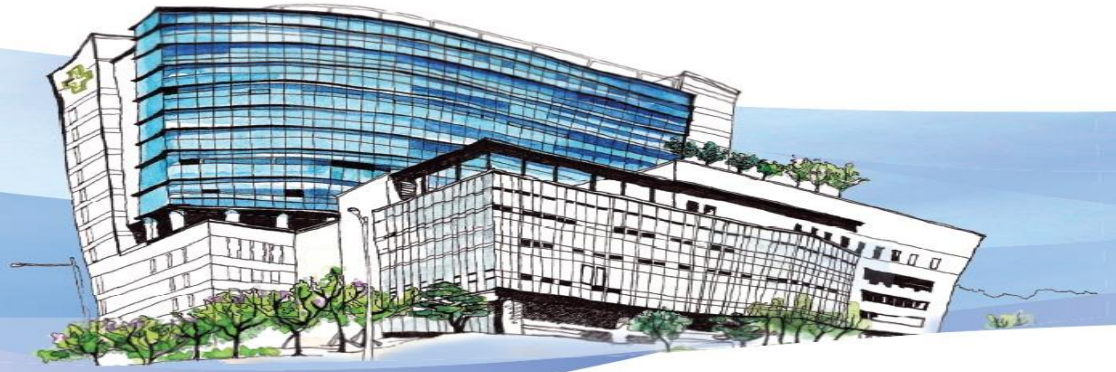


Cough in Interstitial Lung Disease

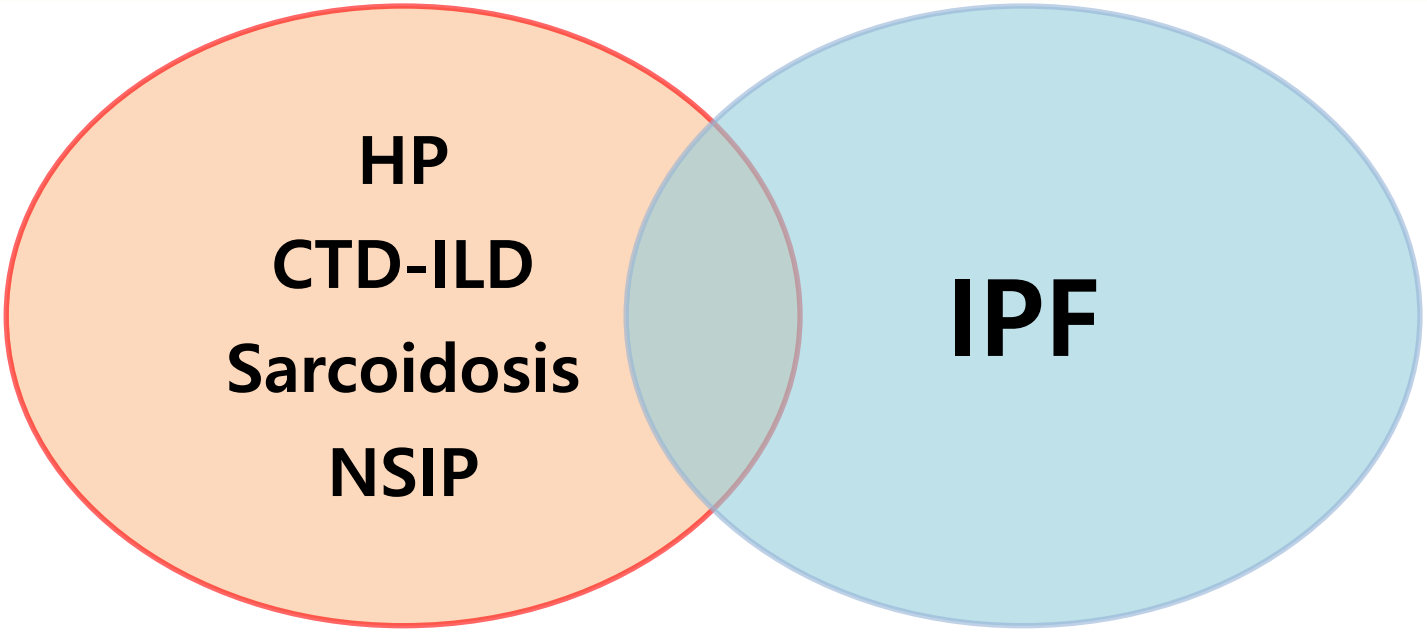
해운대백병원

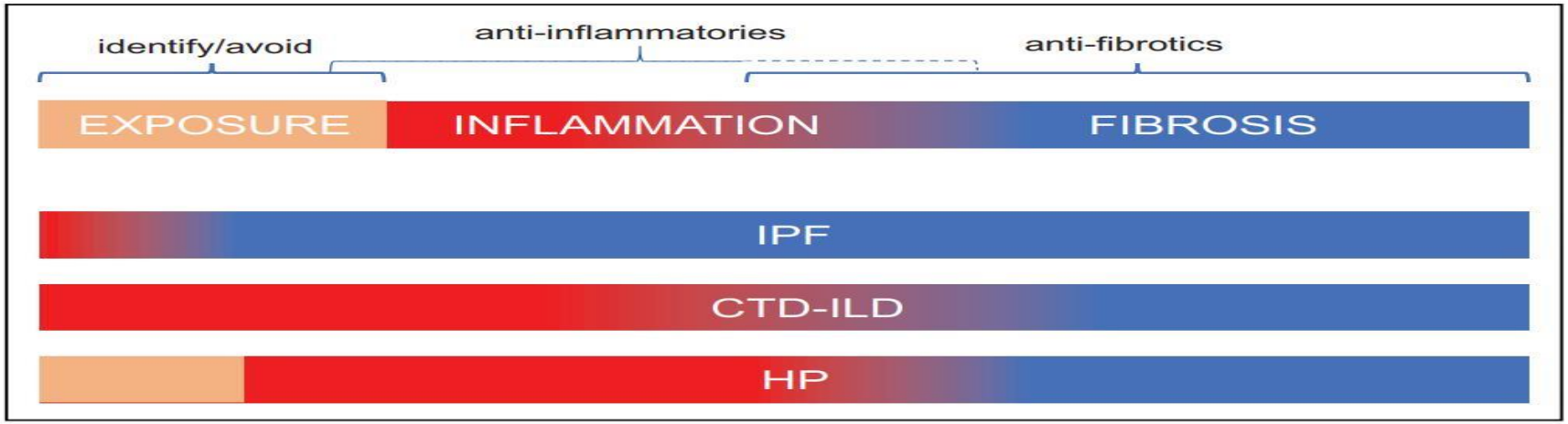
이재하

INJE UNIVERSITY
HAEUNDAE PAIK HOSPITAL

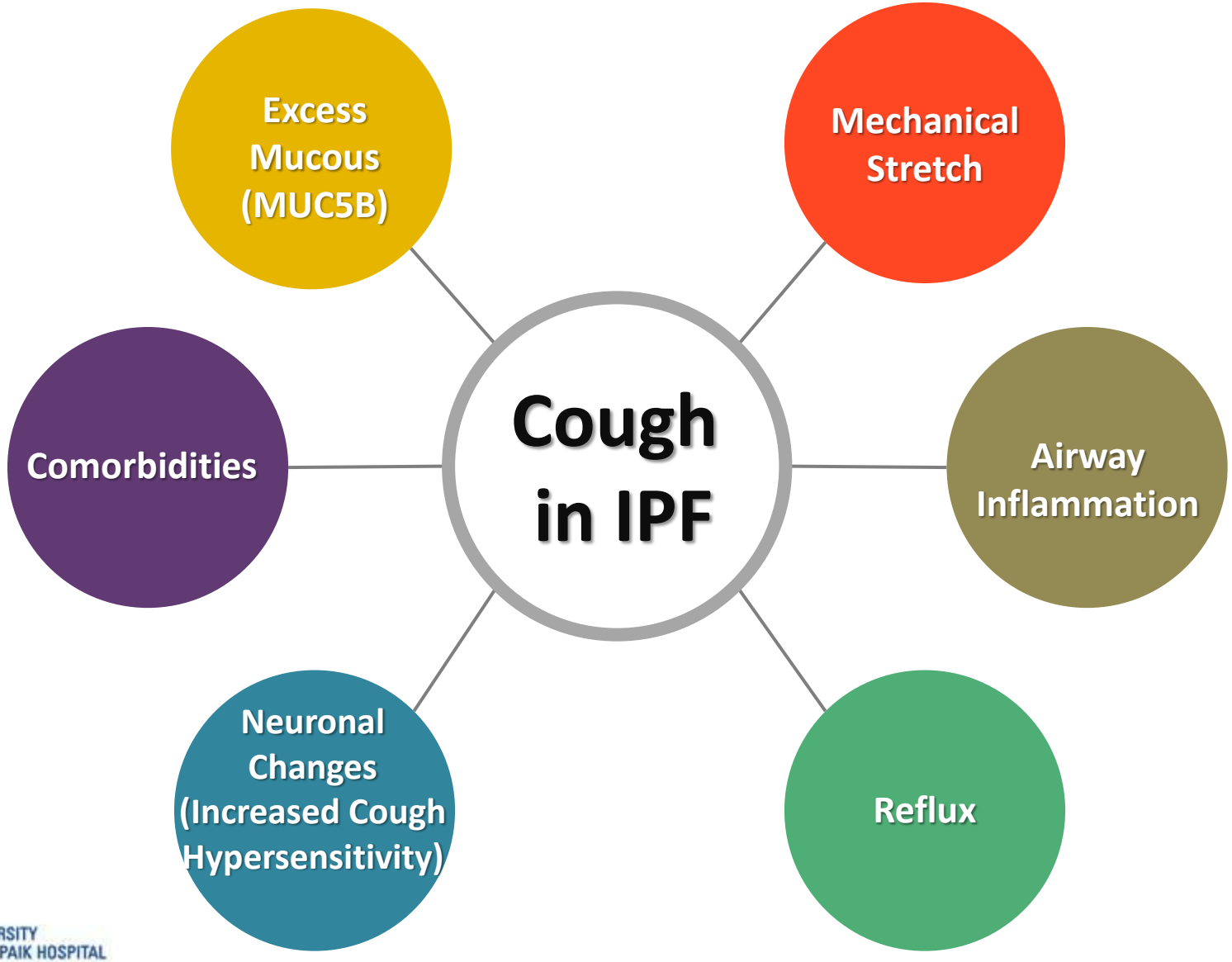
Contents

Cough in ILDs (IPF vs other ILDs)

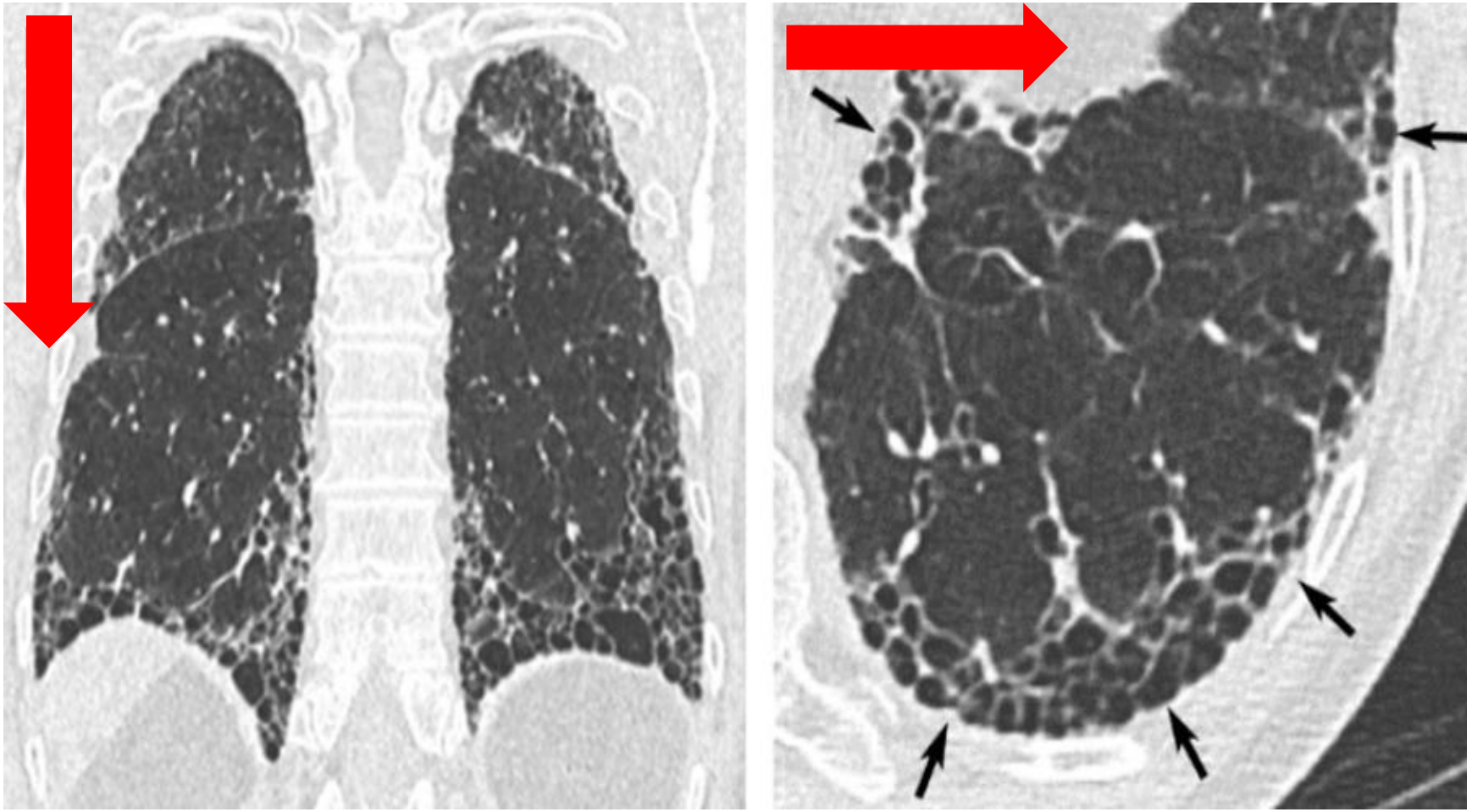




Proposed mechanism of cough in IPF

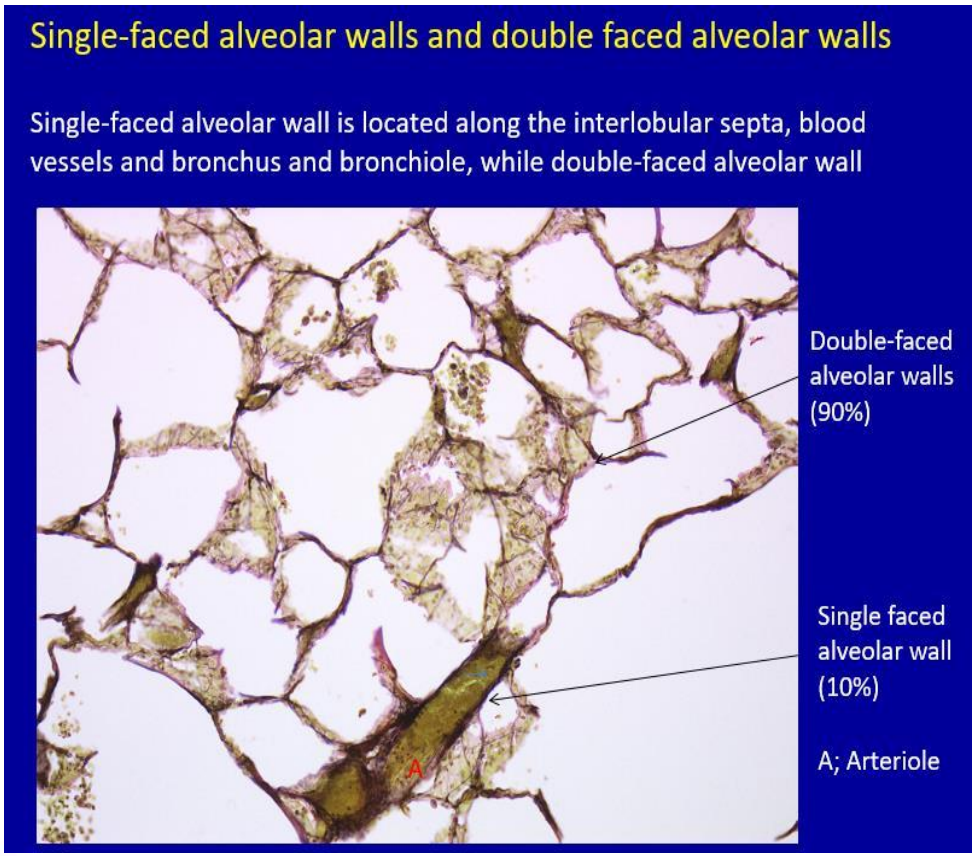


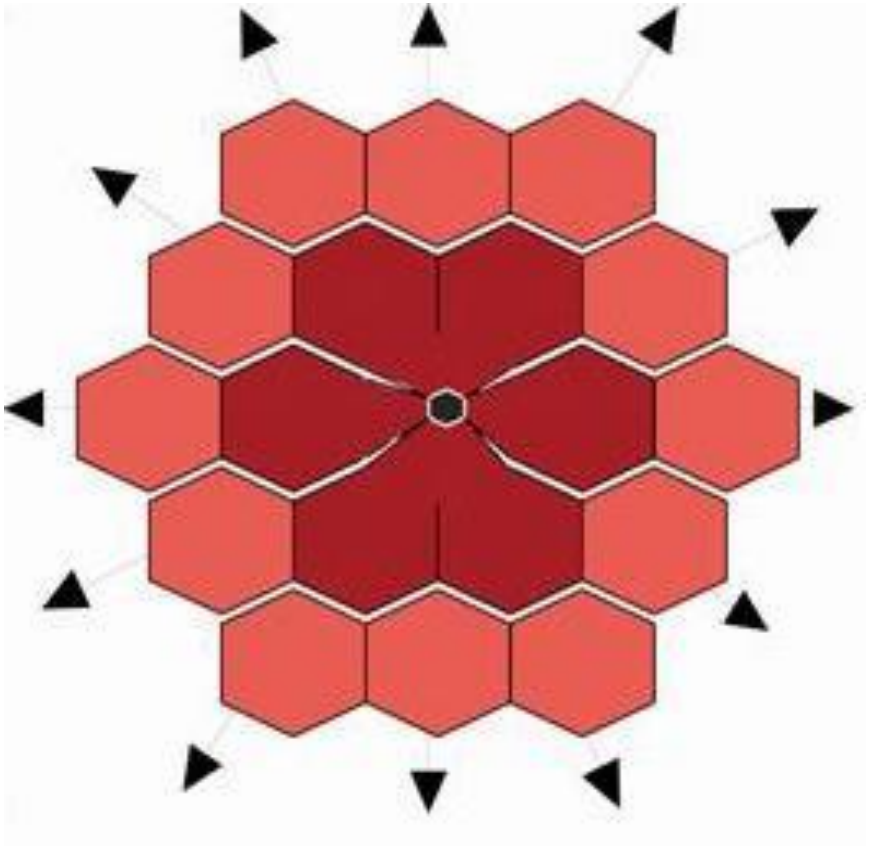
Subpleural and Paraseptal distribution (UIP)



Why does fibrosis occur in the perilobular area?

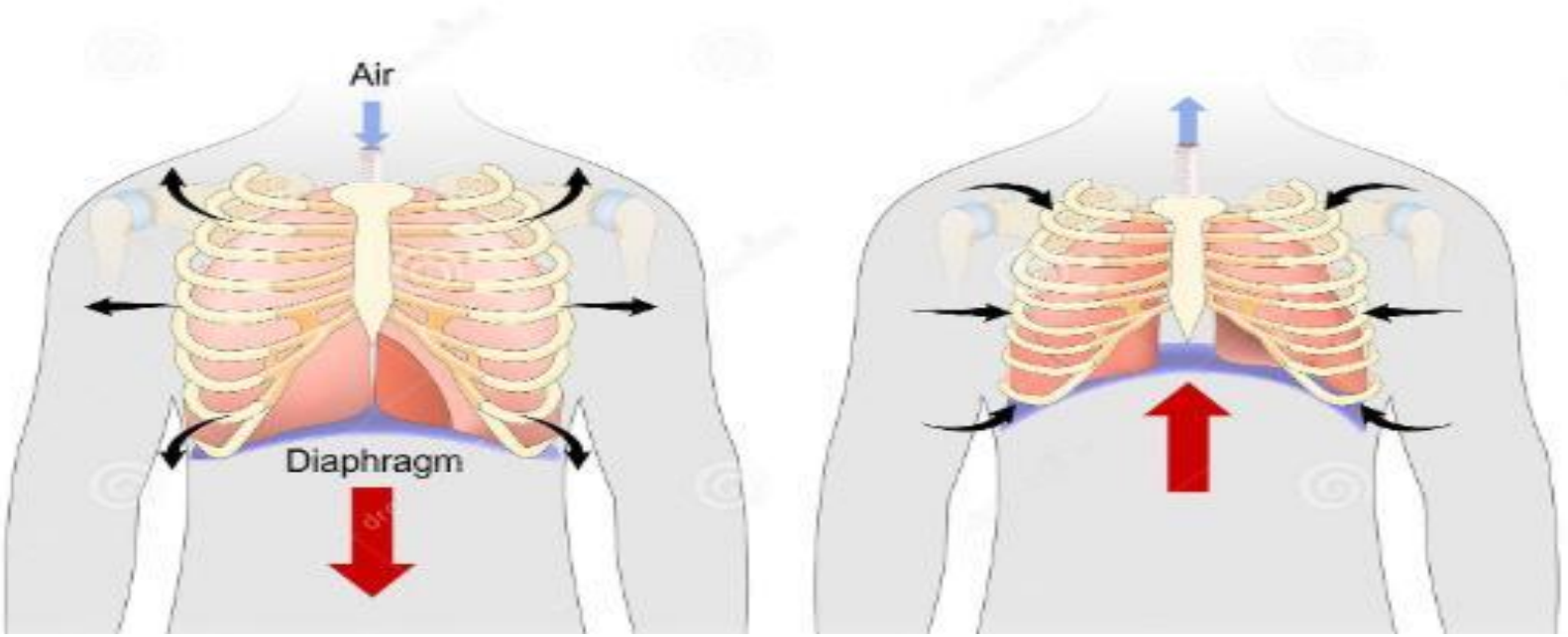
- Collection of venous and lymphatic drainage
- Single-faced alveolar walls in the subpleural and paraseptal area



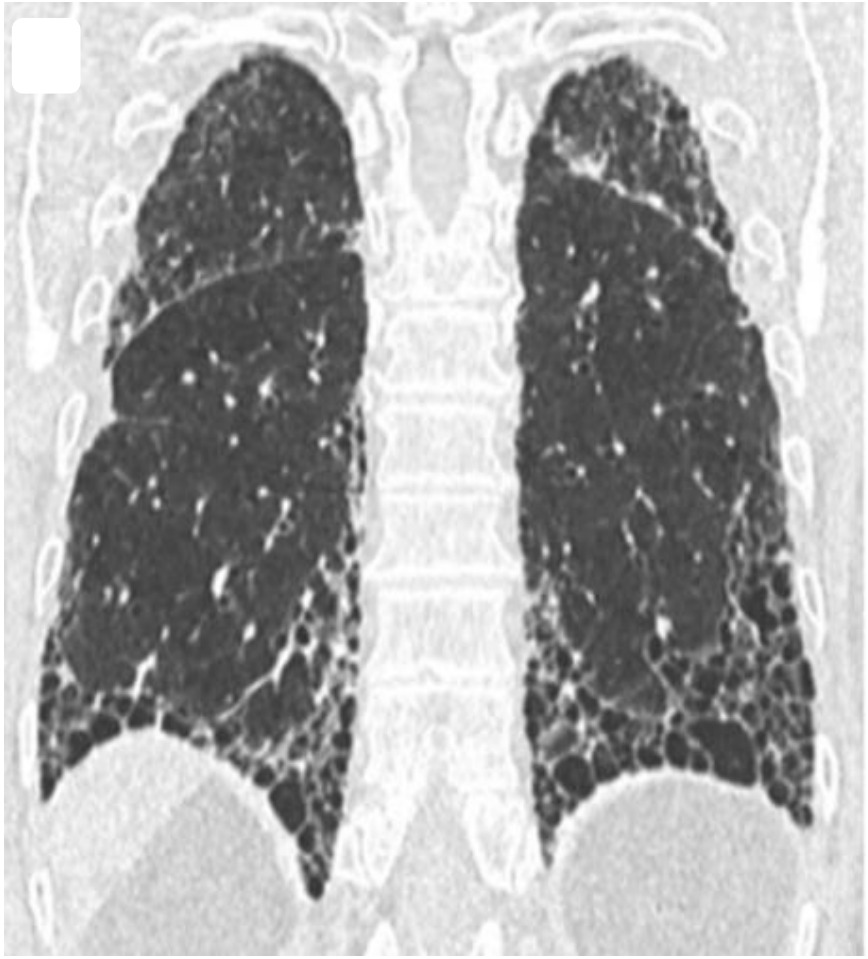


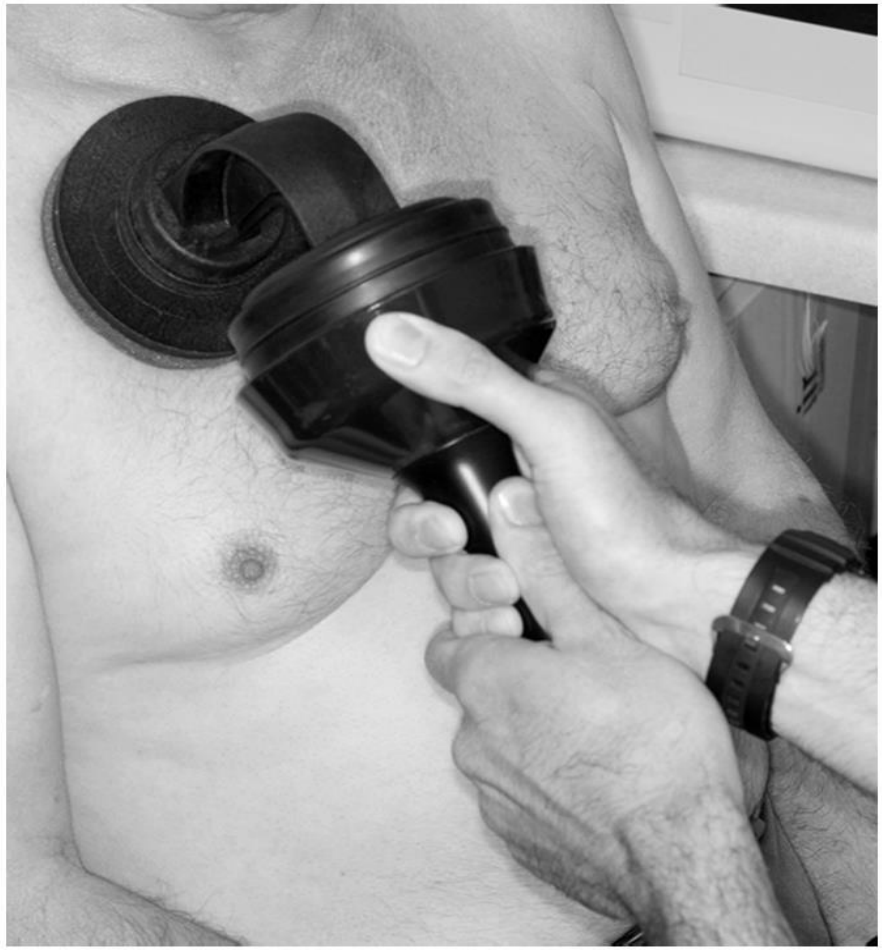
Why does fibrosis occur in the perilobular area?

- Collection of venous and lymphatic drainage
- Single faced alveolar walls in the subpleural and paraseptal area
- Lung movement intensity at the diaphragm
- TGF-β (vulnerable to pressure)



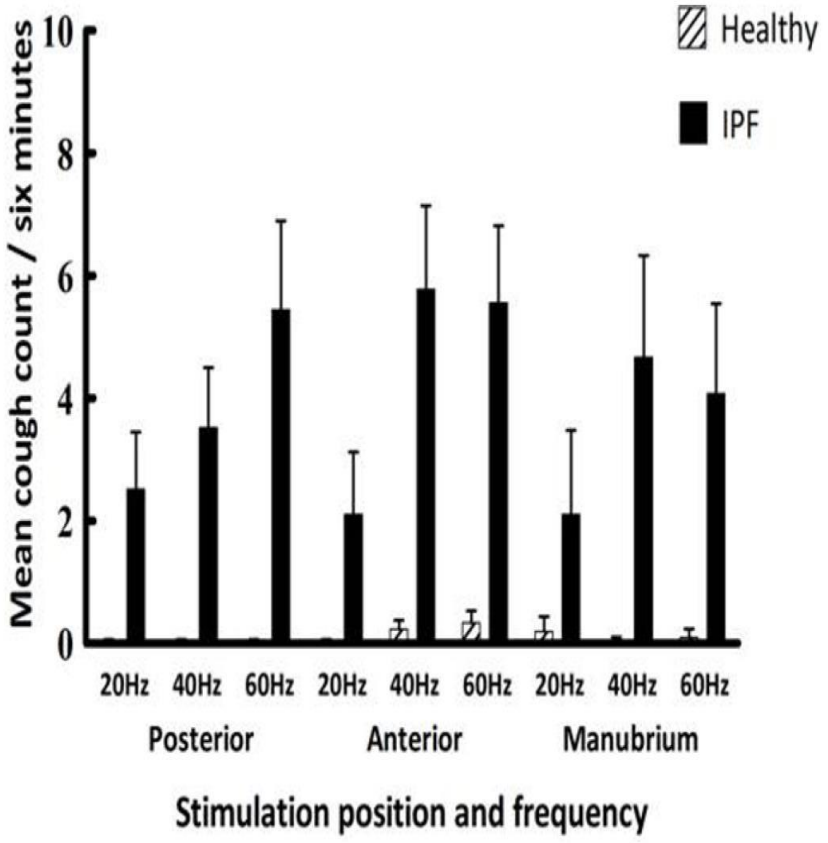
Mechanical induction of cough in IPF

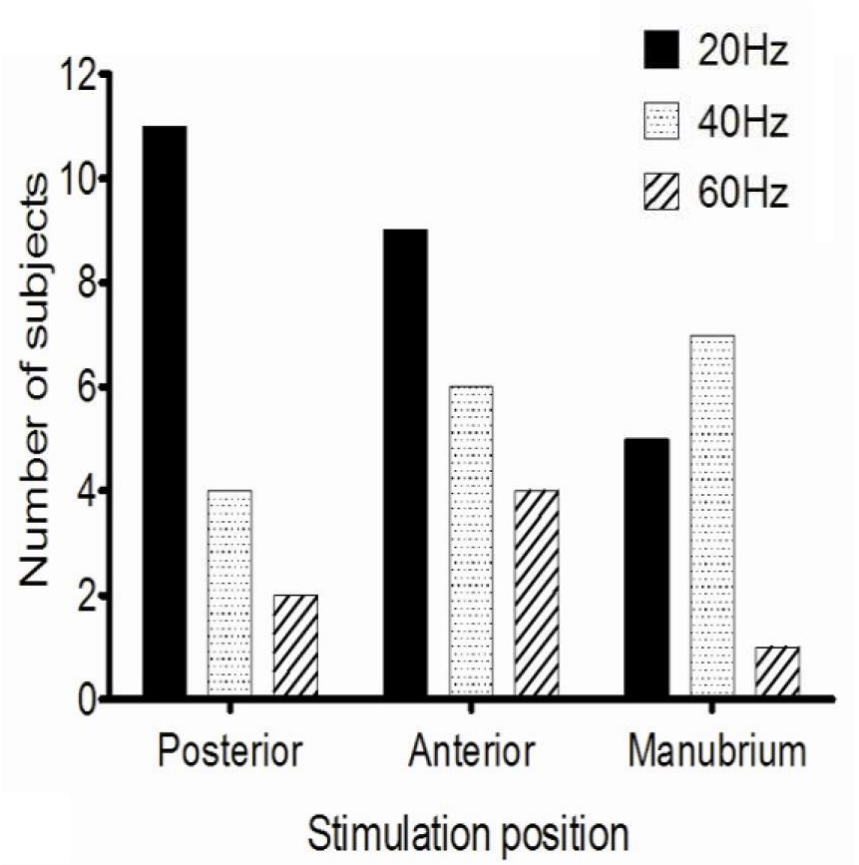




Cough 2011, 7:2

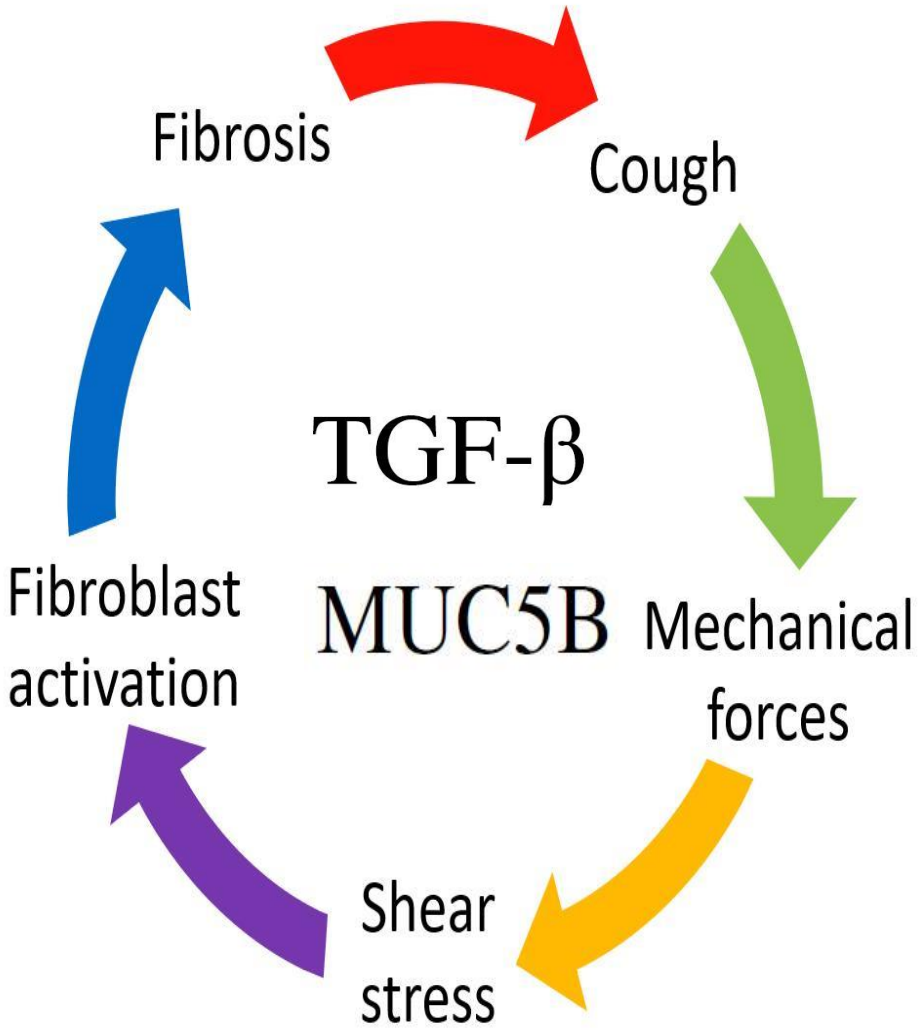
Cough threshold and frequency by mechanical induction





Cough 2011, 7:2

Hypothesis: Cough by mechanical stretch (Architectural distortion)



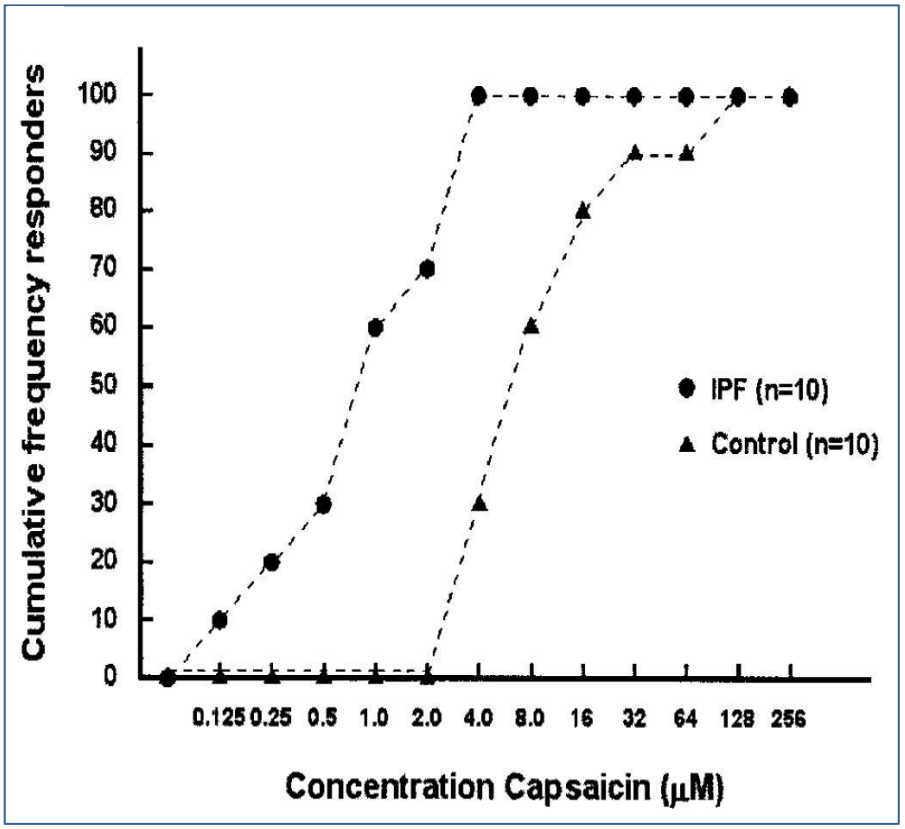
- Rapidly adapting receptors – terminate in the intrapulmonary small airways and are sensitive to mechanical stimulation with destruction of cough inhibition nerve (insensitive to capsaicin or inflammatory mediator)

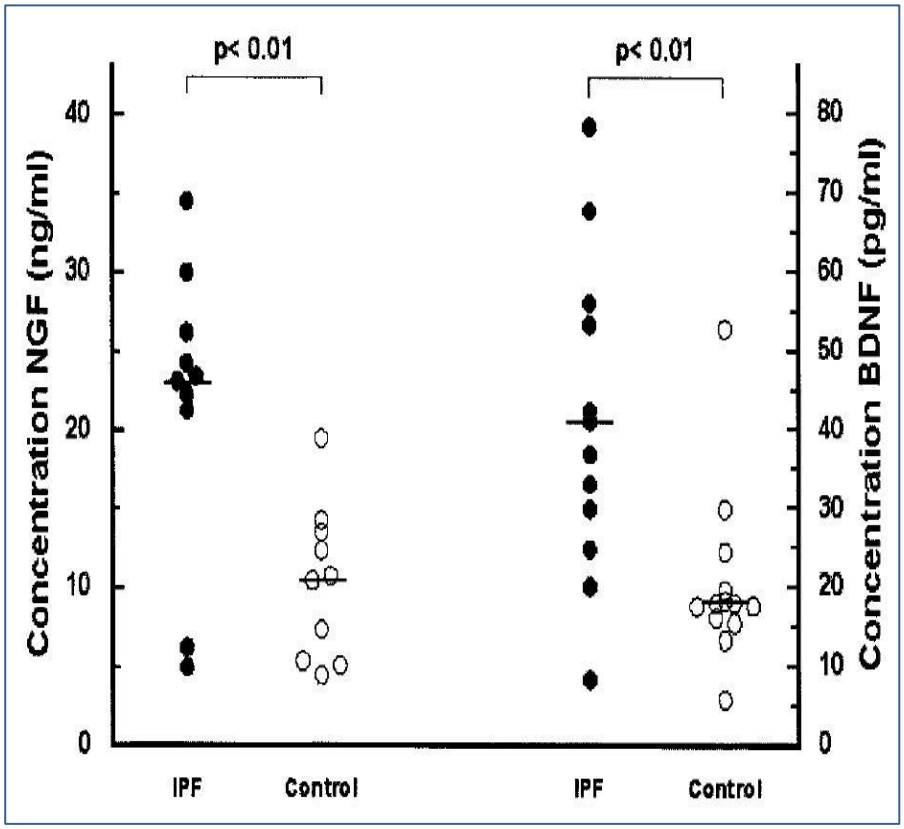
1. Reduced lung compliance directly increases the discharge rate of RARs (with rapid adaptation)
2. Transmission of vibrated impulse from peripheral to better innervated larger bronchi is enhanced in fibrotic lungs

Cough 2011, 7:2

Increased cough hypersensitivity

- Increased cough-stimulating response along with reduced cough inhibition
- Upregulation of thermal and chemical sensory fibers (Nerve growth factor/Brain derived neurotrophic factor within induced sputum.

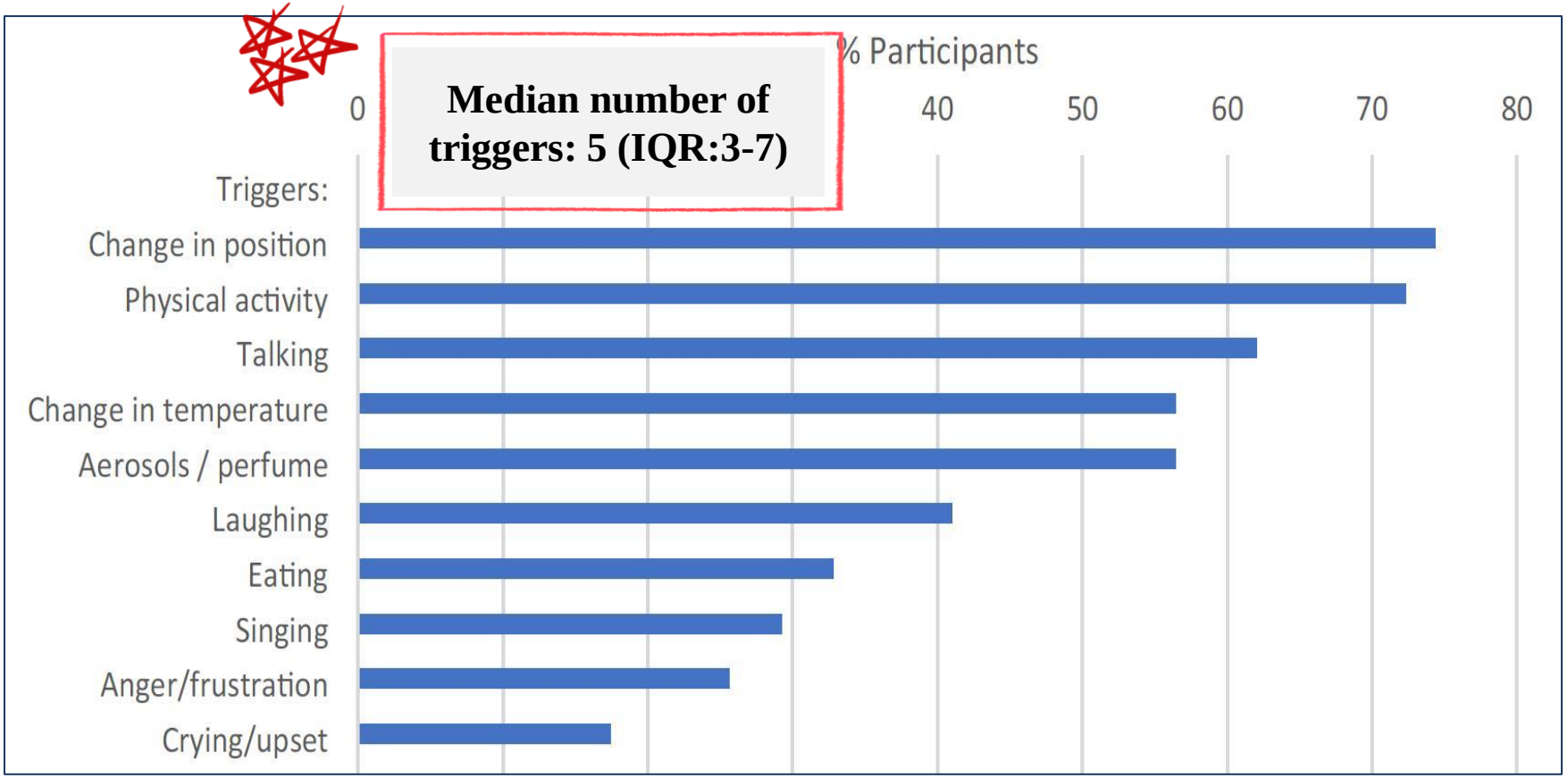




AJRCCM 2003 (168), 995-1002

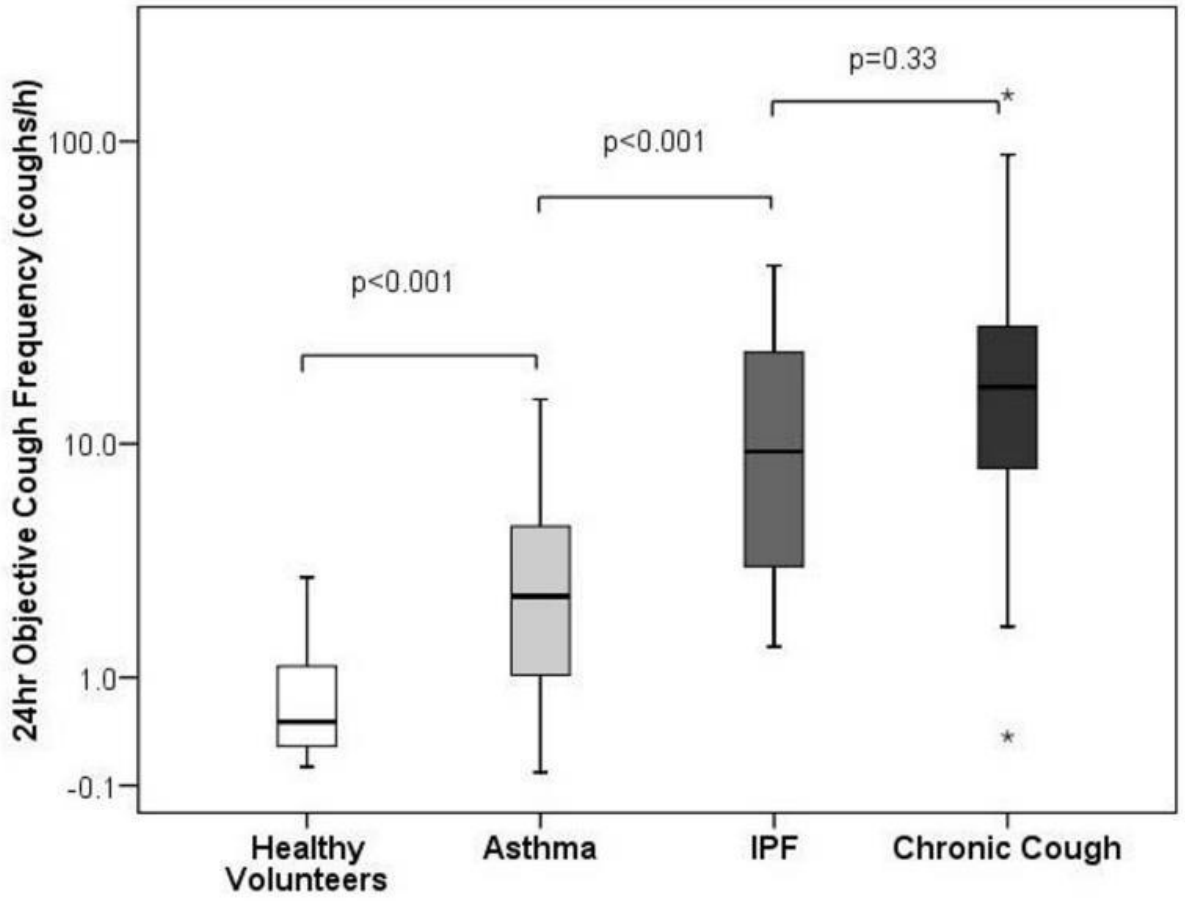
Increased cough hypersensitivity

- A total of 195 patients with ILD and cough
- IPF (75%), CTD-ILD (7%), cHP (5%), NSIP (3%), Sarcoidosis (0.5%)



Lung 2024, 202:425-430

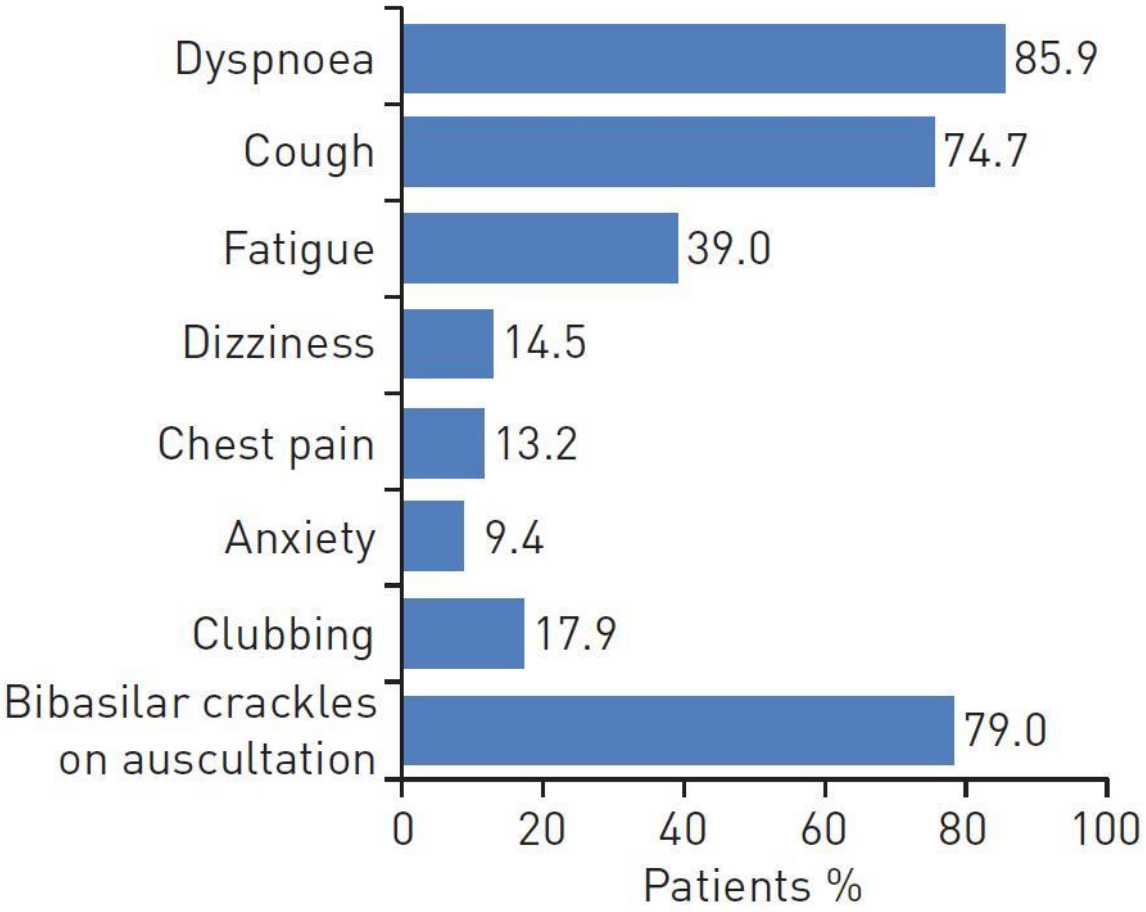
Cough in IPF



Key et al. Cough 2010, 6:4

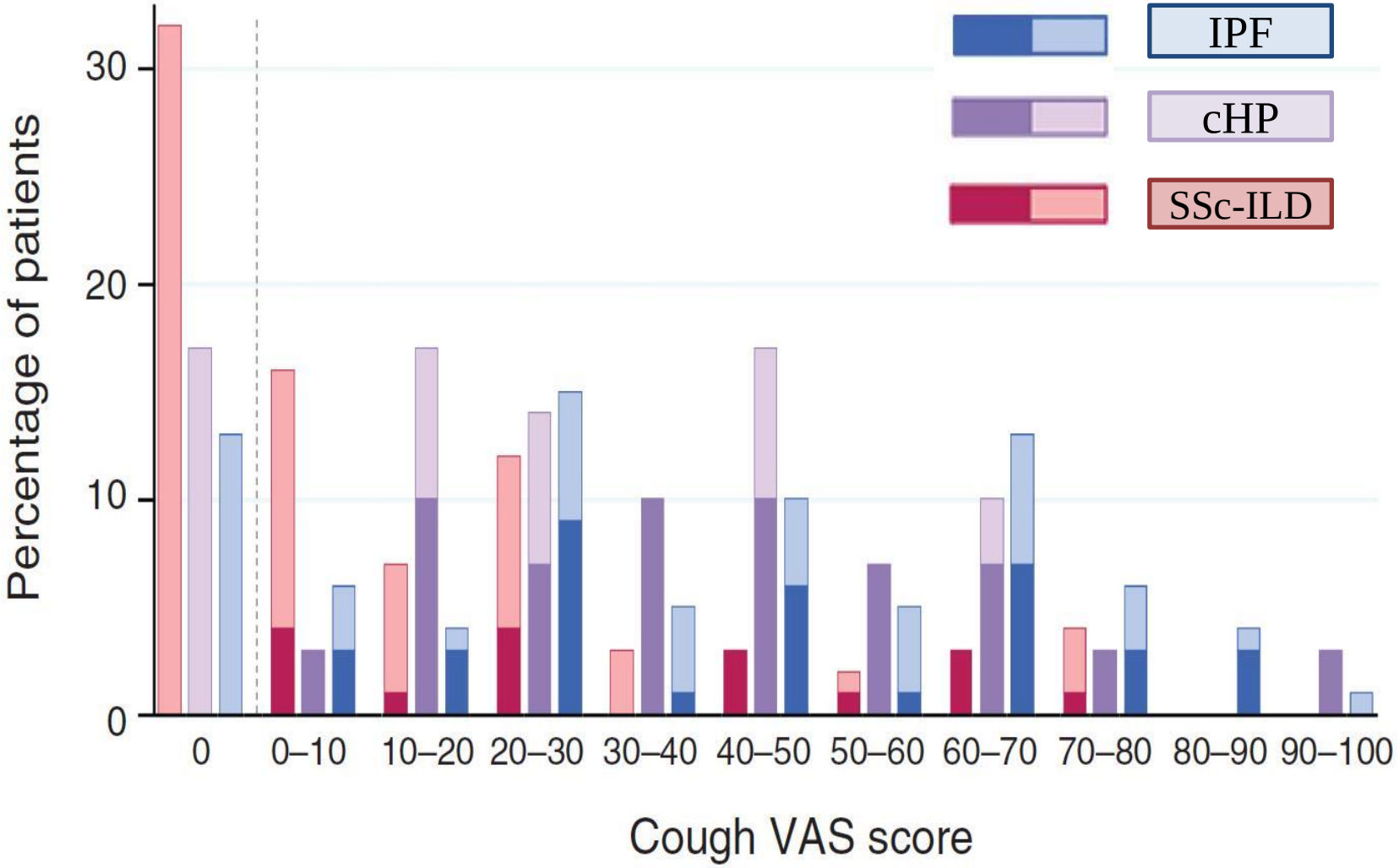
Symptoms in IPF

Symptoms at baseline INSIGHT IPF registry (N=502)



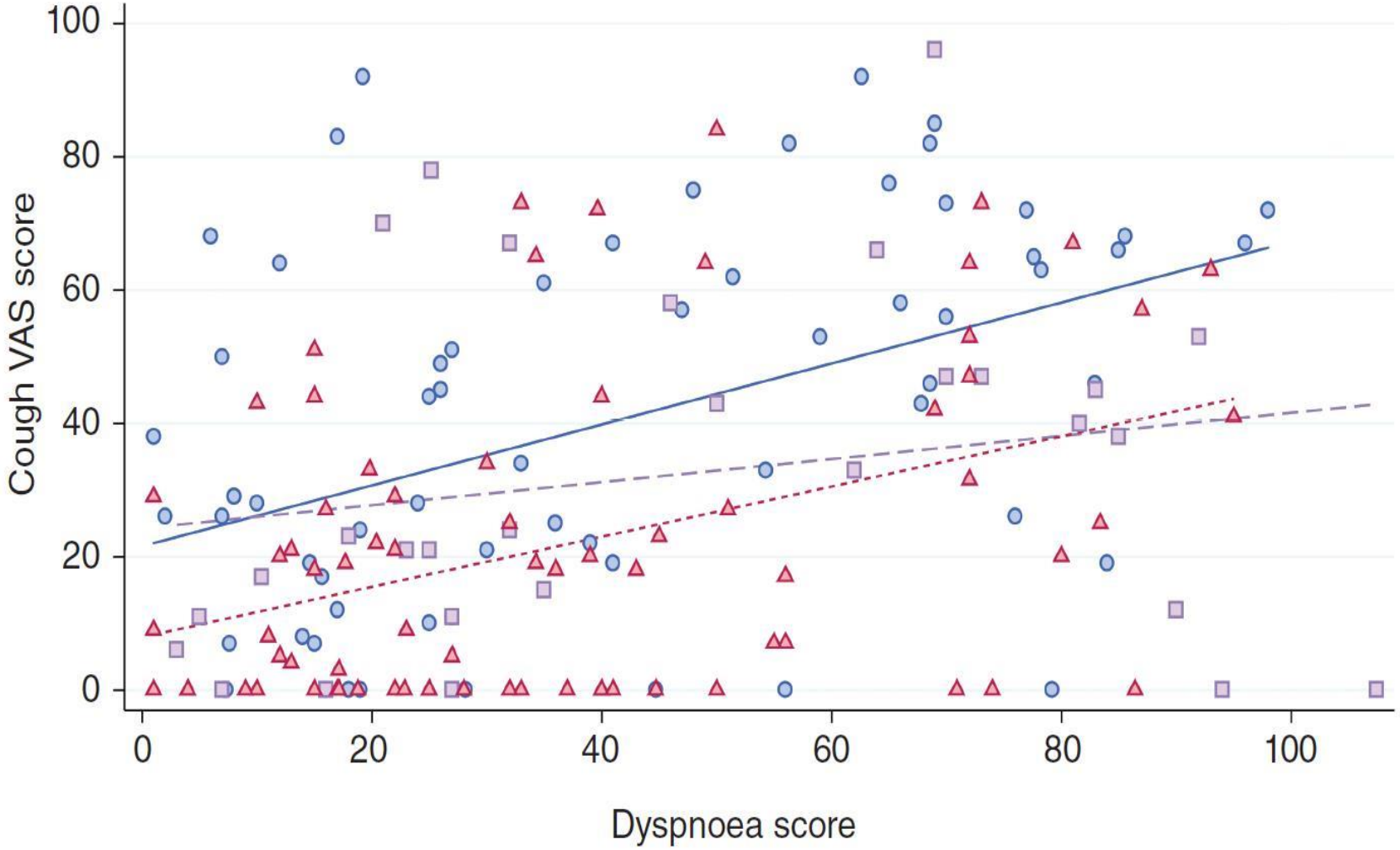
Eur Respir J 2015;46:186-196

Cough severity in ILDs



Respirology ***(2017) 22,*** 1592-1597

Significant association of Cough with Dyspnea in ILDs



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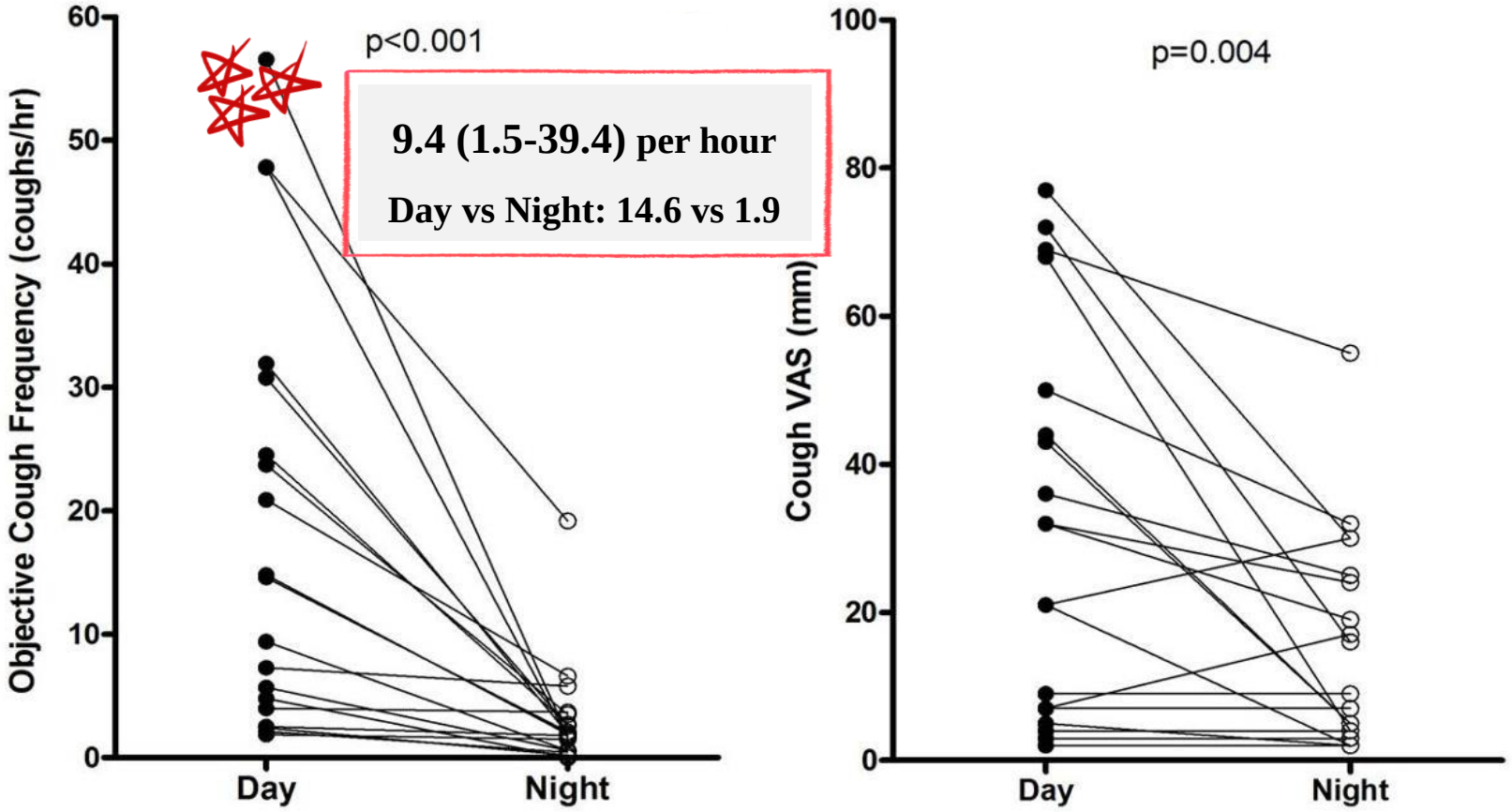
Respirology (2017) 22, 1592-1597

Cough in IPF

- Objective cough frequency in IPF (N = 19)
- 24-hour ambulatory cough recordings, LCQ, and VAS



Key et al. Cough 2010, 6:4

Cough in IPF

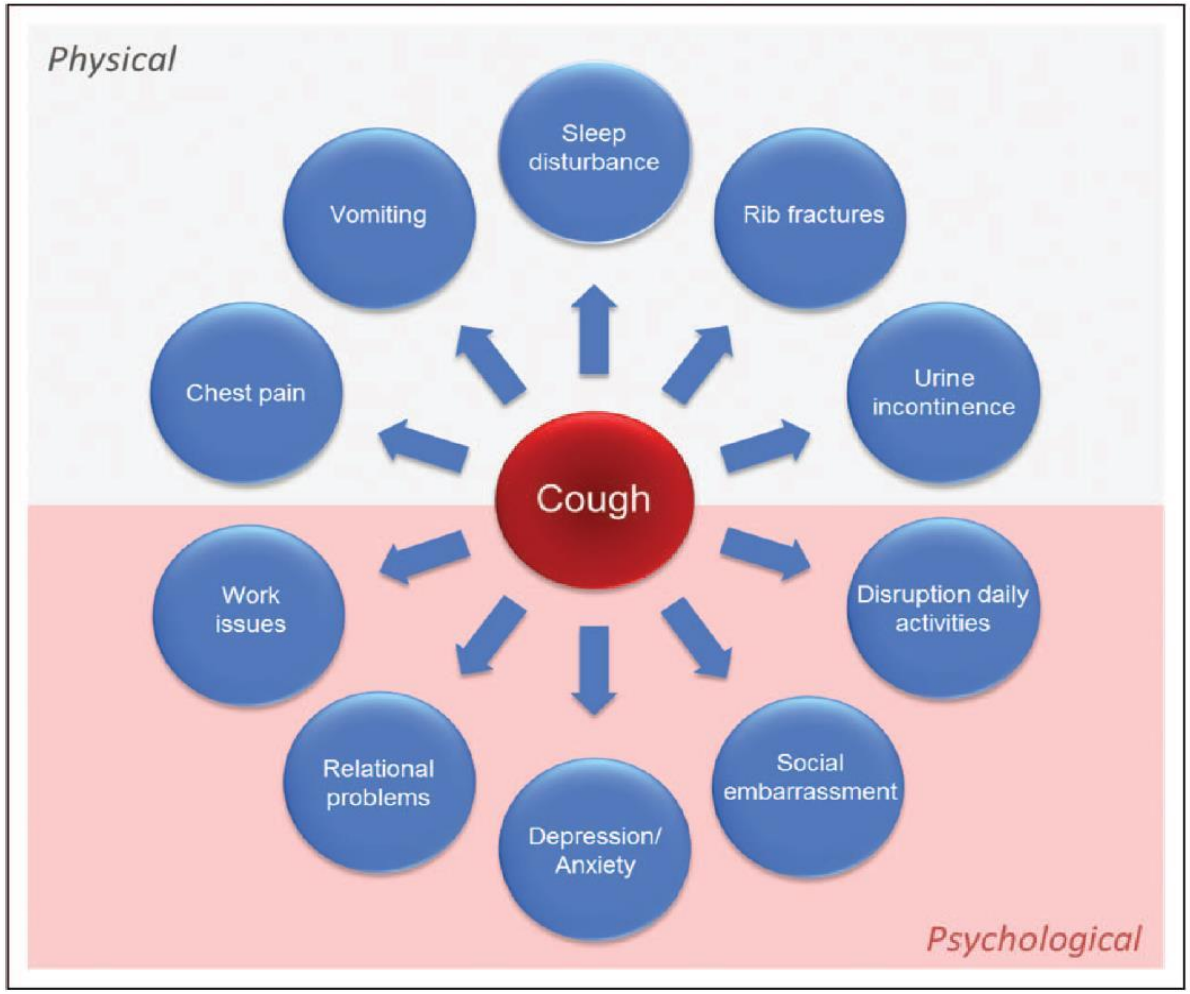
- Coughing can increase feelings of anxiety as it induces breathlessness, fatigue, air hunger, peripheral oxygen desaturation
- The social impact of chronic cough – limited exercise ability, reduced walking distance, and the need to use supplemental oxygen
- 226 – 520: Median coughs per day of an IPF patient
- The urge to cough cannot be relieved by coughing

Patient reported outcome

End-point in clinical trials

- The voice of the patients – “most significant symptoms”, “Cough fits/bouts – prolonged periods of dry, hacking cough”, “debliliating and violent coughing fits”, and “ unable to catch one’s breath”

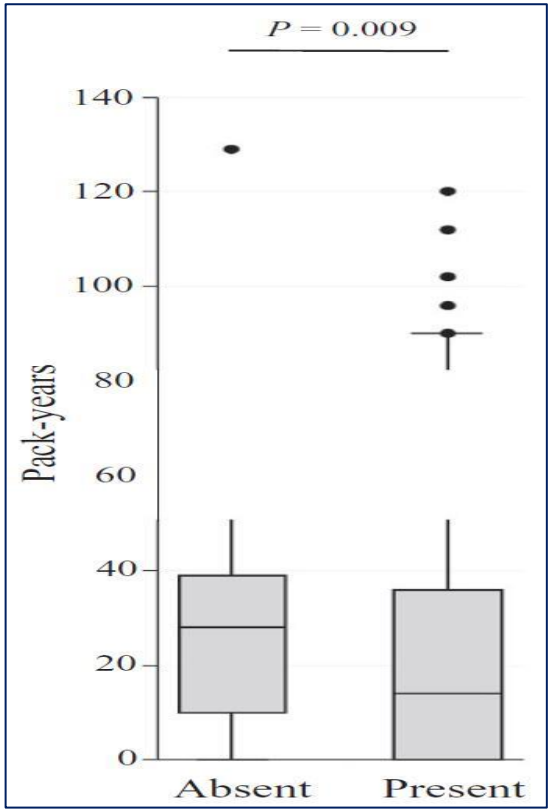
Impact of chronic cough in ILDs

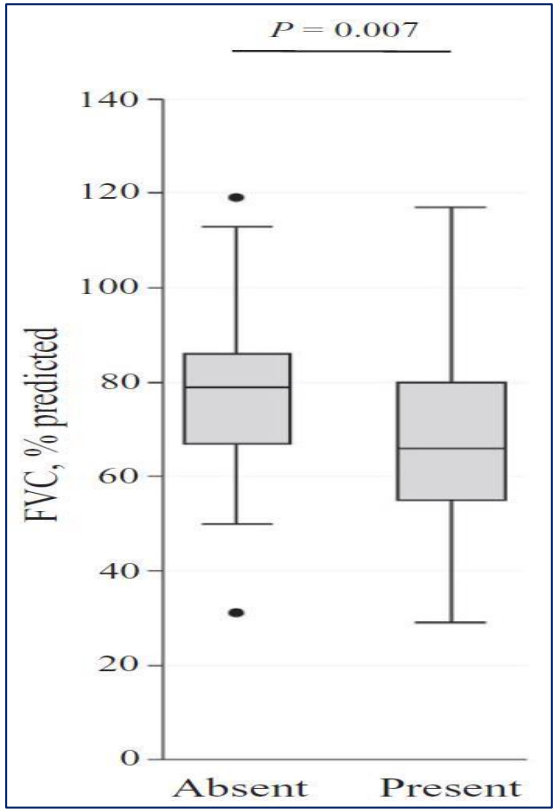


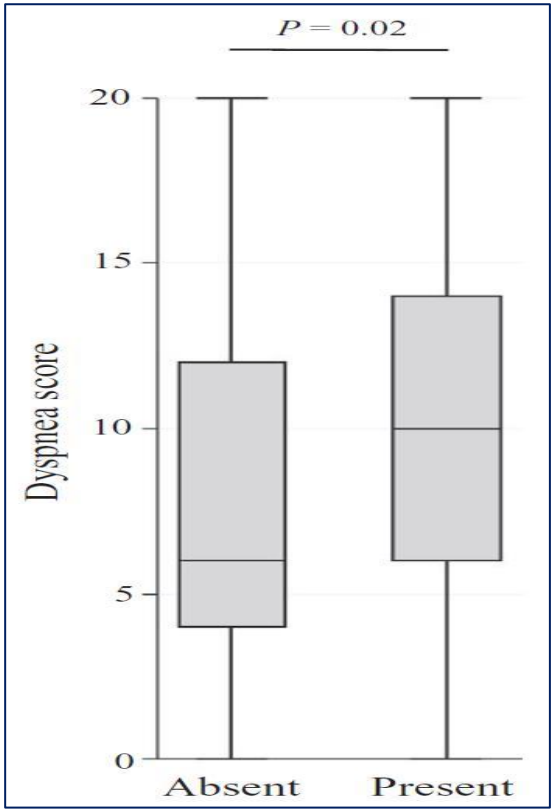
Curr Opin Support Palliat 2019, 13:143-151

Cough predicts prognosis?

- 252 IPF patients in the UCSF database between 2000 and 2010
- Retrospective study to describe the characteristics and prognostic value of cough in IPF → Cough in 84%







Respirology (2011) 16, 969-975

Cough and Prognosis (Death or lung transplantation)

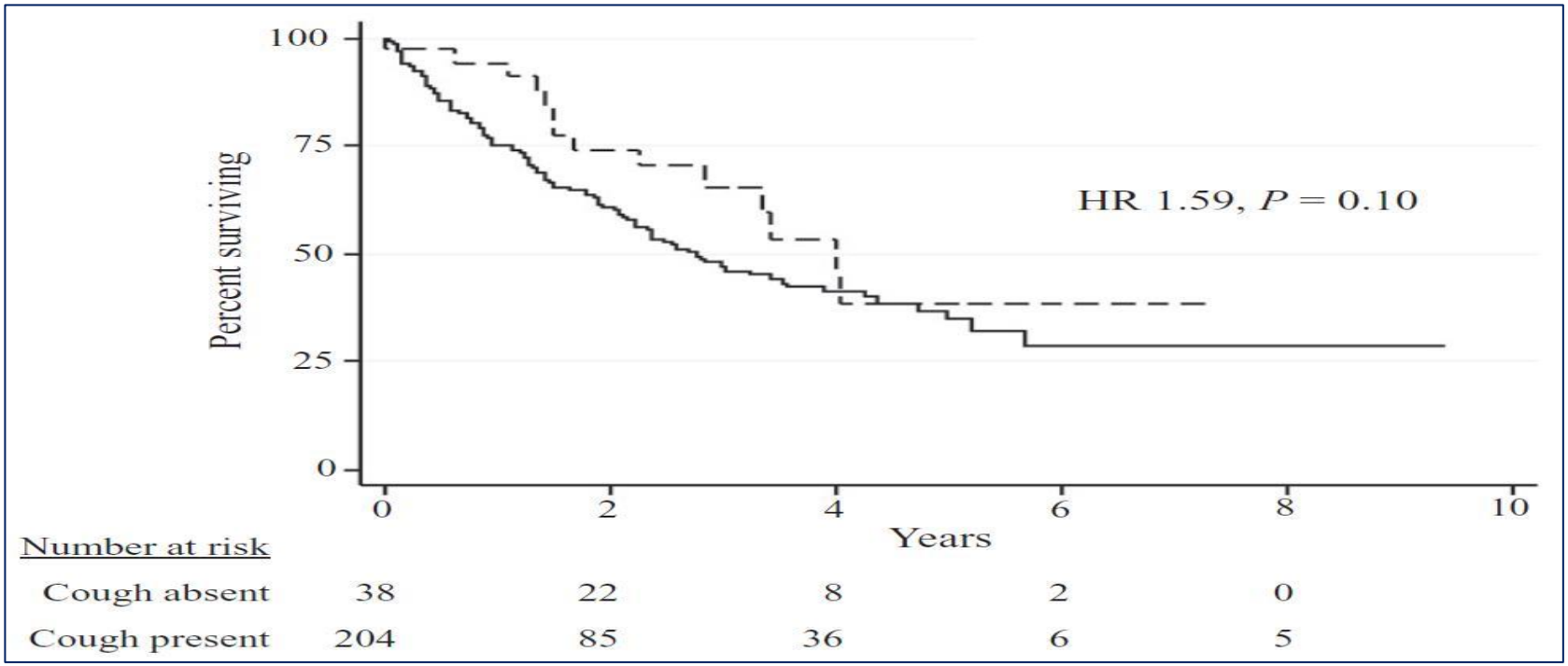


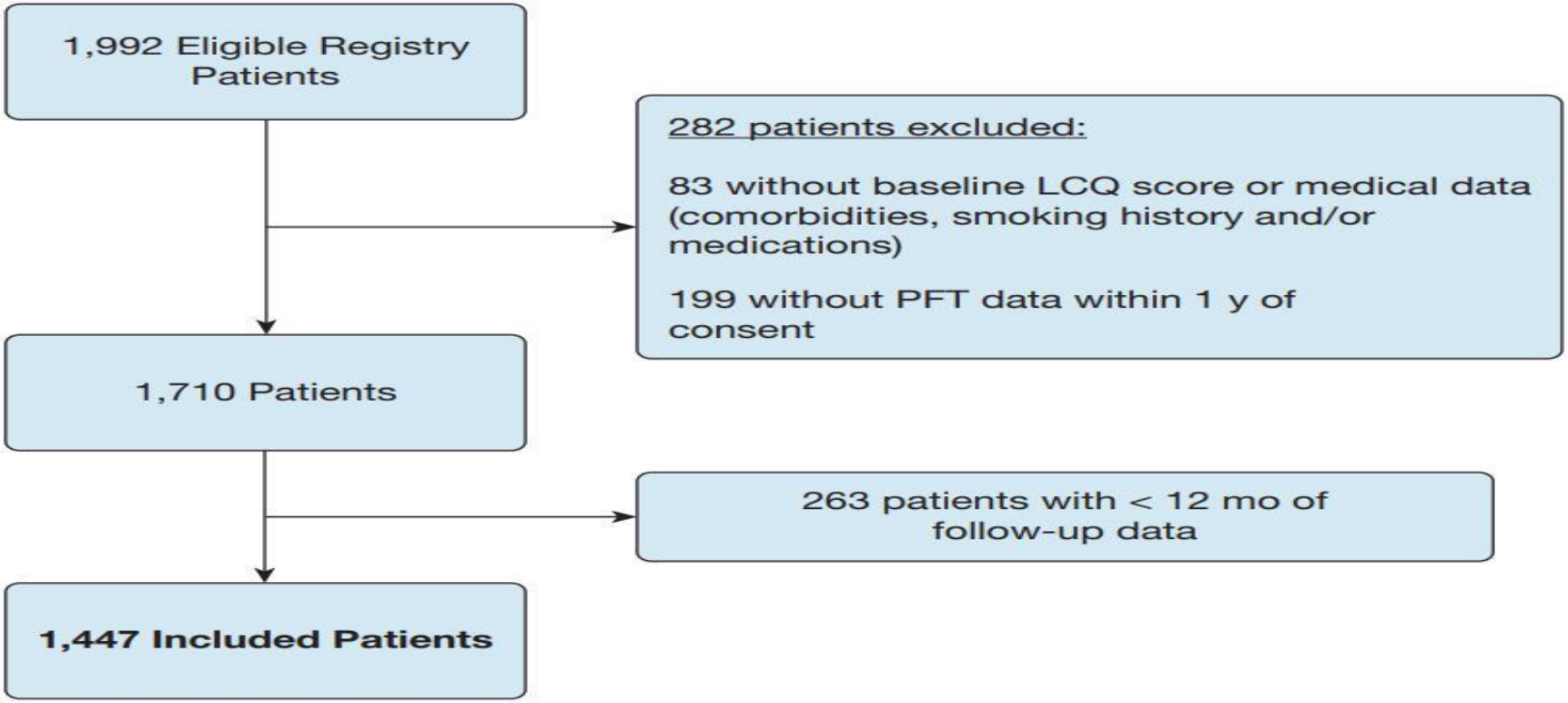
Table 5 Multivariate model of time to death or lung transplant

Variable	Unadjusted hazard ratio	Adjusted hazard ratio	95% CI	*P*-value
Cough	1.59	1.78	0.94–3.35	0.08
Long-term oxygen therapy	4.80	3.28	2.03–5.30	<0.0005
TLC, % predicted†	0.79	0.86	0.75–0.98	0.03
DL_{CO}, % predicted†	0.69	0.81	0.69–0.96	0.01

Respirology (2011) 16, 969-975

Cough-specific quality of life and prognosis

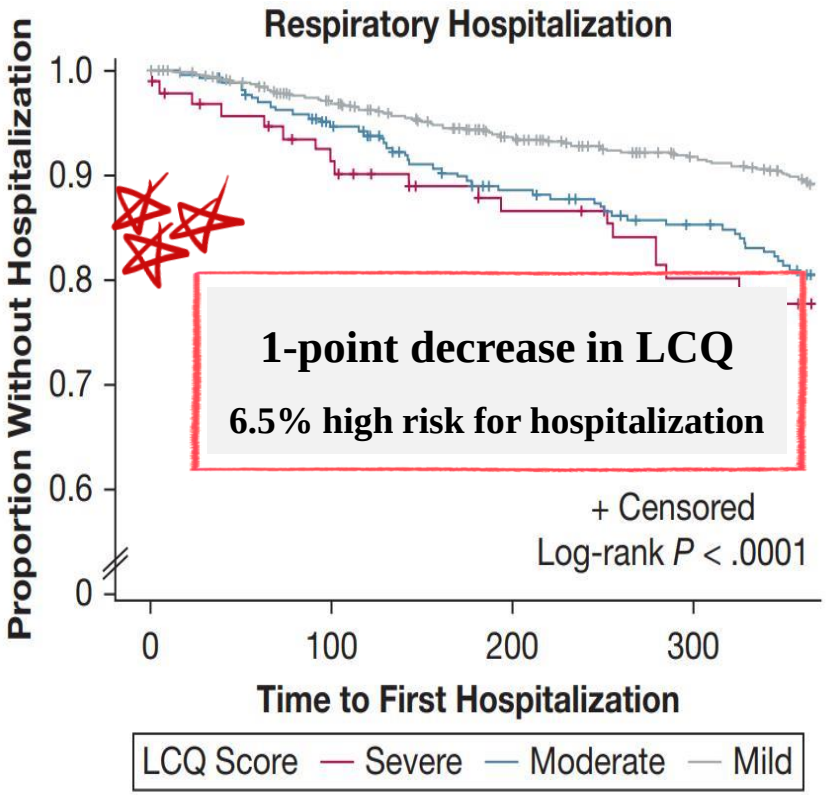
- 1,447 ILD patients in the Pulmonary Fibrosis Foundation registry (multi-center and well characterized populations) in USA
- Baseline LCQ and minimum 1-year f/u with medical data

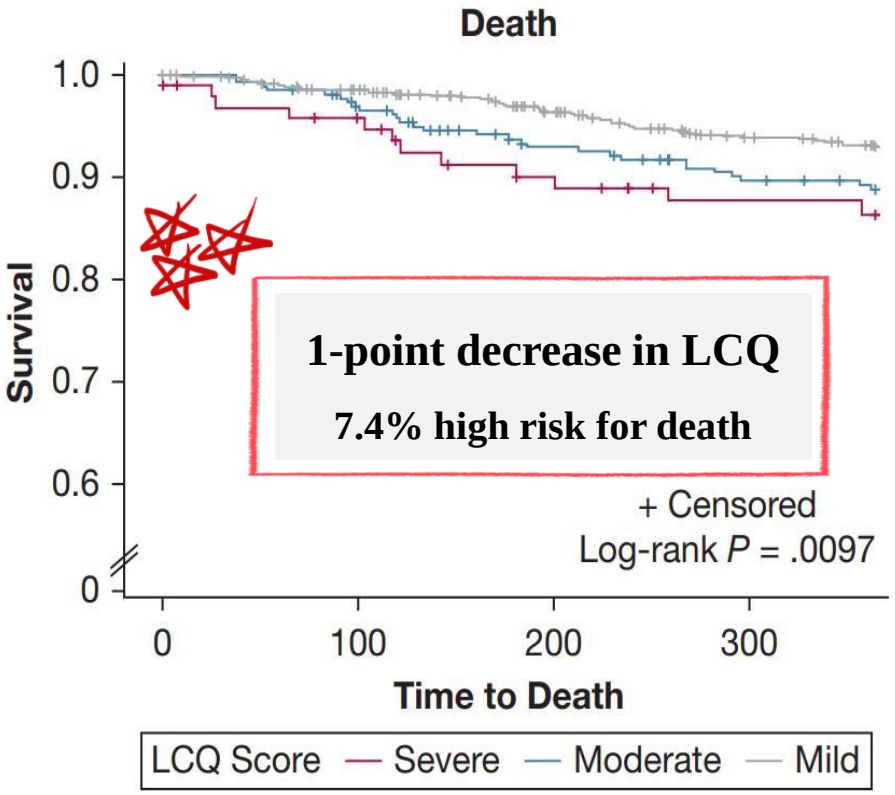


CHEST (2022); 162(3):603-613

Cough-specific quality of life and prognosis

Characteristic	Data
Mean ± SD	16.5 ± 3.7
Mild disease (≥ 14)	1,088 (75.2)
Moderate disease (10 to < 14)	264 (18.2)
Severe disease (< 10)	95 (6.6)





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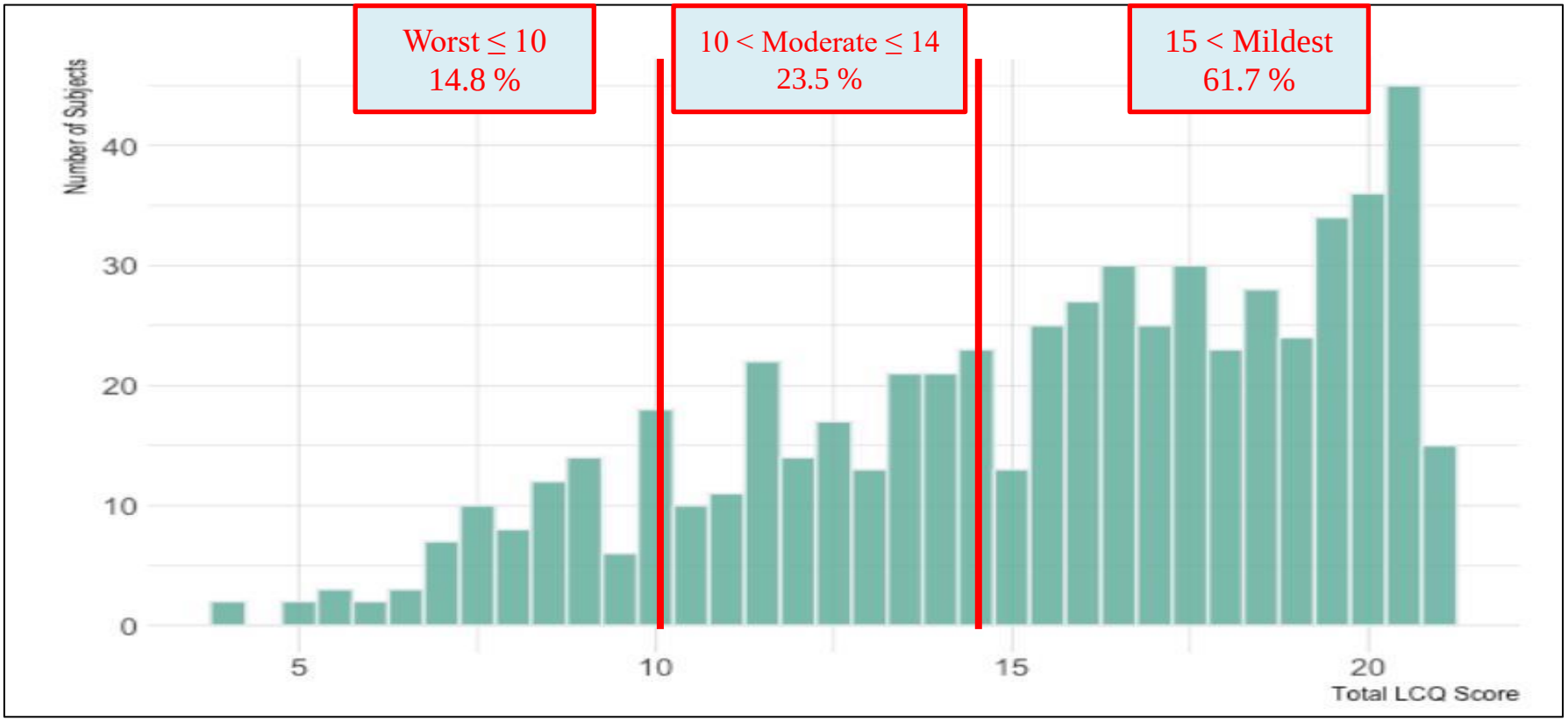
CHEST (2022); 162(3):603-613

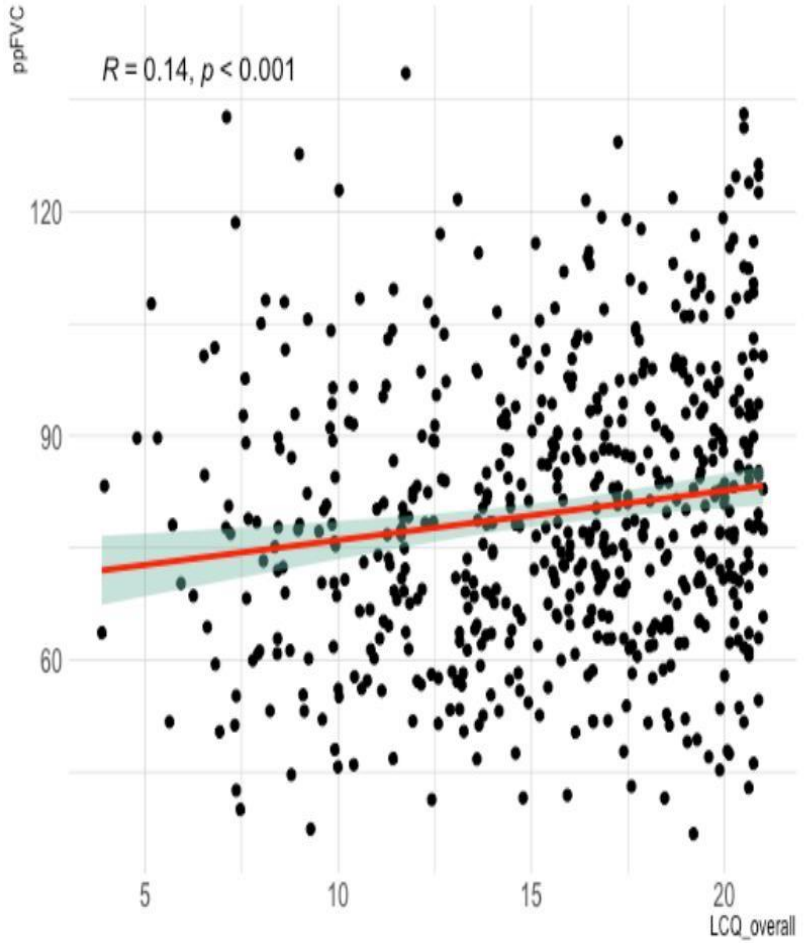
Impact of cough in IPF (the PROFILE study)

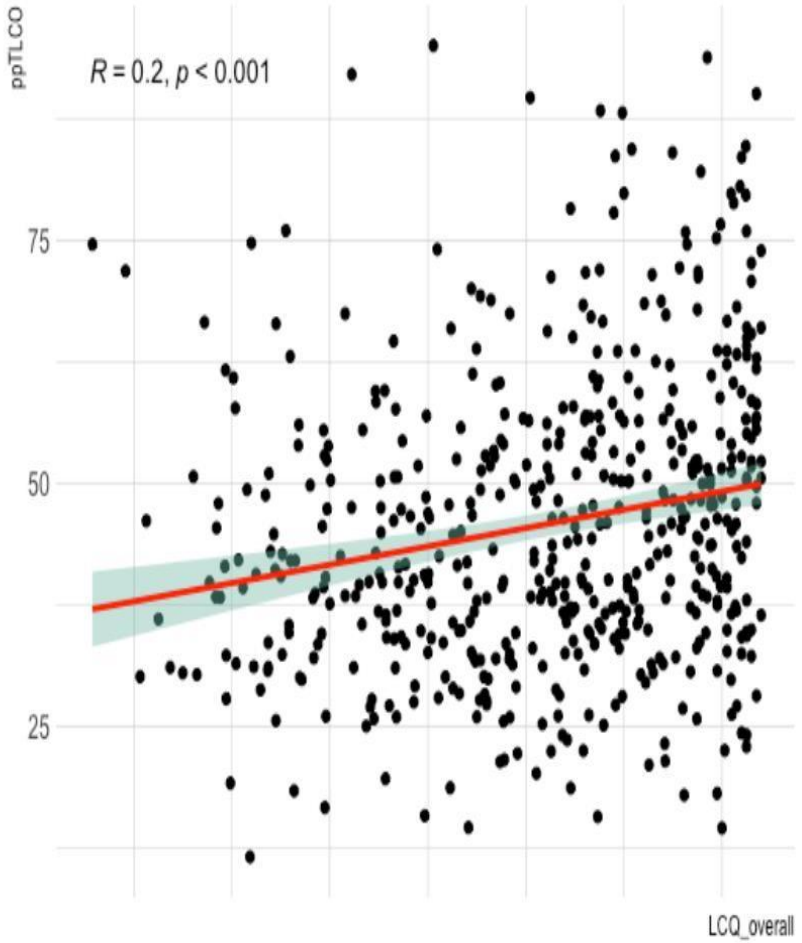
- 632 IPF patients in the PROFILE study (a prospective, multicenter, observational, longitudinal cohort in the UK.
- LCQ at baseline (Median total score: 16.1), 6 months, and 12 months



Ann Am Thoracic Soc (2023); 20(9):1267-1273

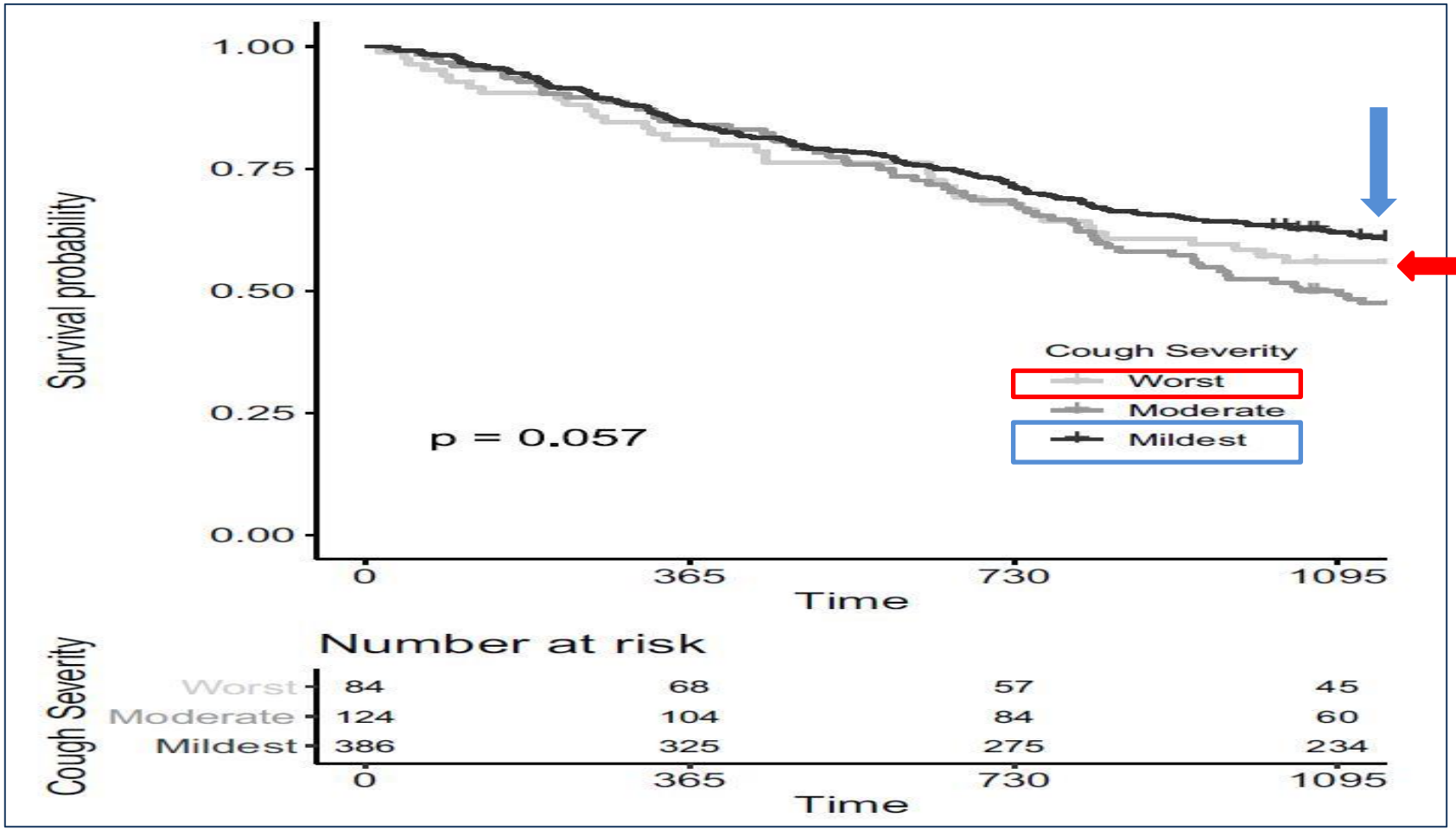
LCQ correlates weakly with FVC and DLco





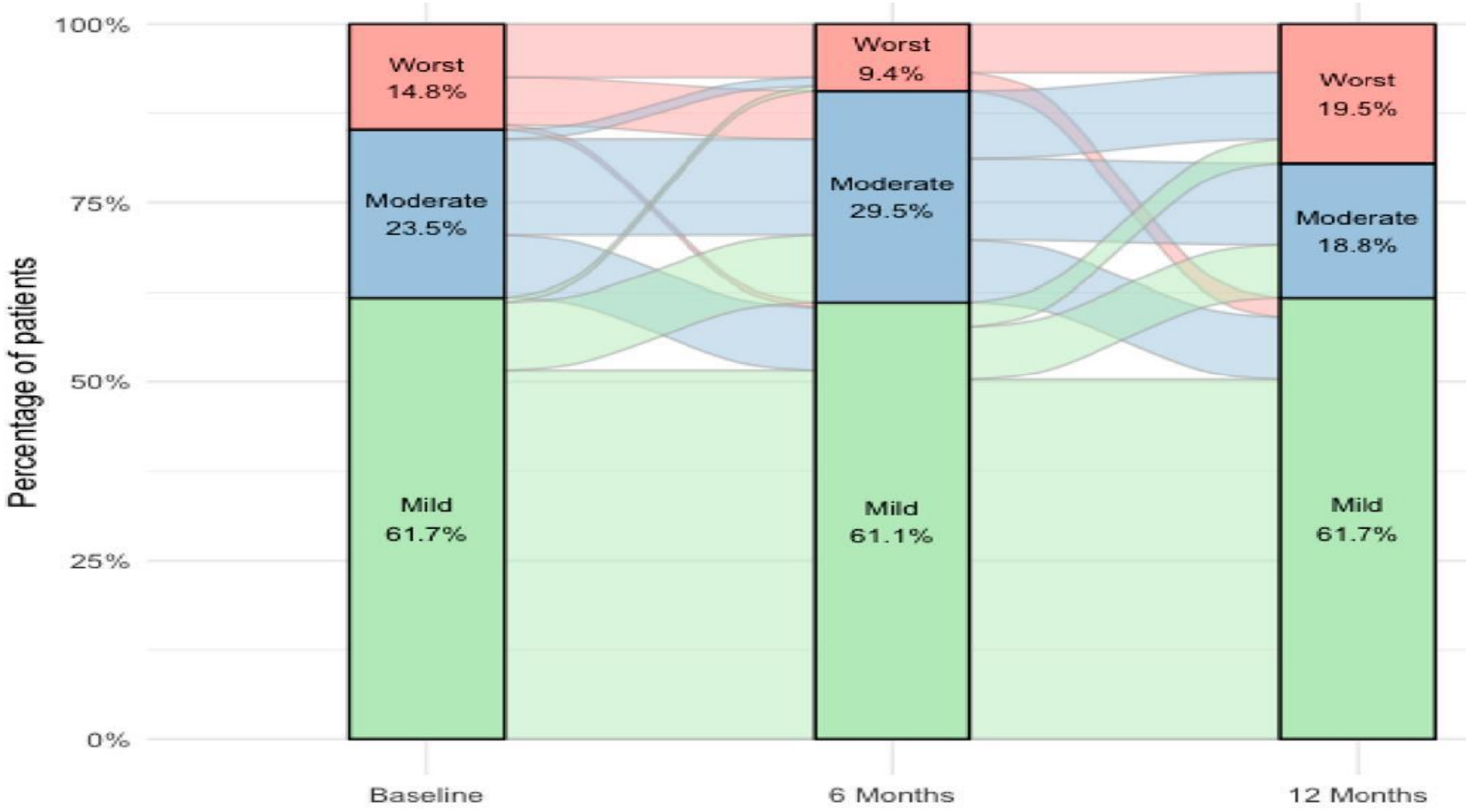
Ann Am Thoracic Soc (2023); 20(9):1267-1273

LCQ correlates weakly with FVC and DLco



Ann Am Thoracic Soc (2023); 20(9):1267-1273

Chang of LCQ



Ann Am Thoracic Soc (2023); 20(9):1267-1273

Work-up of patients with chronic cough in IPF

Identify treatable trait

History, Physical Examination
Imaging, Pulmonary Function, Bloods

Potential treatable traits

Reflux
Nasal inflammation
Laryngeal dysfunction
Airway obstruction
Eosinophilic inflammation
OSA

Medications
Exposures
Infections
Malignancy

Sometimes treatment effect

Consider further investigations

Major pulmonary complications of autoimmune rheumatic disease (connective tissue disease)

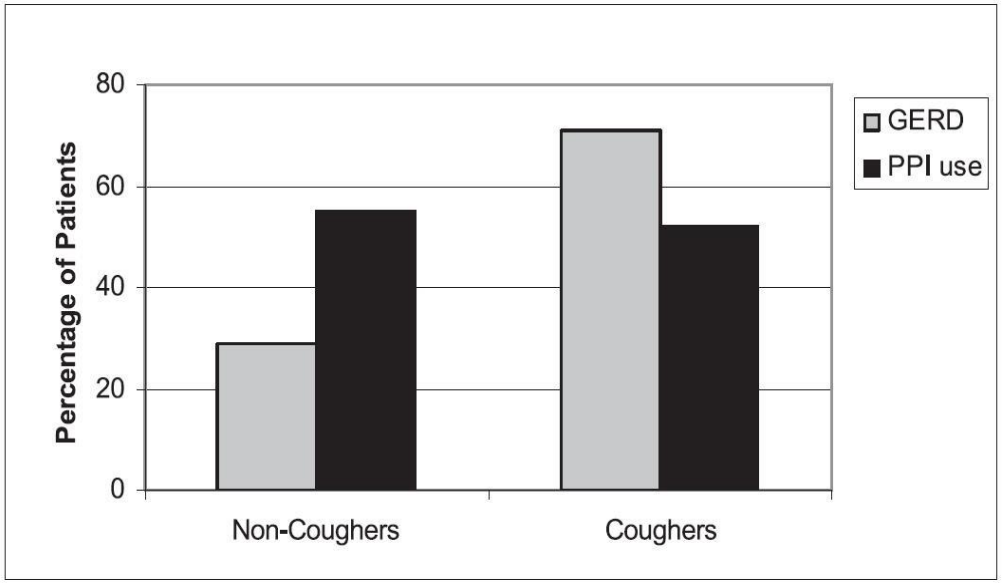
Scleroderma/systemic sclerosis	Rheumatoid arthritis
• Interstitial lung disease (+++) • Aspiration pneumonia (++) • Pulmonary hypertension (+++) • Chest wall restriction	• Interstitial lung disease (++) • Pleural disease (++) • Bronchiolitis obliterans (+) • Drug-induced (+)
Mixed connective tissue disease	**ANCA vasculitis**
• Interstitial lung disease (++) • Pulmonary hypertension (++)	• Pulmonary haemorrhage (++) • Interstitial lung fibrosis (especially MPO +)
Polymyositis/Dermatomyositis	**SLE**
• Respiratory muscle weakness (++) • Interstitial lung disease (especially anti-synthetase +)	• Serositis (+++) • Diffuse Alveolar Hemorrhage (++) • Interstitial lung disease

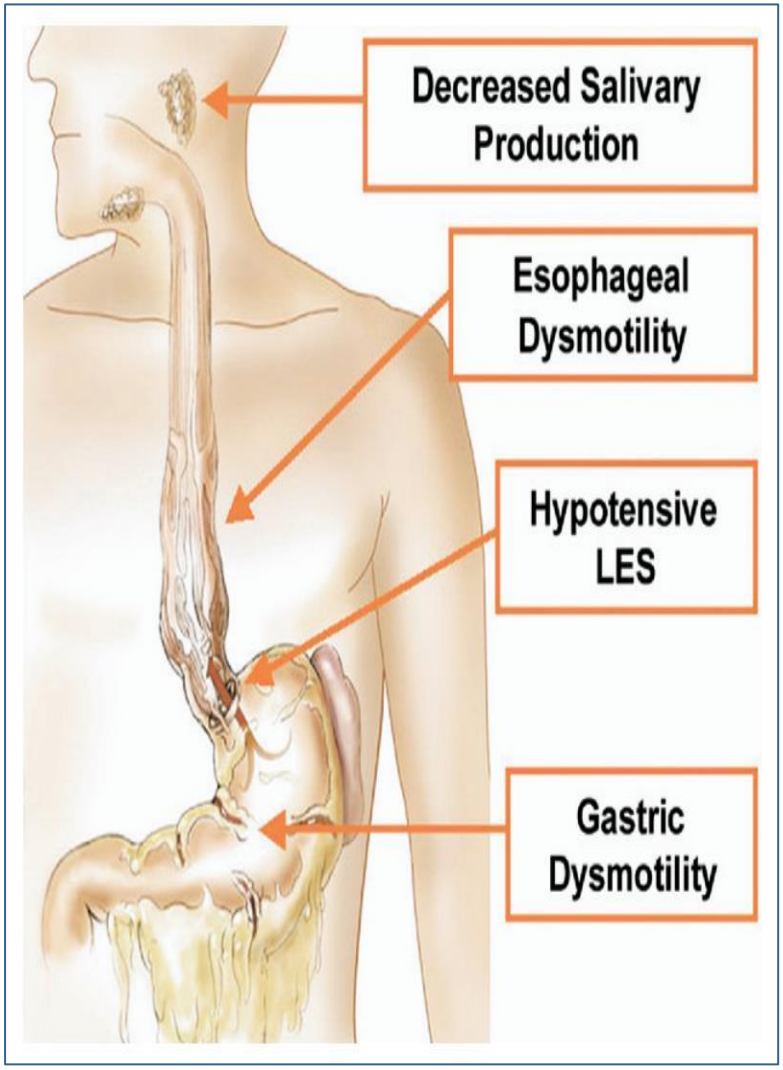
Cough in SSc-ILD

- Cough – a common and significant symptom in 73% (mild 62.3%, moderate: 32.5%, severe: 5.2%) – a major contributor to poor quality of life
- Mechanism – inflammation, fibrosis, GERD, and increased cough sensitivity
- Correlation of fibrosis in the skin and lung, diffuse scleroderma, and neutrophilic alveolar inflammation (associated with the loss of lung function). In SENSCIS trial, a cough at baseline had a greater extent of fibrotic ILD.
- In SLS 1 → cough could be a useful surrogate measure of ongoing fibrosis and inflammation.
- GERD should be considered.

Cough and Reflux in Scleroderma

- Gastro-intestinal symptoms in scleroderma (up to 90 %)
- Cough (73%) - 2nd most common symptom in the SLS I
- (mild 62.3%, moderate: 32.5%, severe: 5.2%)





CHEST 2012;142(3):614-621

Cough in Sjogren-related ILD

- Pulmonary complication 9-20% (Airway involvement is common)
- Suggested mechanism

  → Airway dryness (lymphocytic destruction of glandular epithelial mucosa), airway inflammation, impaired mucociliary clearance, and bronchial hyperresponsiveness

  → Bronchiectasis (7-54%)

Cough in Sarcoidosis-related ILD

- Chronic cough: 3-53% → impact on quality of life
- Suggested mechanisms

  1) Airway inflammation, and hyper-responsiveness by granulomatous inflammation

  2) Compression of the vagus nerve by lymphadenopathy, fibrotic alteration of the airway, and vascular

  3) Granulomatous tracheitis

Curr Opin Support Palliat Care 2019, 13:143-151

Work-up of patients with chronic cough in IPF

Identify treatable trait

History, Physical Examination
Imaging, Pulmonary Function, Bloods

Potential treatable traits

Reflux
Nasal inflammation
Laryngeal dysfunction
Airway obstruction
Eosinophilic inflammation
OSA

Medications
Exposures
Infections
Malignancy

Manage treatable trait(s)

Sometimes treatment effect

Consider further investigations

Cough likely due to PF

Treat the pulmonary fibrosis

No registered therapies; target the cough hypersensitivity

Refer for trials

CASE – Other ILD

▶ F / 68

▶ Chief complaint: Cough

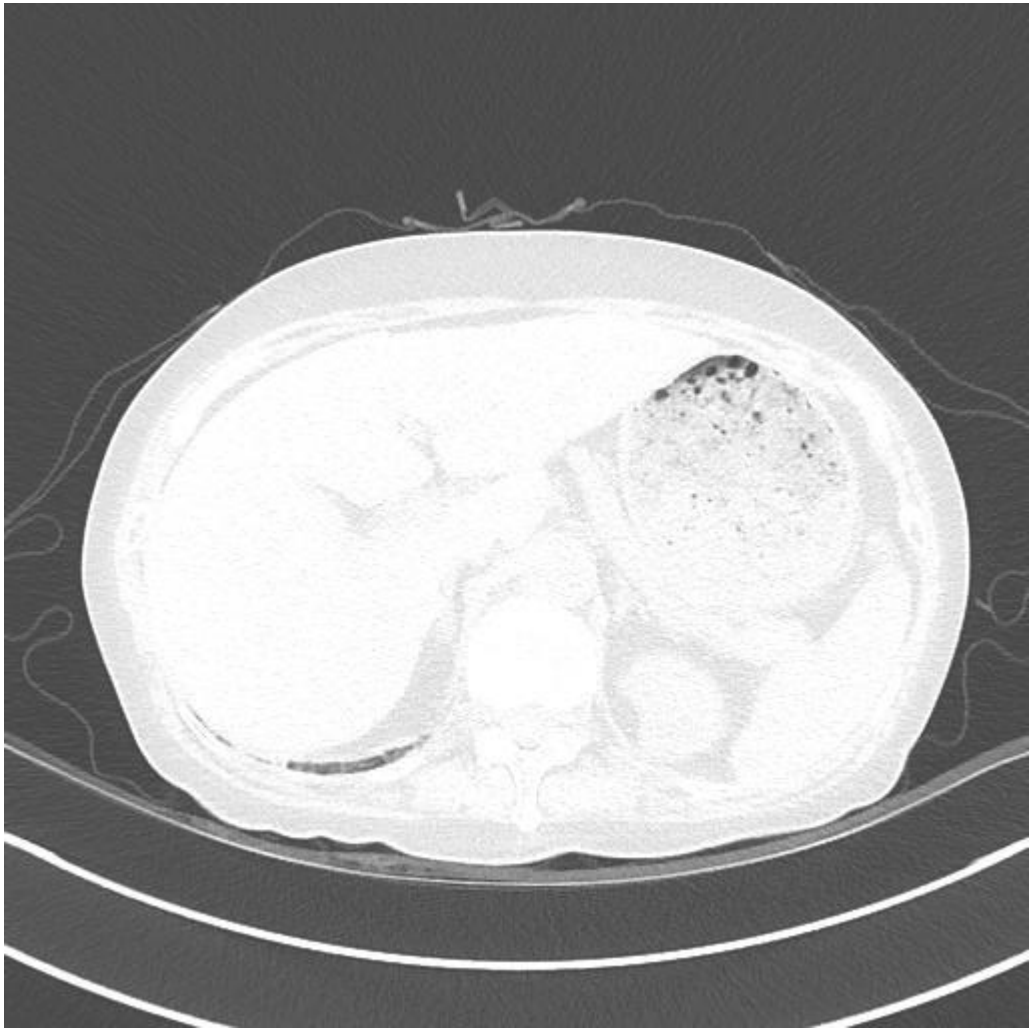
▶ PI : 68세 여자 환자가 raynaud phenomenon으로 2020년 부터 A 대학병원 류마티스 내과 진료 중, 3개월 전부터 시작되어 악화되는 기침으로 본원 호흡기내과에 내원하였다. 전화하거나 말 할 때 심해지고, 발작적이며 하루 종일 지속된다고 한다. 등산을 해도 호흡곤란은 없다고 한다. 근육 생검 하였으나, 류마티스 질환은 진단되지 않고 추적 관리 중이라고 함.

▶ Arthritis (-) Raynaud (+) Sicca symptom (-)

▶ Never-smoker ▶Family history (-)

▶ Hyperlipidemia(2012), Osteoporosis(2021)

HRCT



Multidisciplinary discussion

Clinical probability for IPF
Low

CC	Dyspnea	KL-6
Cough	mMRC 0	524.4 U/mL

PFT	FVC (%)	DLco (%)
	109	73

6MWT	Initial SpO_2(%)	Lowest SpO_2(%)	Distance
	99 %	96 %	485 m

HRCT
NSIP pattern vs indeterminate for UIP

Anti Nuclear Ab	Positive: nucleolar (1:320)
ANCA	Negative
Anti-CCP Ab	0.7
RA	< 10.0
Anti-SS-A (Ro) Ab	Negative(4.1)
Anti-SS-B (La) Ab	Negative(0.2)
Anti-ds DNA IgG 정량 (IU/mL)	Negative(1.7)
Anti-RNP Ab	Negative(1.3)
Anti-Sm (Smith) Ab	Negative(2.8)
C3	118.8
C4	17.4

MDD

PFT	FVC (%)	DLco (%)
	109	73

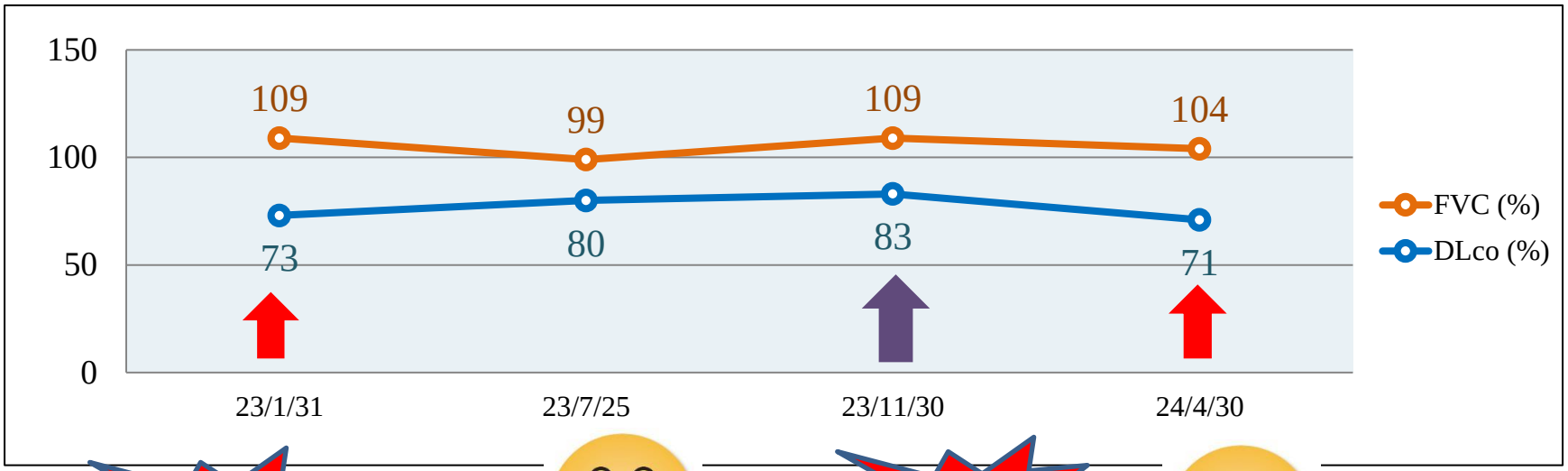
HRCT
NSIP pattern Fibrosis extent - mild

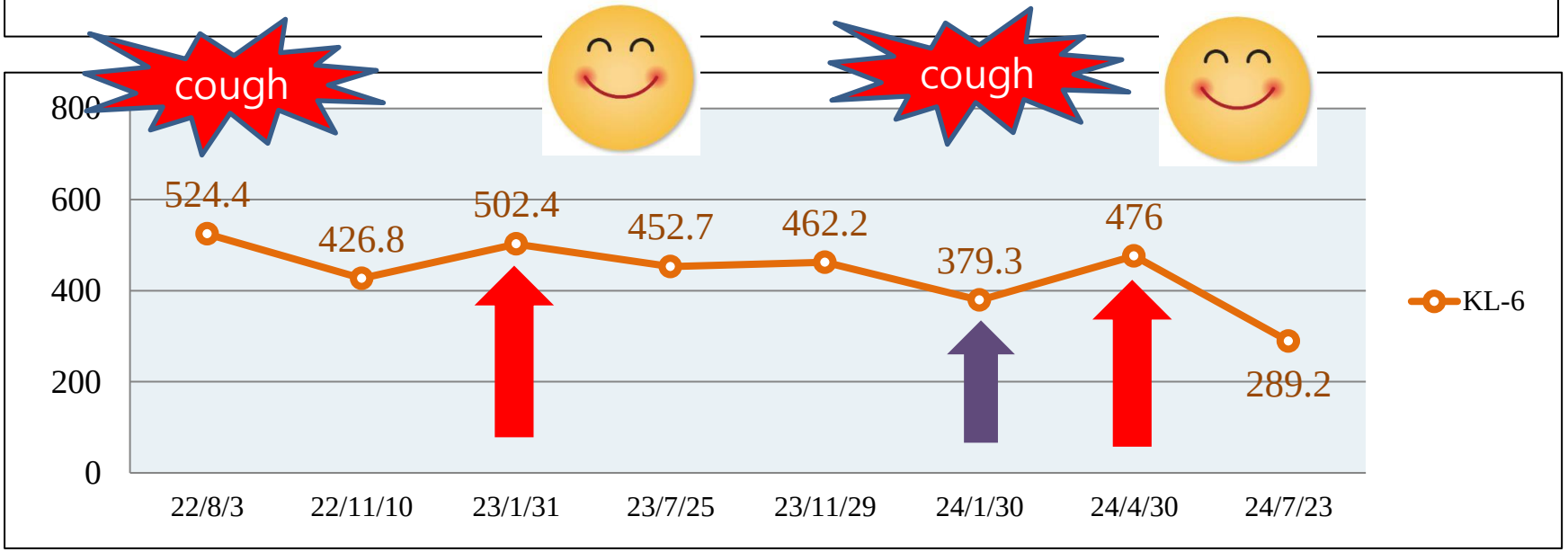
Idiopathic (IPAF)

Discussion

- VATS ?
- BAL ?
- Close monitoring for disease progression ?
- Treatment ?

Treatment and Progress





Treatment – Pirfenidone

- International, multicentre, prospective, and observational study (2013-2016)
- IPF (FVC > 50% and DLco > 30%)
- Ambulatory cough monitoring system, LCQ, and VAS after Pirfenidone use

	Baseline	At 12 weeks	Change# (95% CI)	p-value#
Subjects n	43	31		
24-h cough	520 (91 to 3394)	392 (75 to 1746)	−34% (−48 to −15%)	0.002
Coughs per hour	23 (4 to 141)	17 (3 to 73)	−35% (−49 to −17%)	<0.001
Daytime	28 (5 to 171)	20 (4 to 121)	−33% (−47 to −14%)	0.003
Night-time	7.2 (0.7 to 101)	3.3 (0 to 54)	−34% (−54 to −5%)	0.029
LCQ	12±4	15±4	2.0 (1.0 to 3.0)¶	<0.001
VAS cough	67±15	47±27	−19 (−28 to −10)	<0.0001
VAS urge-to-cough	68±16	49±25	−18 (−26 to −10)	<0.0001
K-BILD total	50±22	55±23	3.4 (−2.3 to 9.1)	0.245
HADS anxiety	8.5±4	8.5±4	0.7 (−0.6 to 1.9)	0.291
HADS depression	4.7±3	6.0±3	1.6 (0.5 to 2.6)	0.004
GAD-7	5.8±6	5.9±6	0.7 (−0.9 to 2.3)	0.396
FVC % pred	78±15	79±17		
T_{LCOc} % pred	51±13	51±16		

Eur Respir J 2017;50:1701157

Effect of Nintedanib on symptoms in PPF

INBUILD trial - Main secondary end points: K-BILD

Overall population: 0.55 (nintedanib) vs -0.79, Difference (HR): 1.34 (-0.31 to 2.98)

The Living with Pulmonary Fibrosis questionnaire

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
M. WIJSENBEEK ET AL.

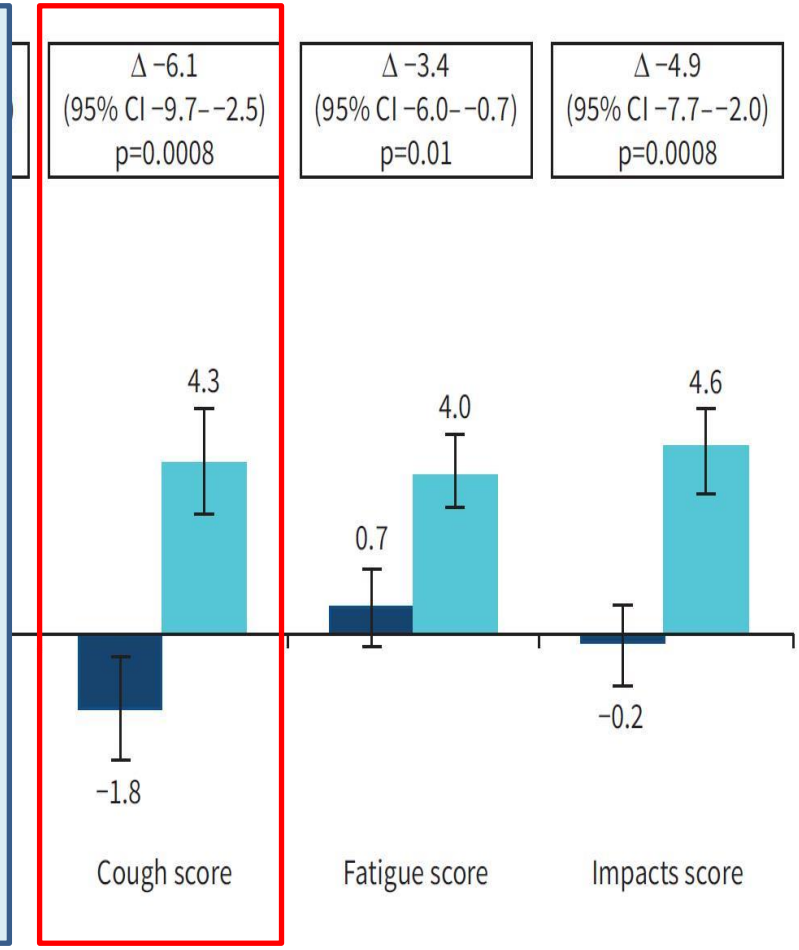
Effects of nintedanib on symptoms in patients with progressive pulmonary fibrosis

Marlies Wijsenbeek[1], Jeffrey J. Swigris[2], Yoshikazu Inoue[3], Michael Kreuter[4,5], Toby M. Maher[6,7], Takafumi Suda[8], Michael Baldwin[9], Heiko Mueller[10], Klaus B. Rohr[9] and Kevin R. Flaherty[11] on behalf of the INBUILD Trial Investigators

ERJ 2024; 63:2300752

Effect of antifibrotics on cough in PPF

- The L-PF vs The K-BILD ?
- Actual mechanism behind the effect of Nintedanib on symptoms?
- Preserving lung function might be beneficial in preventing deterioration in symptoms and patients-reported outcomes



ERJ 2024; 63:2300752

Morphine (PAciFy COUGH trial)

Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial

- A phase 2, multicenter (UK), double-blind, placebo-controlled, crossover trial
- IPF diagnosis and chronic cough (over 8 weeks), VAS over 30mm (0 to 100mm)
- FEV1/FVC ratio > 0.7, DLco > 30%, FVC > 45%
- Morphine 5mg twice orally, Treatment period: 14 days, washout: 7 days
- 24-hour ambulatory cough monitoring, VAS, and patient-reported outcomes

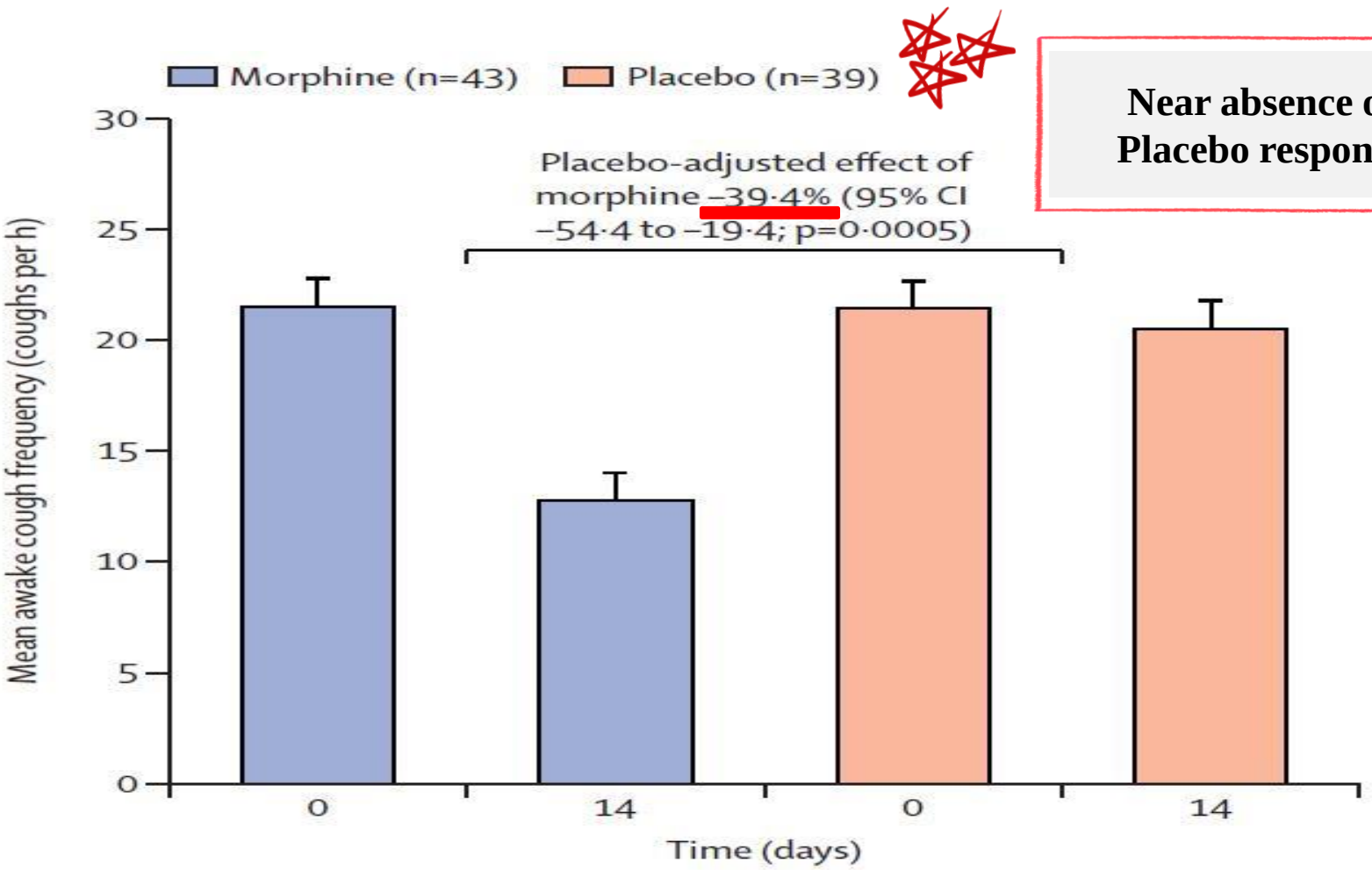
Lancet Respir Med 2024;12:273-80

Morphine (PAciFy COUGH trial)

	Total (n=44)
Sex	
Male	31 (70%)
Female	13 (30%)
Age, years	71 (7·4)
Ever smokers	24 (54%)
Ethnicity	
Caucasian	40 (91%)
Indian	4 (9%)
Gastroesophageal reflux disease	19 (43%)
Lung function	
FEV_1, L	2·2 (0·60)
Predicted FEV_1, %	87·1 (18·1)
FVC, L	2·7 (0·76)
Predicted FVC, %	82·4 (17·3)
DLCO, CO min^{-1} kPa^{-1}	4·0 (1·17)
Predicted DLCO, %	48·5 (10·9)
Antifibrotic therapy	26 (59%)
Nintedanib	22 (50%)
Pirfenidone	4 (9%)
Proton pump inhibitor	13 (30%)
Ambulatory oxygen	4 (9%)

Lancet Respir Med 2024;12:273-80

Morphine (PAciFy COUGH trial)



Near absence of Placebo response

Lancet Respir Med 2024;12:273-80

Effect of Morphine (PAciFy Cough trial)

	Morphine			Placebo			Difference at 14 days	
	Baseline	Day 14	Change	Baseline	Day 14	Change	Placebo-adjusted effect of morphine()95%CI)*	P-value
Cough VAS	61.5 (2.4) n=43	45.5 (3.7) n=43	-16.1 (-22.3 to -9.9) P<0.0001	57.7 (2.8) n=41	57.3 (2.7) n=41	-0.4 (-5.8 to 4.9) p=0.88	-14.6 (-22.8 to -6.5)	0.0004
LCQ	13.2 (0.5) n=43	15.0 (0.6) n=43	1.8 (0.9 to 2.8) p=0.0002	13.0 (0.5) n=41	13.6 (0.5) n=41	0.6 (-0.2 to 1.3) p=0.15	1.3 (0.4 to 2.3)	0.0047
Dyspnoea-12	13.0 (1.2) n=43	12.9 (1.3) n=43	-0.1(-1.9 to 1.6) p=0.87	13.5 (1.4) n=41	14.3 (1.4) n=41	0.9 (-0.5 to 2.2) p=0.22	-1.2 (-3.1 to 0.8)	0.24
L-IPF symptoms (total)	40.9 (2.9) n=41	35.7 (3.1) n=41	-5.2 (-8.9 to -1.4) p=0.0078	40.9 (3.3) n=40	41.4 (3.4) n=40	0.5 (-2.5 to 3.4) p=0.75	-6.7 (-11.2 to -2.3)	0.0031
Dyspnea domain	31.9 (3.7)	28.8 (3.6)	-3.1 (-7.9 to 1.8) p=0.22	32.1 (3.9)	31.9 (4.0)	-0.1 (-2.6 to 2.5) p=0.95	-1.5 (-6.2 to 3.2)	0.53
Cough domain	50.3 (3.7)	39.5 (3.8)	-10.8(-16.9 to -4.8) p=0.0004	50.1 (3.6)	49.6 (3.8)	-0.5 (-6.2 to 5.1) p=0.85	-11.9 (-18.7 to -5.1)	0.0006
Energy domain	44.2 (3.3)	44.8 (3.6)	0.6(-4.3 to 5.6) p=0.81	44.5 (3.9)	47.9 (3.9)	3.4 (-1.3 to 8.2) p=0.16	-3.3 (-8.3 to 1.6)	0.19

Lancet Respir Med 2024;12:273-80

Morphine (PAciFy COUGH trial)

	Morphine (n=43)	Placebo (n=42)
Any adverse event	17 (40%)	6 (14%)
Serious adverse events	0	1 (2%)
Gastrointestinal disorders		
Nausea	6 (14%)	3 (7%)
Vomiting	2 (5%)	1 (2%)
Constipation	9 (21%)	0
Nervous system disorders		
Hypersomnia	4 (9%)	2 (5%)
General disorders		
Lethargy	2 (5%)	0
Respiratory disorders		
Lung infection	1 (2%)	1 (2%)

- **No serious adverse events**
- **No need for laxatives**
- **Discontinuation: 1**

❖ **Low burden for short-term use**

Lancet Respir Med 2024;12:273-80

Nalbuphine for cough in IPF

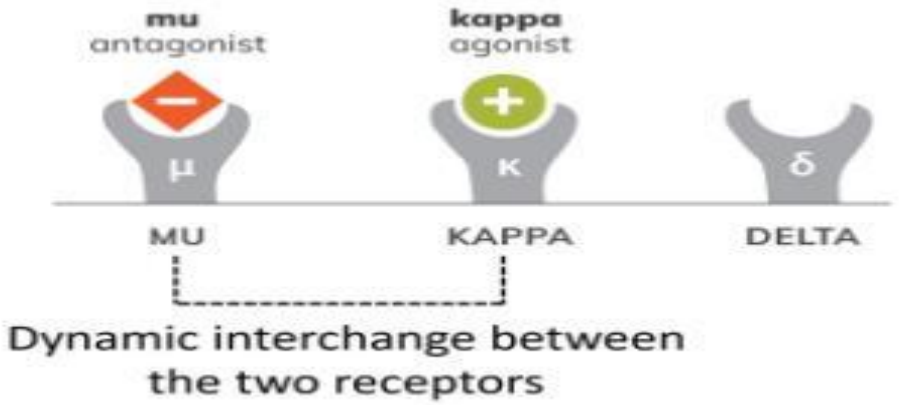
- Nalbuphine: “Dual-acting opioid agonist-antagonists”

  (Opioid receptor – agonist in kappa R and antagonist in mu R)

  → Reverse opioid-induced respiratory depression

Mechanism of Action

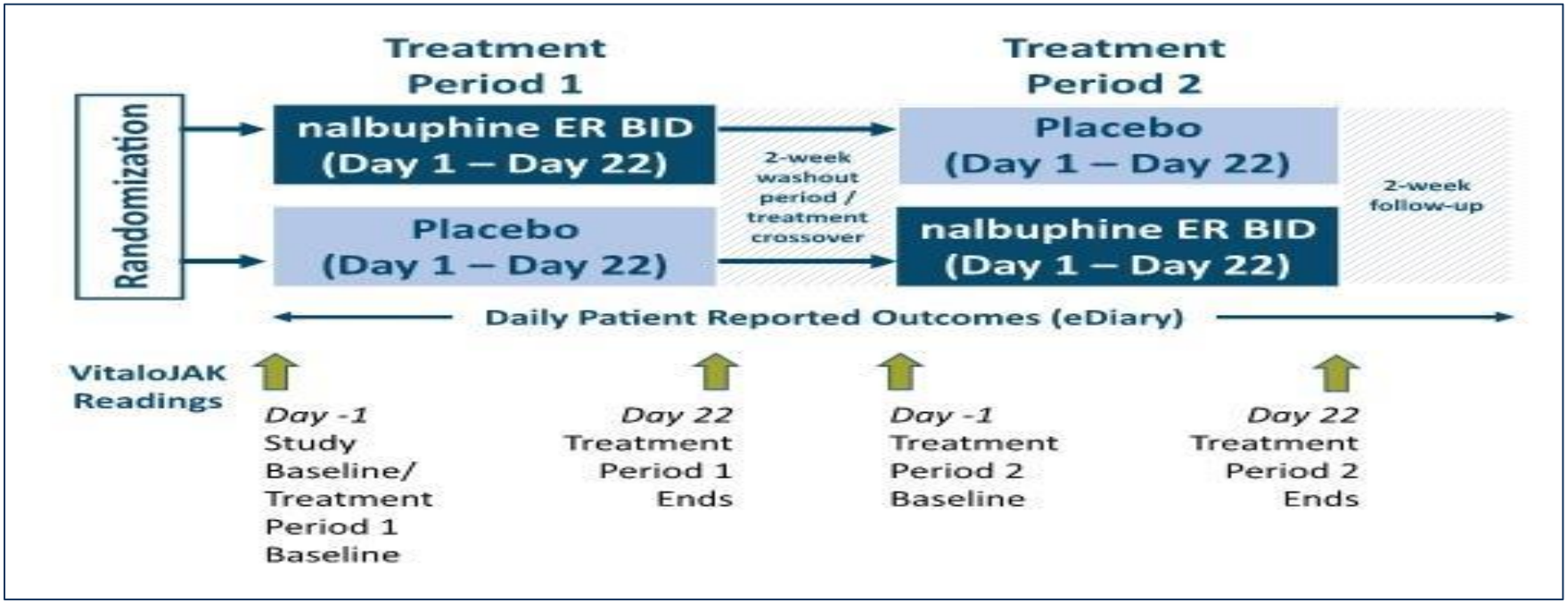
Centrally Active + Peripherally Active



Maher et al. NEJM (2023)

Nalbuphine for cough in IPF

- The randomized, double-blind, placebo-controlled, crossover trial
- The primary endpoint – change (%) in hourly daytime objective cough frequency by an electronic cough monitor
- The secondary endpoint – change in objective 24-hour cough frequency, changes in frequency, severity and patient-reported outcomes



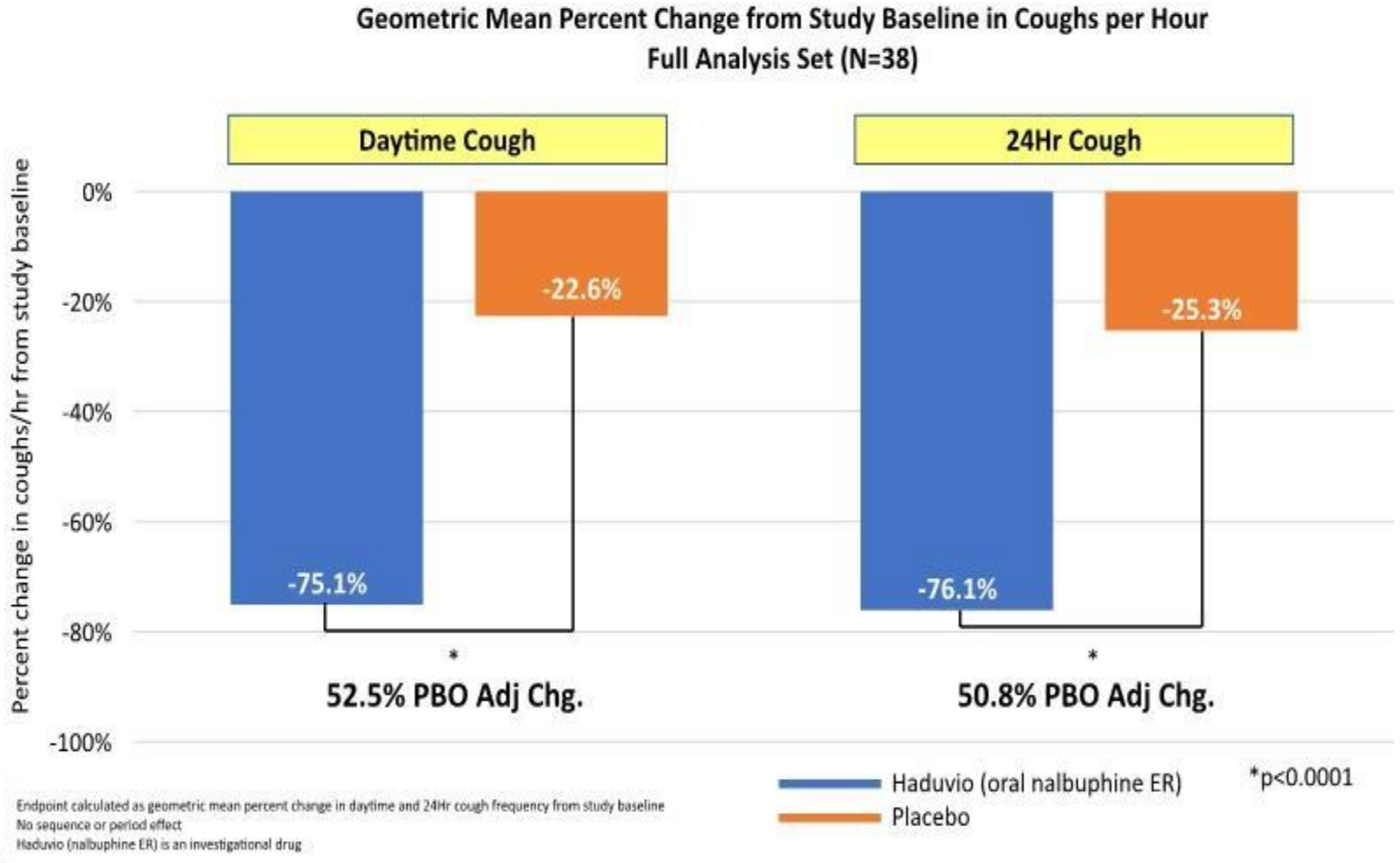
Maher et al. NEJM (2023)

Nalbuphine for cough in IPF

Table 1. Baseline Characteristics.	
No. of patients	38
Mean age — yr	74
Male — no. (%)	32 (84.2)
Antifibrotic usage — no. (%)	18 (47.4)
Proton pump inhibitors — no. (%)*	28 (68.3)
Daytime cough frequency (coughs/hour)	
Mean	28.0
Median	20.0
Minimum–maximum	3.2–92.4
24-hour cough frequency (coughs/hour)	
Mean	21.2
Median	16.0
Minimum–maximum	3.1–66.4

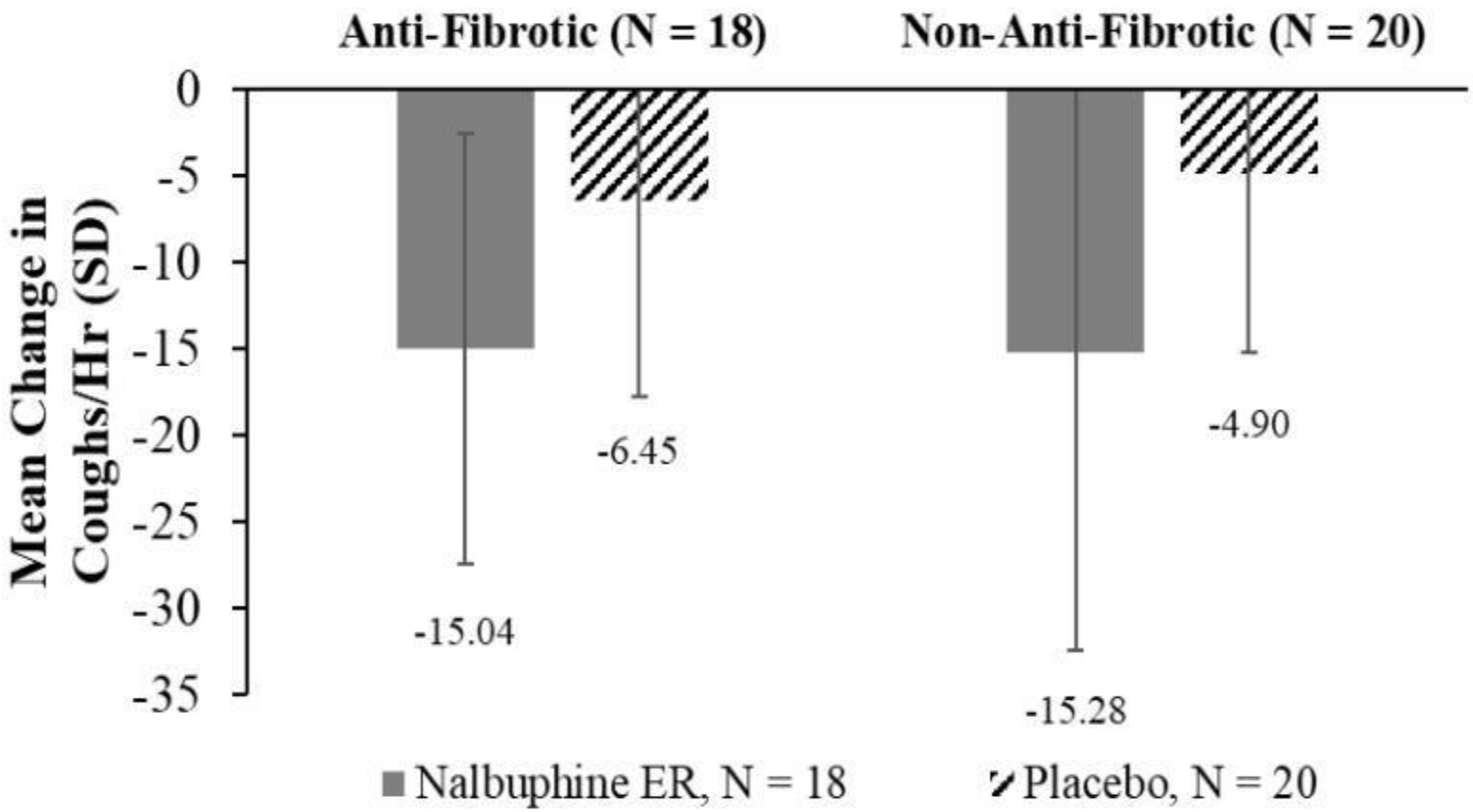
Maher et al. NEJM (2023)

Nalbuphine for cough in IPF



Maher et al. NEJM (2023)

Nalbuphine for cough in IPF



Maher et al. NEJM (2023)

Adverse events of Nalbuphine

Discontinuation d/t adverse events: 9 patients

6 on Day 5 and 3 on Day 14 (GI and central nervous system)

	Nalbuphine BID N=38, n(%)			Placebo N=40, n(%)			Total N=41, n(%)		
GRADE	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Nausea	9 (24)	7 (18)	-	-	-	-	9 (22)	7 (17)	-
Fatigue	8 (21)	3 (8)	1 (3)	1 (3)	1 (3)	1 (3)	9 (22)	4 (10)	2 (5)
Constipation	8 (21)	3 (8)	-	1 (3)	1 (3)	-	9 (22)	4 (10)	-
Dizziness	7 (18)	3 (8)	-	-	-	-	7 (17)	3 (7)	-
Somnolence	7 (18)	2 (5)	-	1 (3)	-	-	7 (17)	2 (5)	-
Vomiting	4 (11)	3 (8)	-	5 (13)	-	-	7 (17)	3 (7)	-
Headache	2 (5)	3 (8)	-	5 (13)	-	-	7 (17)	3 (7)	-
Anxiety	2 (5)	1 (3)	2 (5)	-	-	-	2 (5)	1 (2)	2 (5)
Depression	3 (8)	-	1 (3)	-	-	-	3 (8)	-	1 (2)

Maher et al. NEJM (2023)

Treatment of cough in IPF

- Antifibrotics (Pirfenidone vs Nintedanib)
- Treatable traits (other causes and co-morbidities)
- Opioids (Morphine and Nalbuphine)
- Clinical Trials

Treatment of cough in other ILDs

- Corticosteroid
- Immunosuppressants
- Treatable traits (other causes and co-morbidities)
- Other pulmonary complication
- Opioids
- Clinical Trials

Other treatment options in guideline

- Speech therapy → temporarily improved cough-specific quality of life and cough frequency (the addition of pregabalin to speech therapy may lead to a more significant improvement in severity)
- Cough when they are hypoxemic → supplemental oxygen
- Short-term (2 weeks) – low dose (10-20mg) prednisone in IPF

CHEST 2021; 160(5):1774-1782

Summary

- Cough in ILDs – common and severe burden
- Pathophysiology of ILDs (fibrosis and mechanical stress)
- Correlation with disease severity → Phenotype
- Work-up for cough
- Antifibrotics in IPF and

  Corticosteroid/Immunosuppressants in other ILDs
- Opioids and Clinical Trials (End-point)

감사합니다