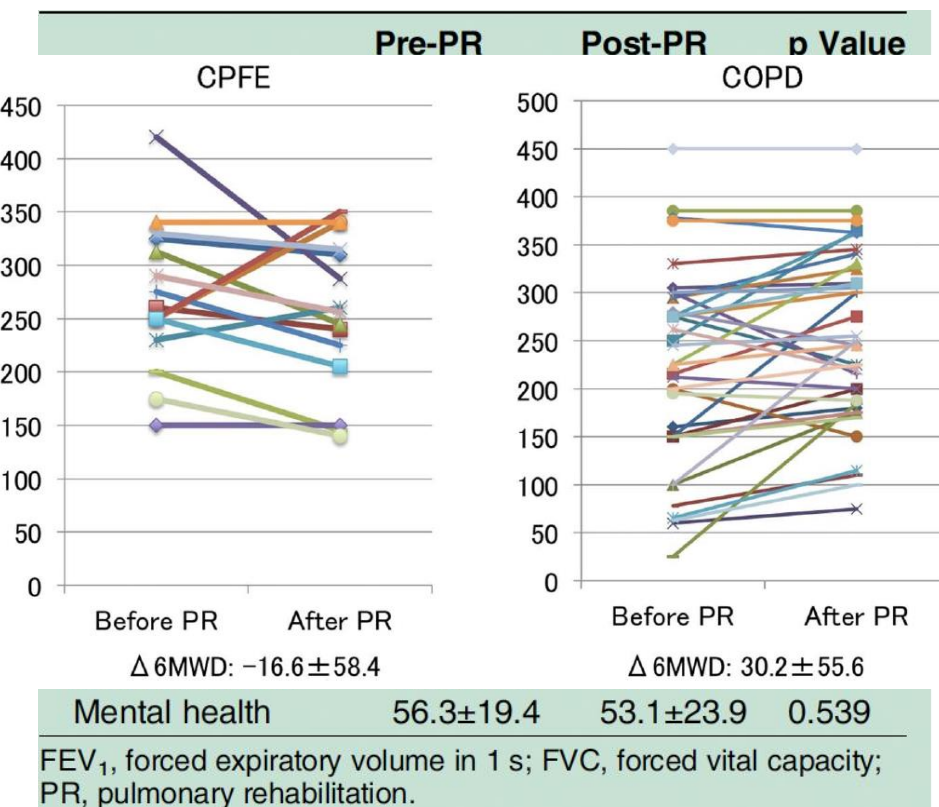
Treatment

Inhaled

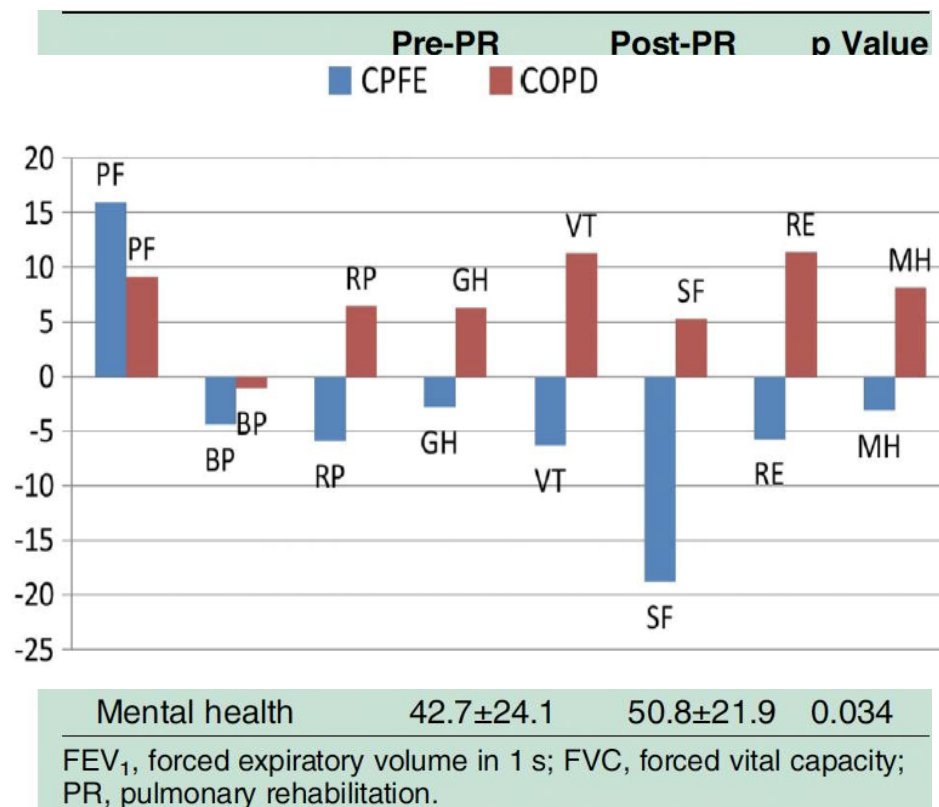


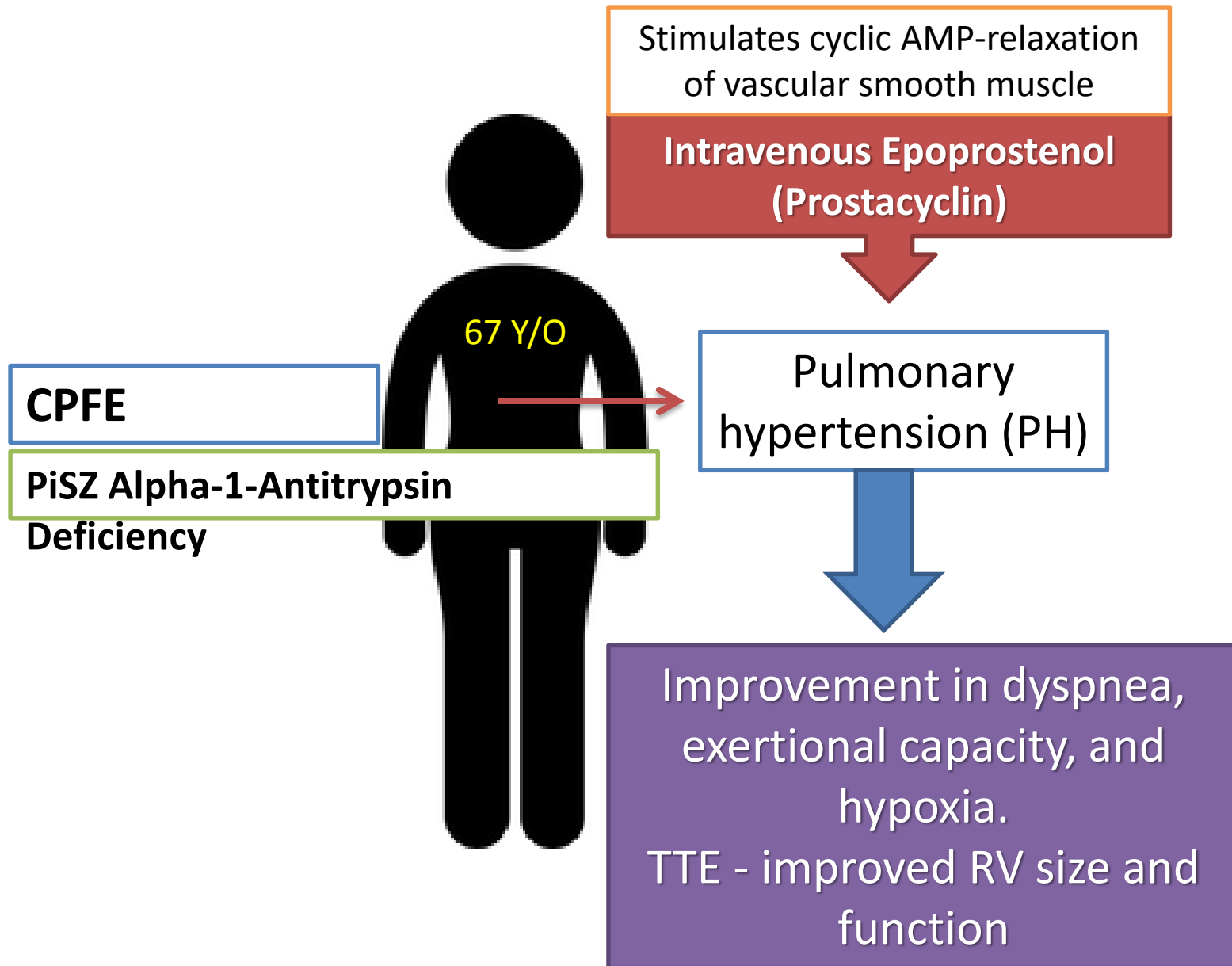
Effect of Pulmonary Rehabilitation on CPFE and COPD

CPFE

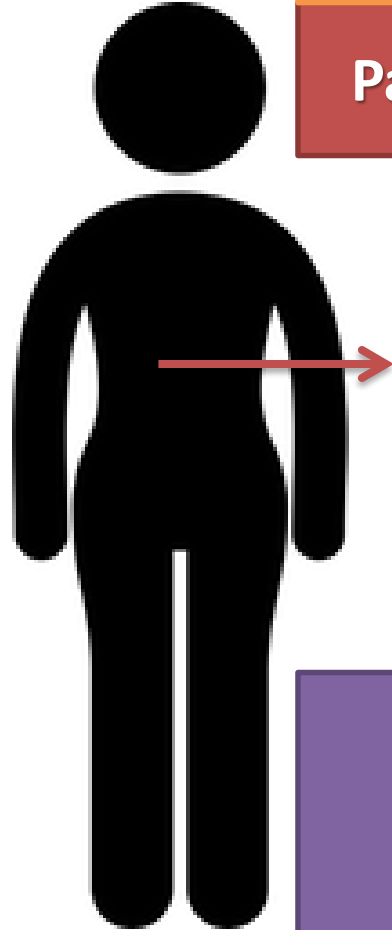


COPD





IPF (3)
CPFE(3)
Bronchiolitis
obliterans and
smoking-related
interstitial
fibrosis (2)



Intravenous/subcutaneous
epoprostenol or treprostinil

Parenteral prostanoids



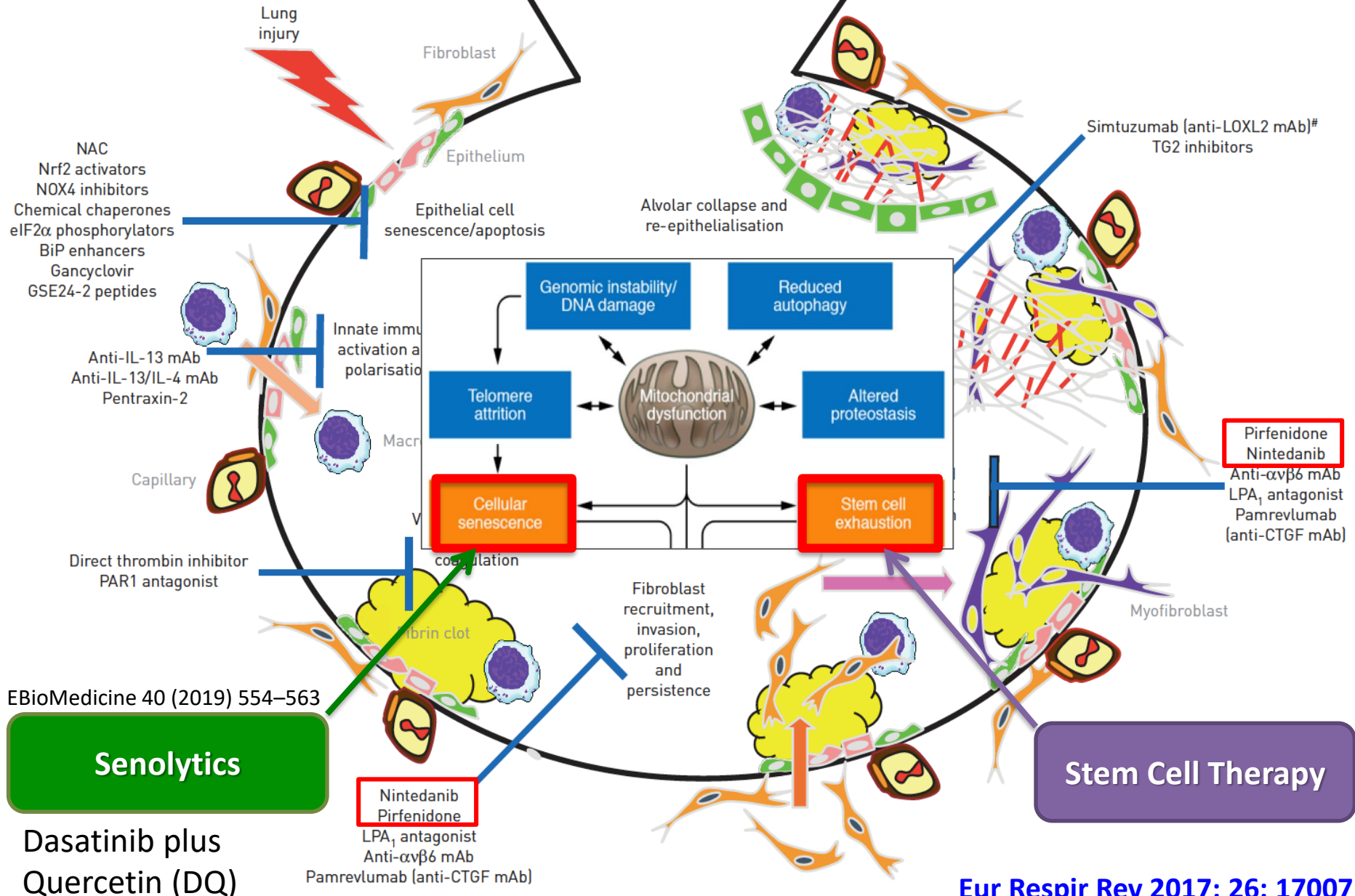
Severe Group 3
Pulmonary
hypertension (PH)



**Improvement in
hemodynamics and
6MWD**

Investigational Therapies for Severe IPF (CPFE?)

Targeting Aberrant Responses to Injury



Reassessment during disease course

Enhance Tailored Treatment in CPFE

Integrating Patient Perspectives into Personalized Medicine

Monitoring on intervention

- Patient-reported outcomes
- Patient-collected outcomes
- Physiological parameters
- Imaging
- Biology (i.e. biomarkers, comorbidities)

Personalized treatment

Individual patient profile

Treatment adjustment

Biology



Genome



Biomarkers



Microbiome

Environment



Environmental factors



Lifestyle



Comorbidities



Co-medication

Patient perspective



Patient needs and perspectives



Patient experiences



Home monitoring



Patient-reported outcomes

The Worst of Both Worlds (Bad and Ugly)

Combined Pulmonary Fibrosis and Emphysema Syndrome

