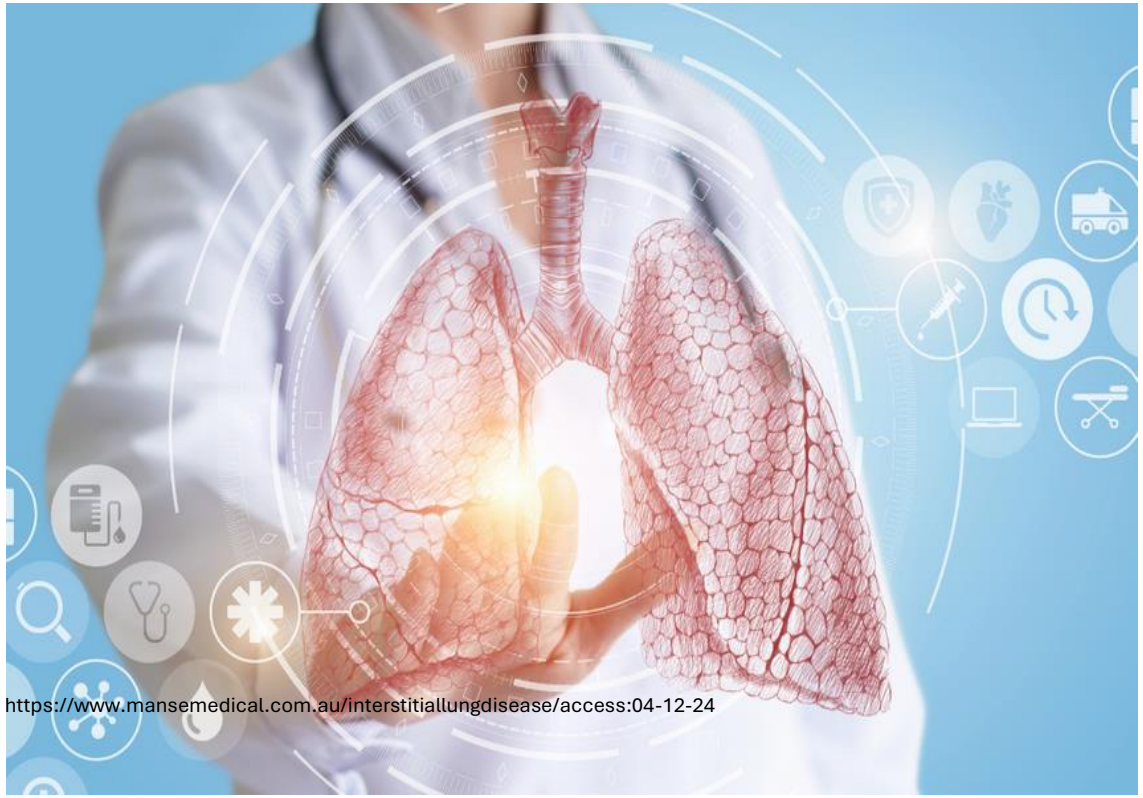

https://www.mansemedical.com.au/interstitiallungdisease/access:04-12-24

VOĐENJE ILD

1. Specijalistički seminar Respiratornog udruženja u BiH

„Bolesti plućnog intersticija“

Opća bolnica „Prim dr Abdulah Nakaš“, Sarajevo

07.12.2024.

Aida Mujaković, MD, PhD
Spec. pulmolog; subspec.intenzivne medicine

Osnovni principi - Gdje početi.....

- Dijagnoza i tretman komorbiditeta
- Farmakoterapija
- Rehabilitacija
- Oksigenoterapija
- Palijativna njega

- Vođenje ILD-a podrazumijeva timski rad

- Vođenje bolesti se mijenja tokom praćenja samog toka bolesti

ILD Treatment Checklist

ATS/ERS/JRS/ALAT ILD Guidelines 2022

Co morbidities are common...

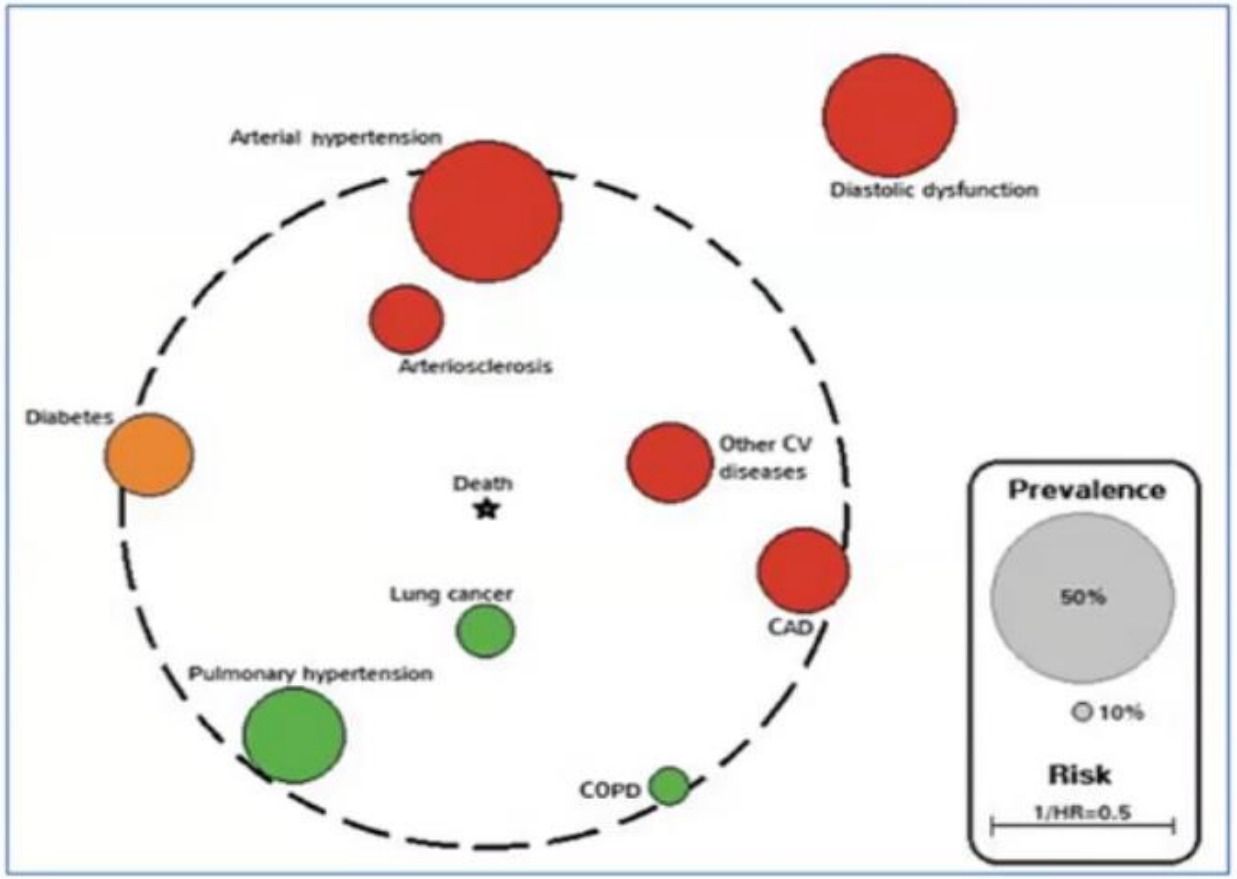


Table 1. (*Continued*)

Parameter	%
Death reason	
Idiopathic pulmonary fibrosis	53.2
Cardiovascular	4.7
Lung cancer	7.6
Other reasons	4.7
Unknown	29.8

Kreuter et al. PLOS 2016.

Co-morbidities in ILD

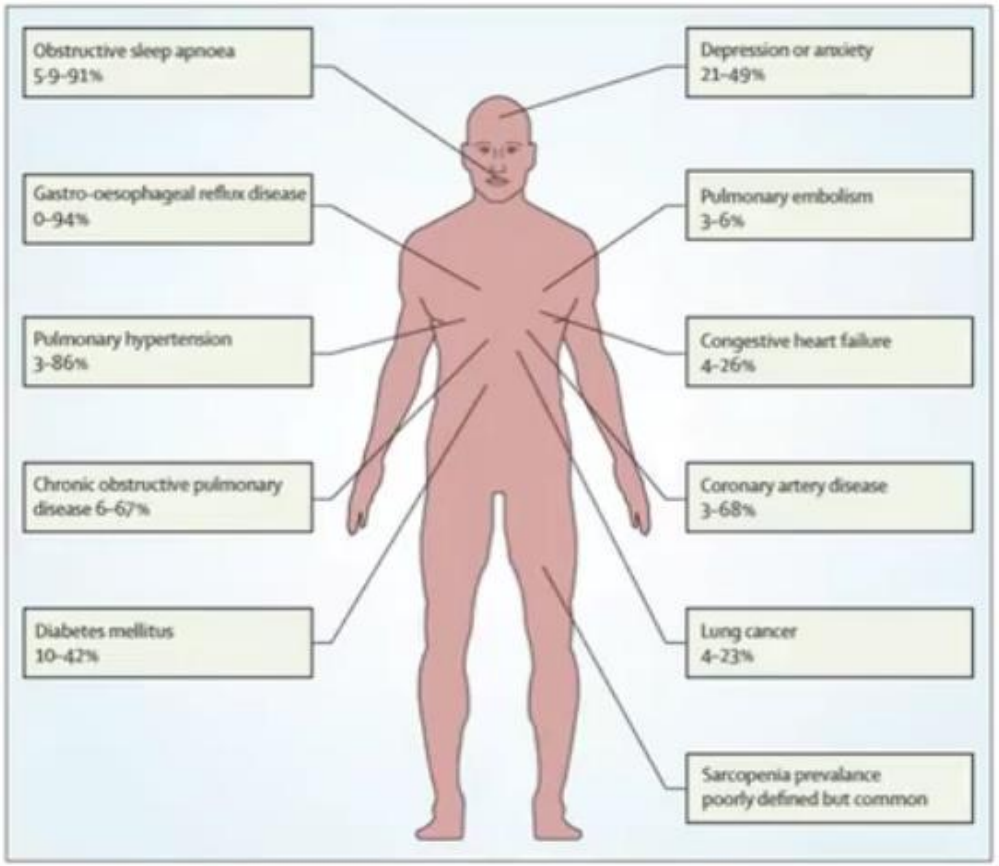


Figure 1: Prevalence of the various comorbidities of idiopathic pulmonary fibrosis

King, Lancet Resp 2017

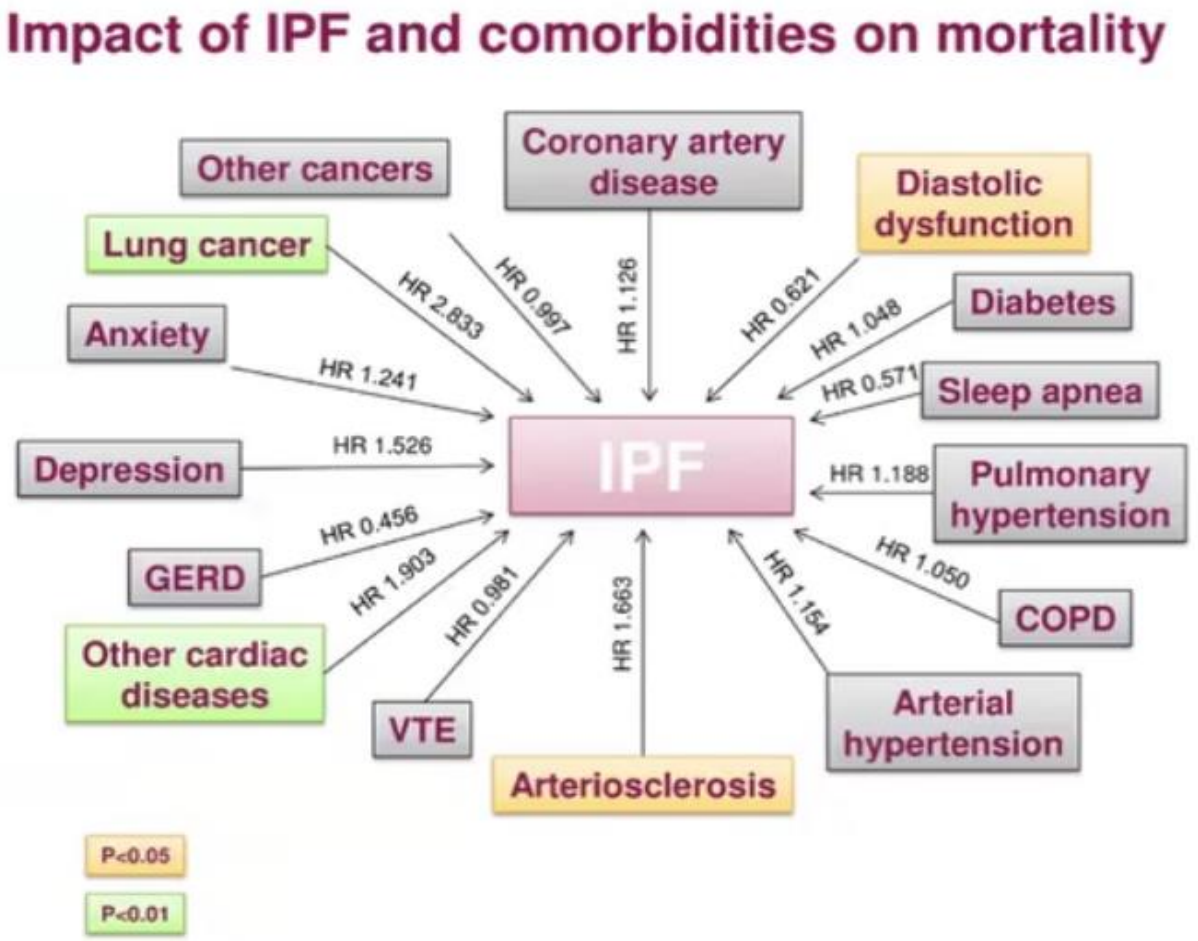
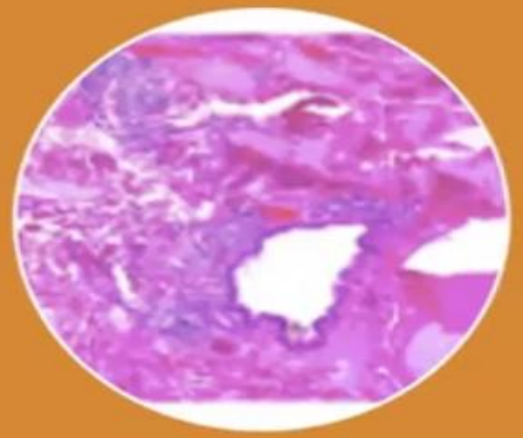


Fig 5. Impact of idiopathic pulmonary fibrosis and comorbidities on mortality. Hazard ratios (HR) have been determined using a predictive multivariate Cox proportional hazards regression model.

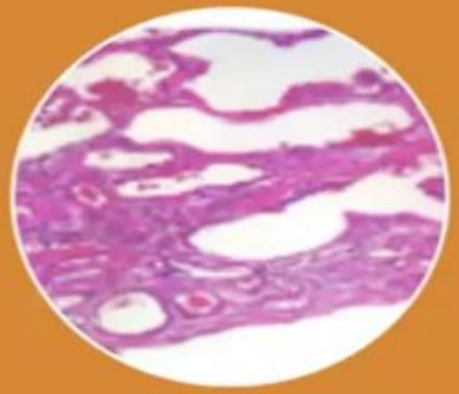
Kreuter, PLOS One 2016

Farmakoterapija

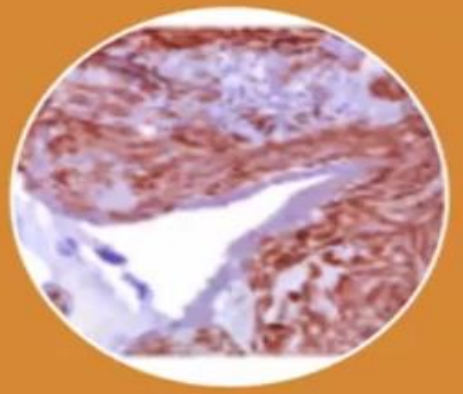
Pharmacotherapy – Treatment Paradigm



Immunomodulatory Agents



Immunomodulatory + Antifibrotic

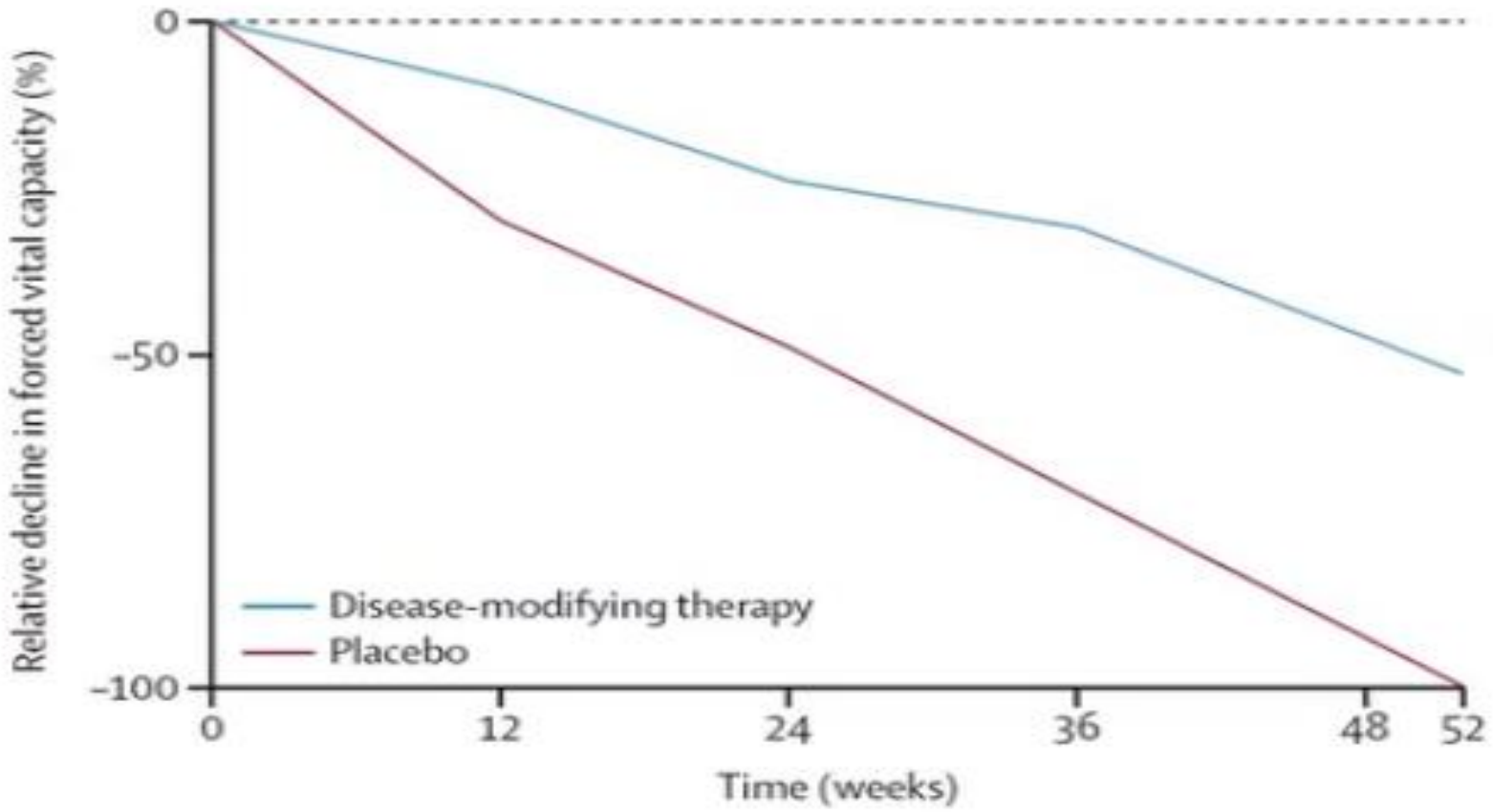


Antifibrotic Agents

	First Line Treatment	Second Line Treatment	Third Line Treatment	Phase 2 or 3 Trials
IPF	Ofev/Esbriet			INPULSIS ASCEND
HP – fibrotic	Ofev/MMF	Pirfenidone	AZA	INBUILD
HP – inflammatory	MMF/AZA	Rituximab		
RAILD – UIP	Ofev/MMF	Pirfenidone	AZA	TRAIL INBUILD
RAILD - NSIP	MMF/AZA	Rituximab		
SSc-ILD GGO	MMF	Rituximab		SLS2
SSc-ILD Fibrosis	Ofev	Pirfenidone		SENSCIS
Myositis-ILD	MMF	AZA	Cyclosporine, tacrolimus, IVIG	

* IPF: idiopathic pulmonary fibrosis, AF: antifibrotic, MMF: mycophenolate mofetil, AZA: azathioprine, HP: hypersensitivity pneumonitis, SSc: systemic sclerosis

Disease-Modifying Therapies Pirfenidone and Nintedanib Significantly Reduce Lung Function Decline



Over 52 weeks, the decline in FVC in an untreated patient with IPF is ~200ml vs ~100 mL with antifibrotic treatment

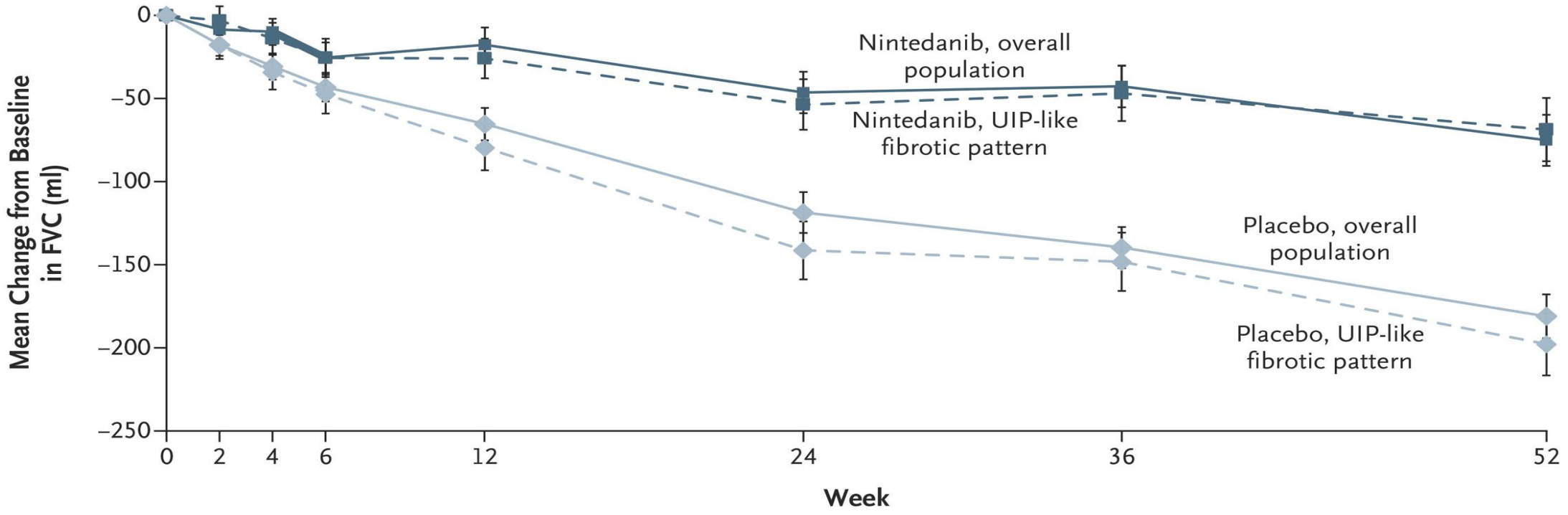
Richeldi L, et al. *Lancet*. 2017;389:1941-1952.

Progressive Fibrosis Treatment - INBUILD

- 663 patients with progressive fibrosing lung disease (PF-ILD) other than IPF randomized to nintedanib or placebo
- HRCT with fibrosis >10% lungs; stratified by UIP pattern
- Progression with past 2 years
  - relative decline in the FVC of at least 10% of the predicted value
  - a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT
  - worsening of respiratory symptoms and an increased extent of fibrosis

Flaherty KR, et al, NEJM, 2019.

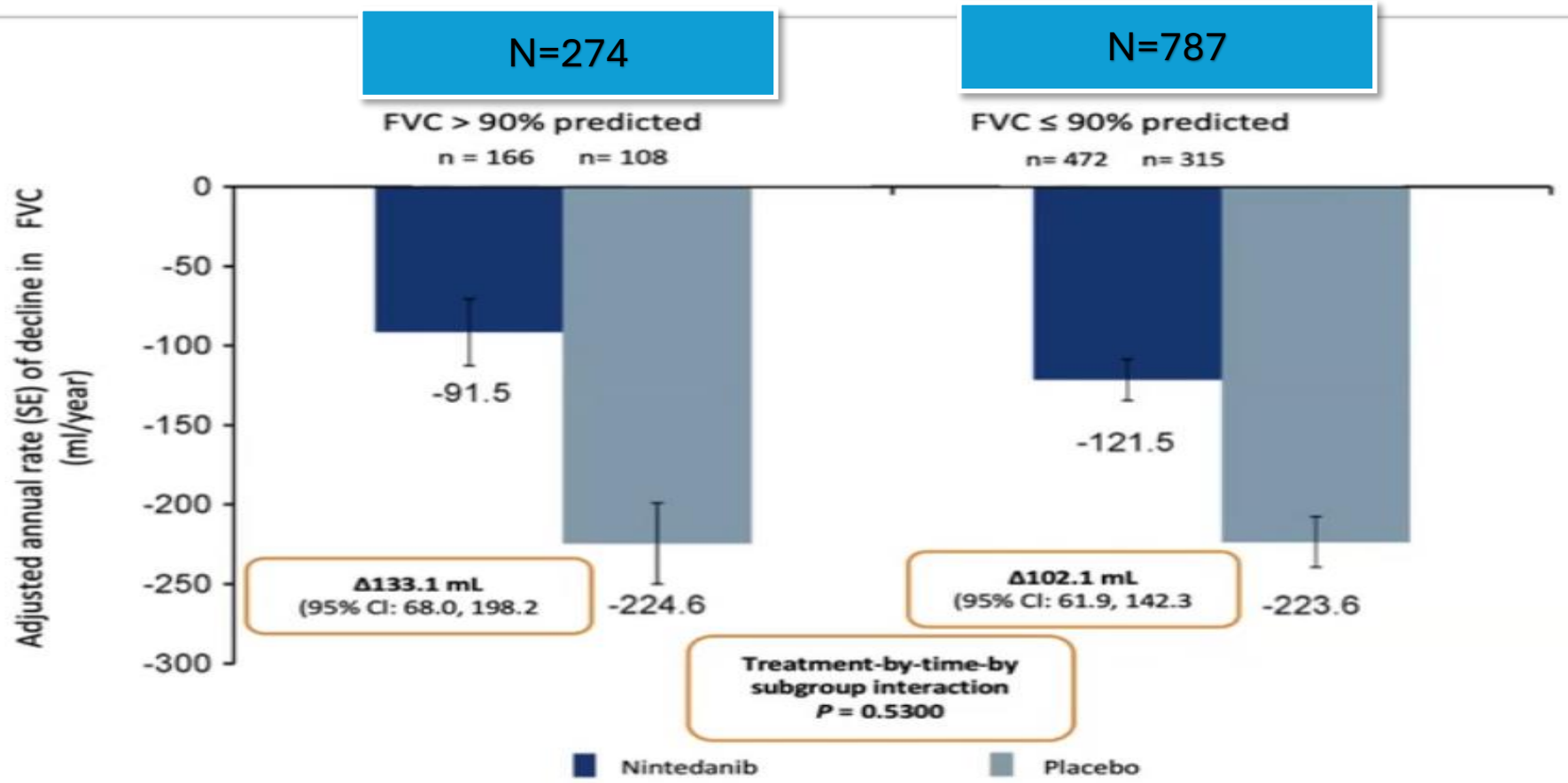
INBUILD- *NEJM* 2019. 187ml vs. 80ml (Nintedanib)



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

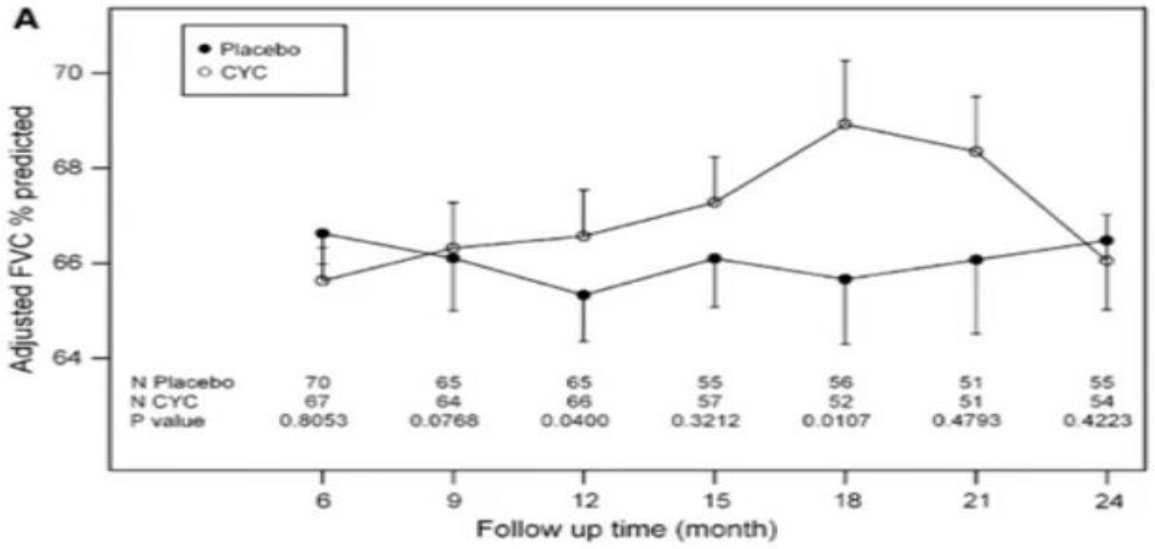
Decline from Baseline in Forced Vital Capacity (FVC). Shown is the observed mean change from baseline in FVC over the 52-week trial period in the overall population and in patients with an imaging pattern of UIP on HRCT in the nintedanib group and the placebo group. The I bars indicate the standard error.

Nintedanib in Patients with Preserved Lung Function



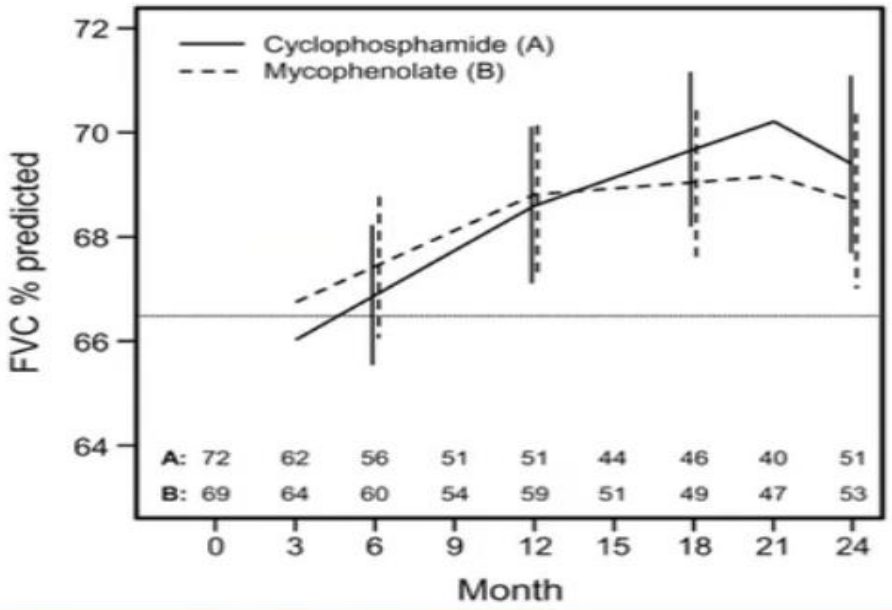
Immunosuppression in SSc – SLS I and II

- Scleroderma Lung Study I
  - 1-year oral cyclophosphamide (CYC) in active symptomatic SSc-ILD
  - Small positive effect on FVC, dyspnea and skin thickness



Tashkin DP et al. *NEJM* 2006
Tashkin DP et al. *AJRCCM* 2007

- Scleroderma Lung Study II
  - 2 years of MMF or 1 year of CYC resulted in improvements lung function, dyspnea, lung imaging and skin disease
  - No differences in outcomes

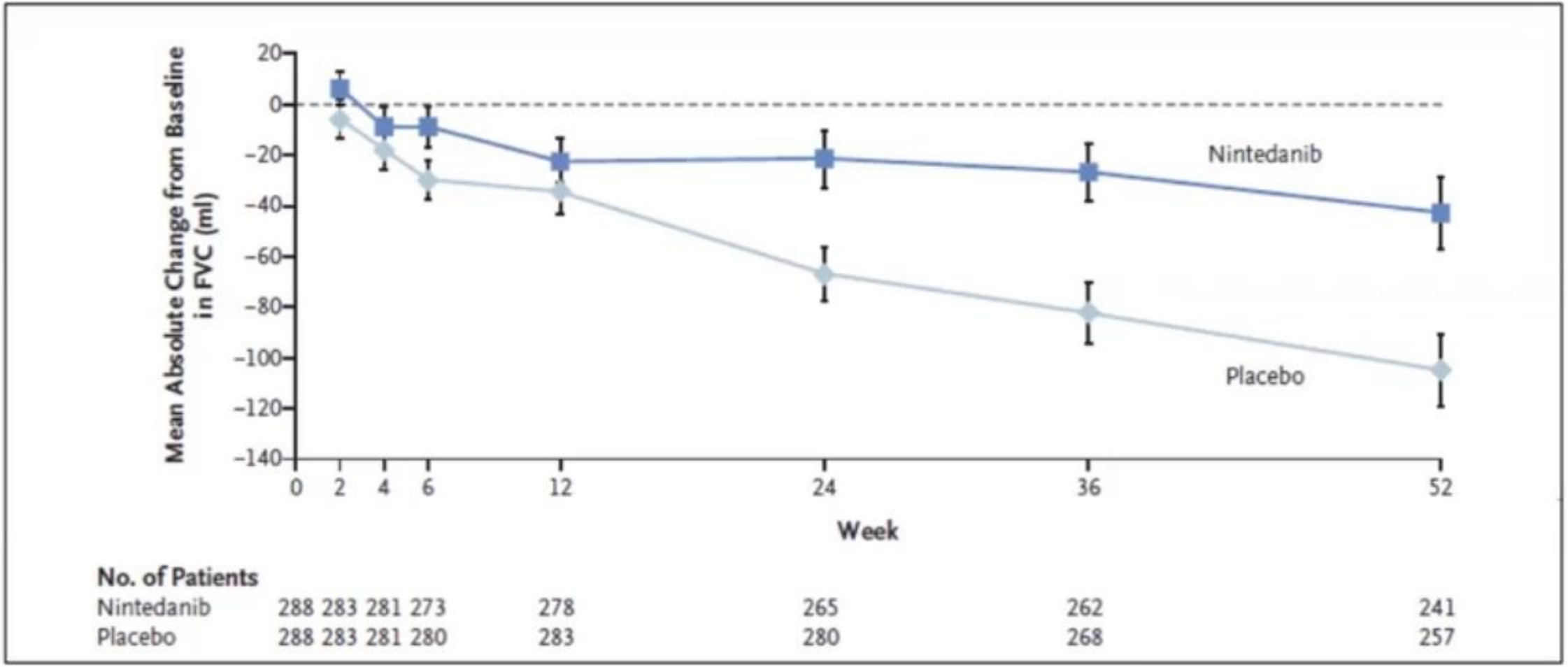


Tashkin et al. *Lancet Resp Med* 2016; 4(9): 708-719

SENSCIS - Nintedanib in Systemic Sclerosis

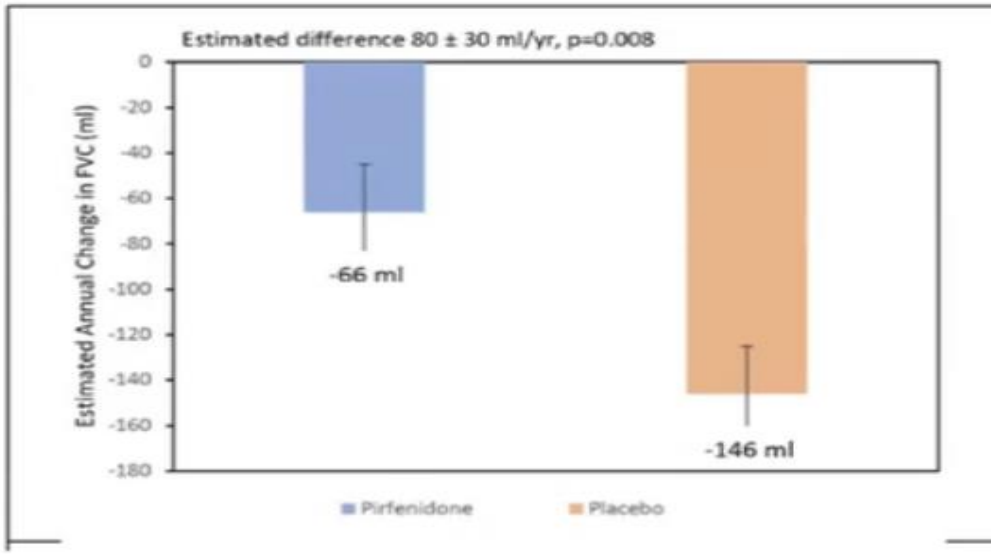
N=576

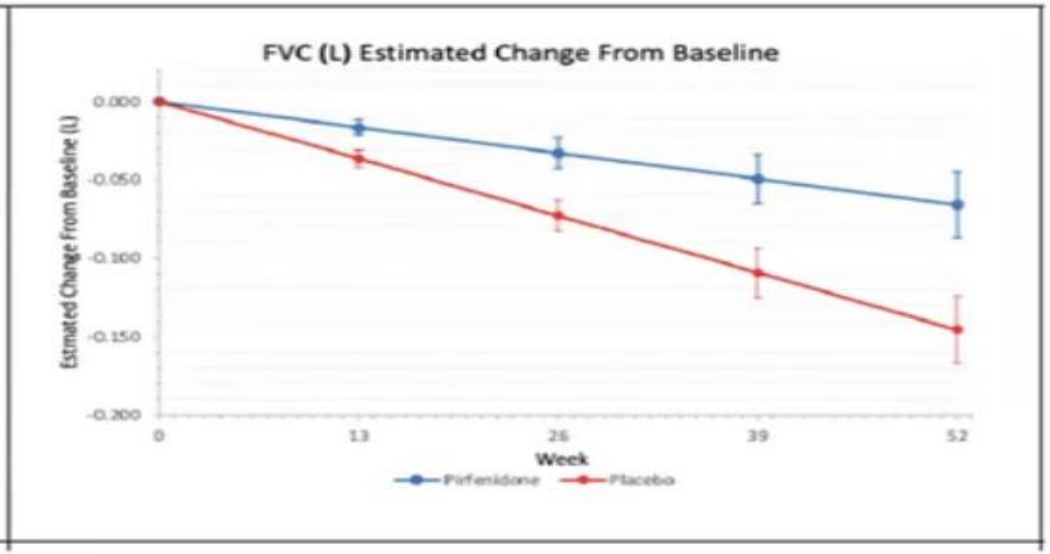
93 ml vs. 52 ml*

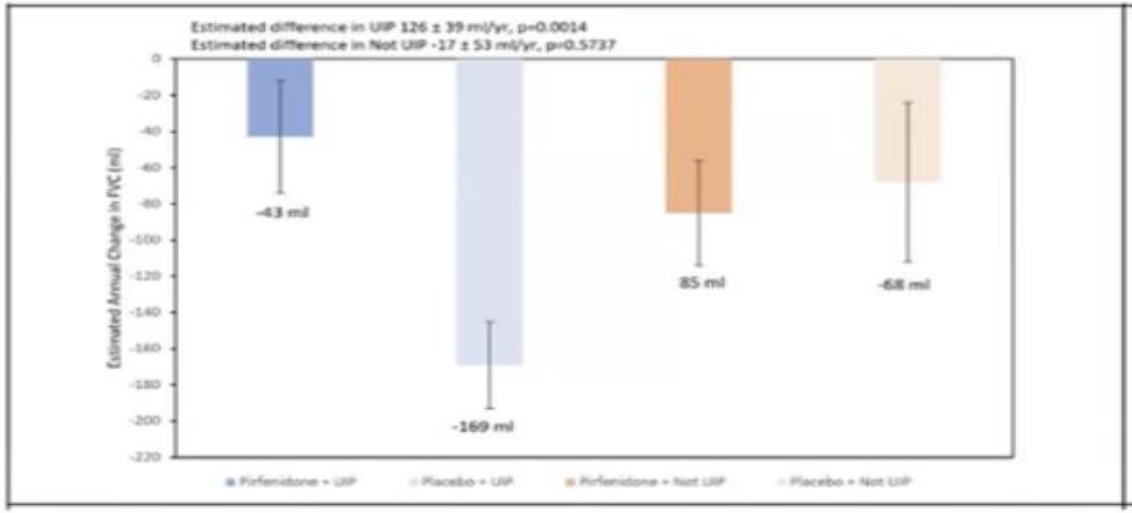


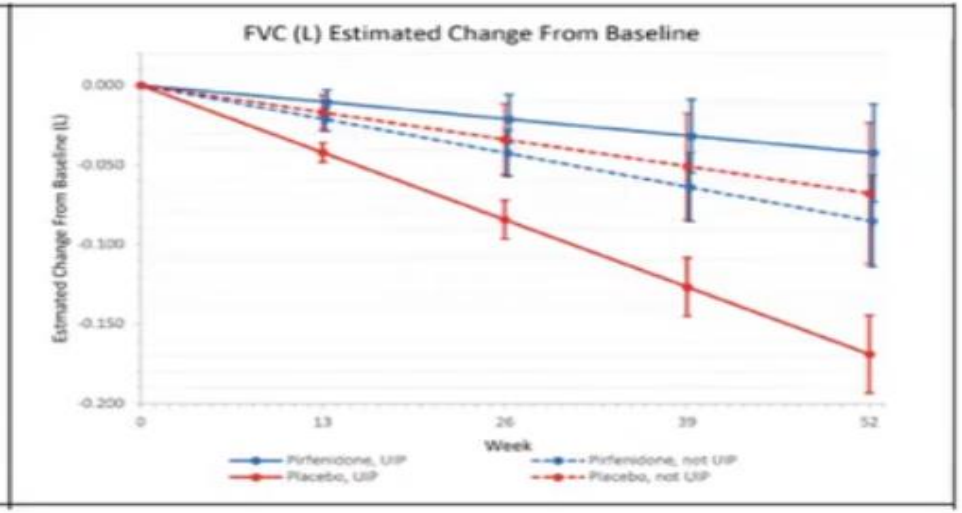
TRAIL Trial – Pirfenidone in RA-ILD

146 ml vs. 66 ml*





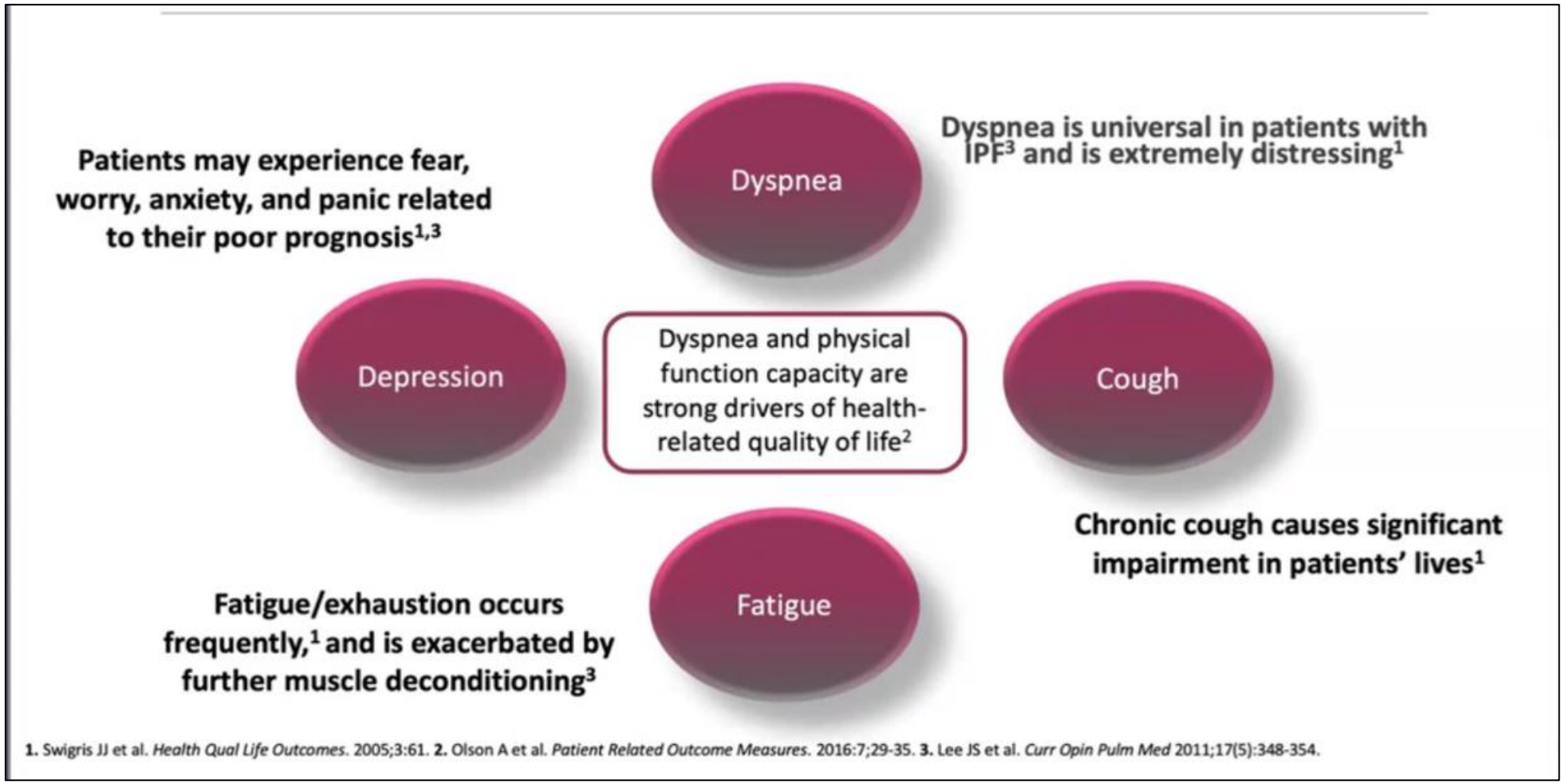




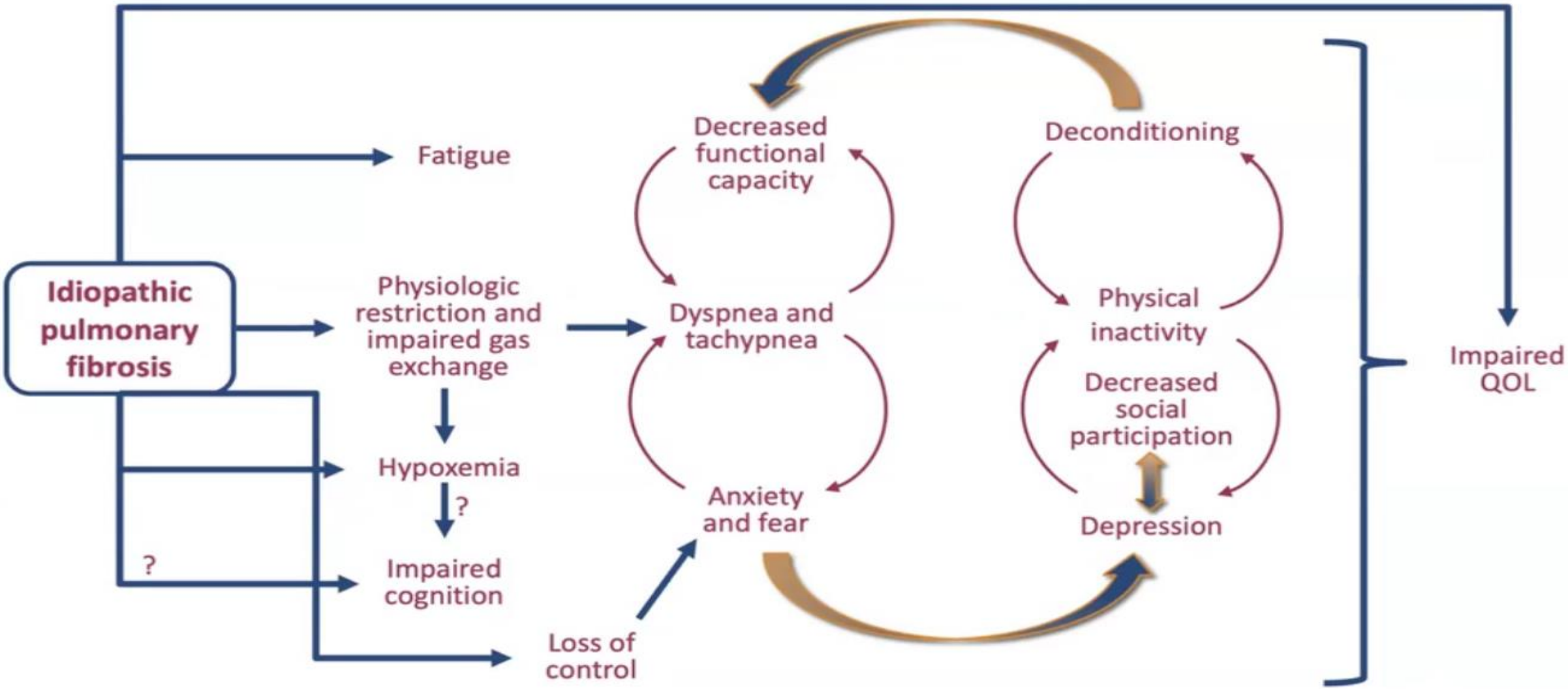
Solomon et al. Lancet Resp 2023

Uloga rehabilitacije u ILD

Kašalj, Dispnea, Umor i Depresija signifikantno utiču na kvalitet života pacijenata sa IPF



Benefits of Pulmonary Rehabilitation in IPF



Adapted from Swigris JJ et al. *Respir Med.* 2008;102:1675-1680.

ATS/ERS/JRS/ALAT preporuke – Većina pacijenata sa IPF treba biti uključena u program plućne rehabilitacije (PR)

- Findings from two randomized, controlled trials on PR in IPF:

Nishiyama et al[2] (N=30) reported:

- ❑ Improvements in 6MWD [mean difference 46.3 m (152 feet)]
- ❑ Improvements in SGRQ total score

Holland et al[3] (N=34) reported:

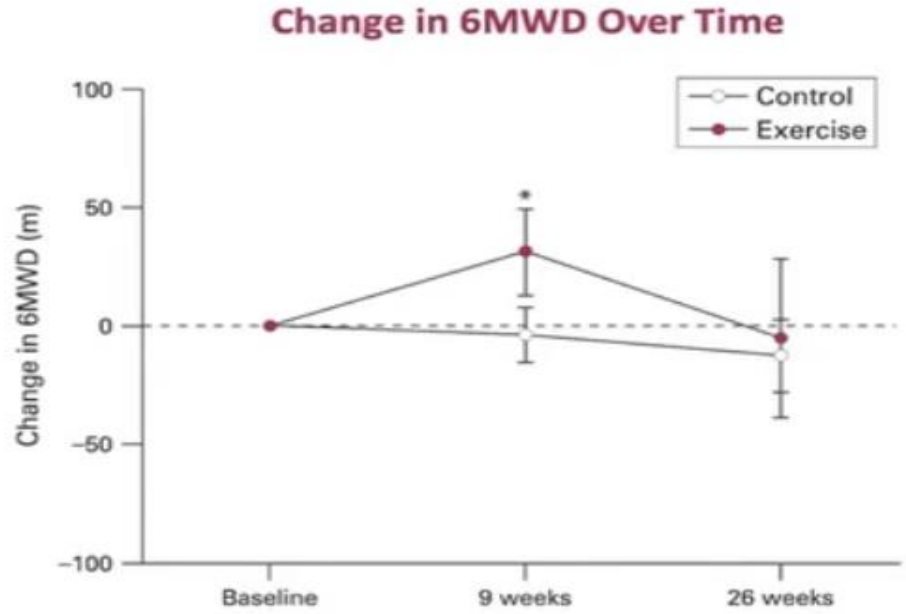
- ❑ Improvements in 6MWD [> 30 m (98 feet)]
- ❑ Improvements HRQL in the dyspnea and fatigue domains of the Chronic Respiratory Questionnaire
- ❑ Significant improvement in the VT domain of the SF-36

- In a pilot study, Swigris et al[4] reported that patients improved their 6MWD by 200 feet
  - Patients also reported trends towards improvement in fatigue, anxiety, depression, and health status[4]
- Subgroup meta-analysis of PR studies in IPF suggest that PR improves:[5]
  - 6MWD
  - O_2 consumption
  - Dyspnea
  - Quality of life

SF-36, Short Form (36) Health Survey; VT, vitality; 6MWD, 6-minute walk distance.

Lack of Long-term Benefits of Pulmonary Rehabilitation in IPF

- The immediate benefits of PR are not sustained after program completion[1]
- Patients should be encouraged to continue PR despite worsening symptoms[2]
- Traditional PR programs were developed for patients with COPD, so certain aspects may not apply to patients with ILD[3]



*$p<0.05$, exercise vs. control group.
Used with permission from Holland AE et al.[1]

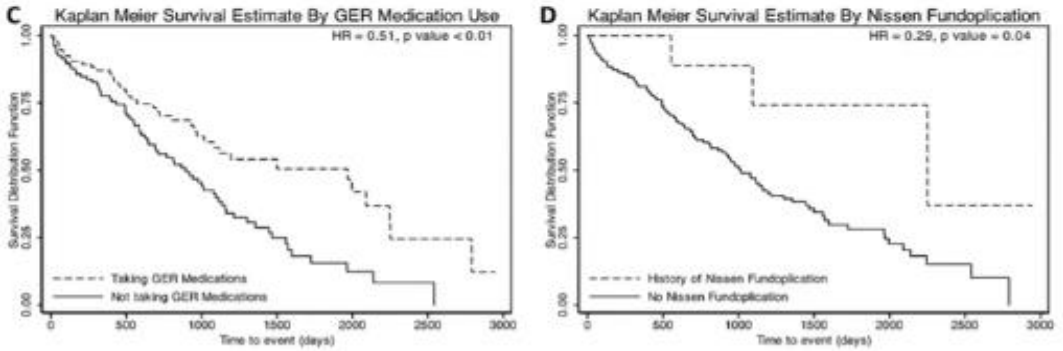
1. Holland AE et al. *Thorax.* 2008;63:549-554. **2.** Spagnolo P et al. *Multidis Respir Med.* 2012;7:42. **3.** Raghu G et al. *Am J Respir Crit Care Med.* 2011;183:788-824 .

GERD

- Higher prevalence in IPF
  - Distal GER reported as high as 88% of patients
  - Proximal GER reported as high as 71% of patients
  - May be silent
- Hypothesized to play a role in progressive lung fibrosis
- Old IPF treatment recommendations
  - Conditional for the treatment of reflux

GERD Therapy Is Associated with Improved Survival

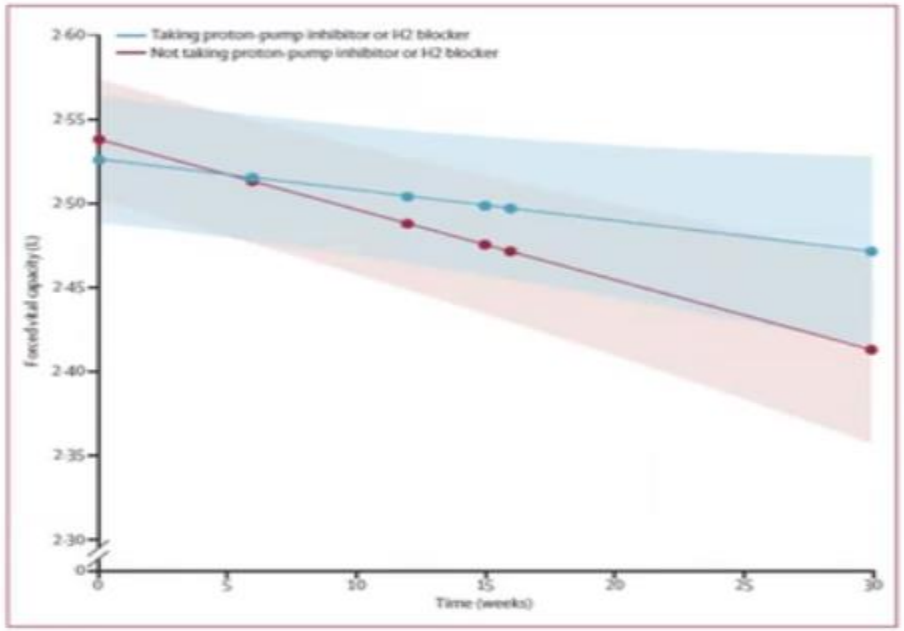
- N = 204 patients, two academic centers, retrospective
- Use of GERD therapies or fundoplication was independent predictor of longer survival in IPF.



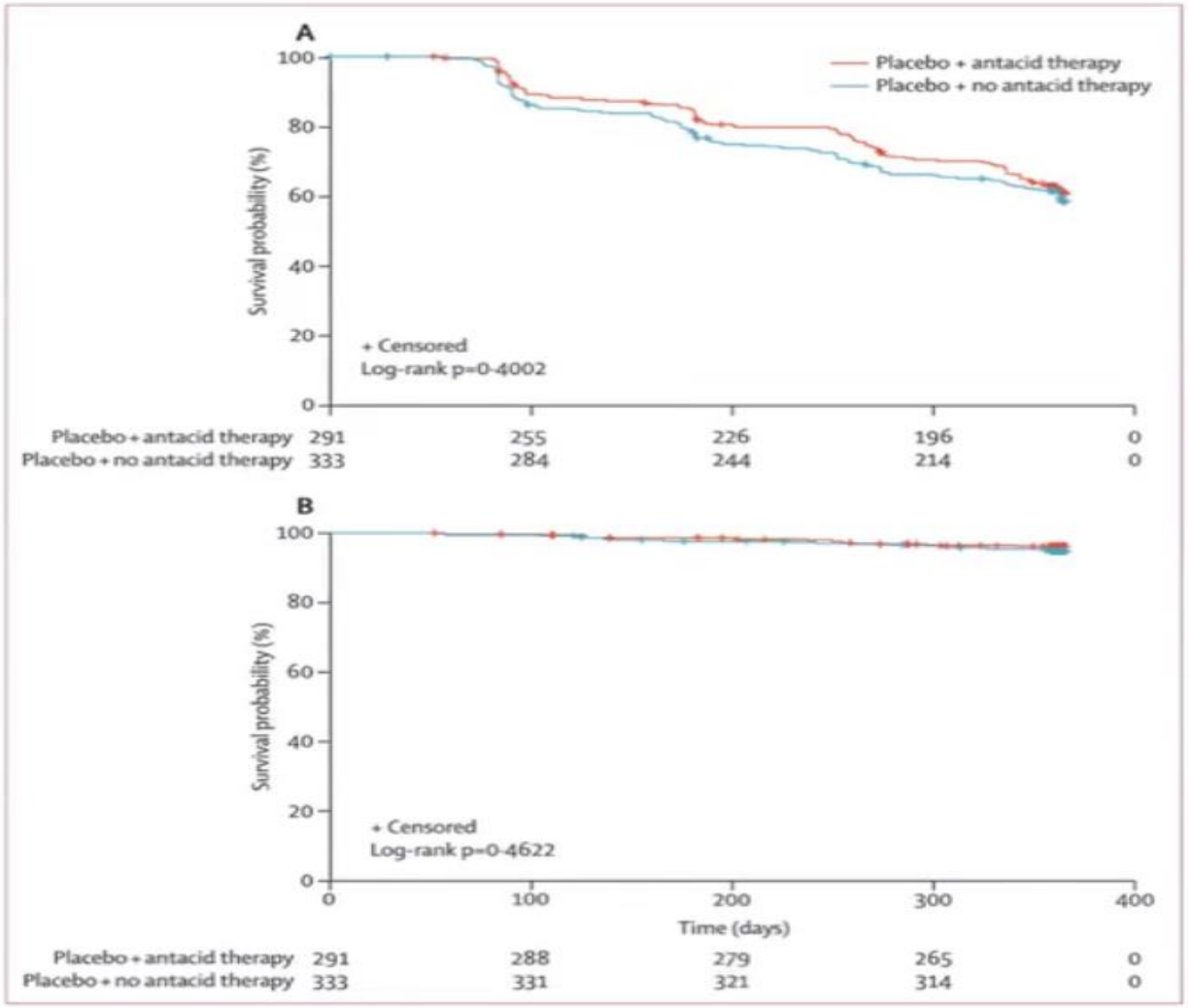
Lee JS, et al. Am J Respir Crit Care. 2011;184:1390-1394.

GERD

- N = 242, retrospective data from three placebo groups of the IPF-NET sponsored trials
- Patients on anti-acid therapy at baseline had a smaller decline in FVC at 30 weeks.



Lee JS, et al. Lancet Respir Med. 2013;1:369-376.



Unadjusted 1 year risk of (A) progression-free survival and (B) IPF-related mortality

GERD and IPF – pooled analysis

Pooled analysis from placebo arms of CAPACITY 004, CAPACITY 006 and ASCEND

N=624

	Antacid therapy* (N=144)	No antacid therapy* (N=164)	p value
Side-effects			
Gastrointestinal side-effects	83 (58%)	97 (59%)	0·7888
Infections	107 (74%)	101 (62%)	0·0174
Pulmonary infections	20 (14%)	10 (6%)	0·0214
Length of follow-up (days)	337 (73)	342 (71)	0·5461

Side Effects in those with FVC <70%

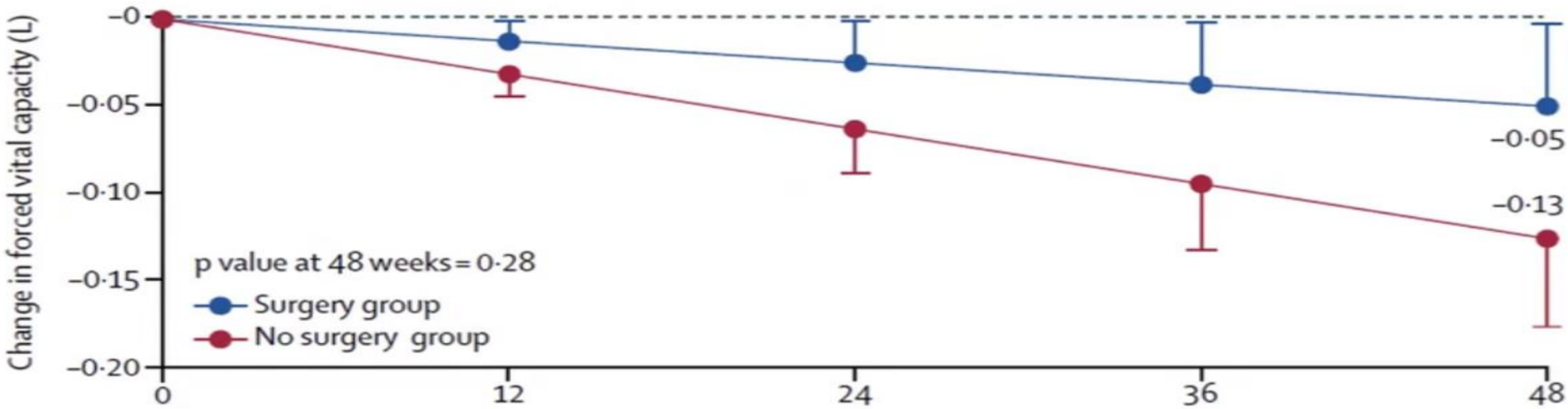
Kreuter, Lancet Resp 2016

WRAP-IPF

- Phase 2
- Primary outcome: decline in FVC between enrollment and 48 weeks
- Enrollment 58
- Inclusion criteria:
  - Confirmed diagnosis of idiopathic pulmonary fibrosis
  - Abnormal GER on 24-hour pH monitoring (DeMeester score > 14.7)
  - Able to provide informed consent
  - Willing to undergo laparoscopic anti-reflux surgery

Raghu G, et al. *Lancet Respir Med*. 2018;6:707-714.

WRAP-IPF Primary Endpoint: Change in FVC from Baseline to Week 48



The adjusted rate of decline in FVC over 48 weeks was –0·05 L (95% CI –0·15 to 0·05) in the surgery group and –0·13 L (–0·23 to –0·02) in the no surgery group (p=0·28)

Acute exacerbation, respiratory-related hospitalization, and death was less common in the surgery group

Raghu G, et al. *Lancet Respir Med*. 2018;6:707-714.

Meta-Analysis of GERD and IPF

- 18 case-control studies
- 3206 patients with IPF; 9638 control subjects
- GERD association with IPF, OR: 2.94 [95% CI, 1.95-4.42]
- In meta-regression, after adjusting for smoking status, the direction of the association reversed and was not statistically significant

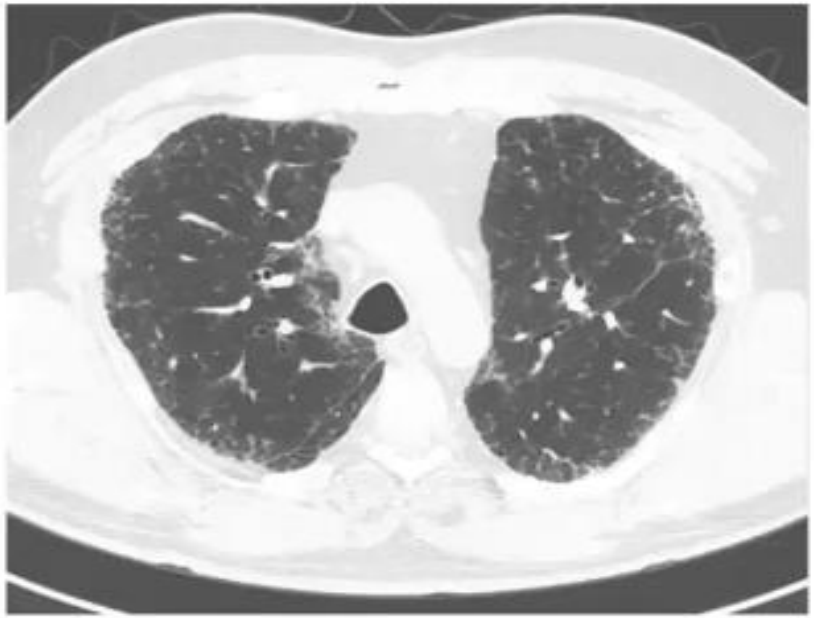
Methot DB, et al. *CHEST.* 2019;155:33-43.

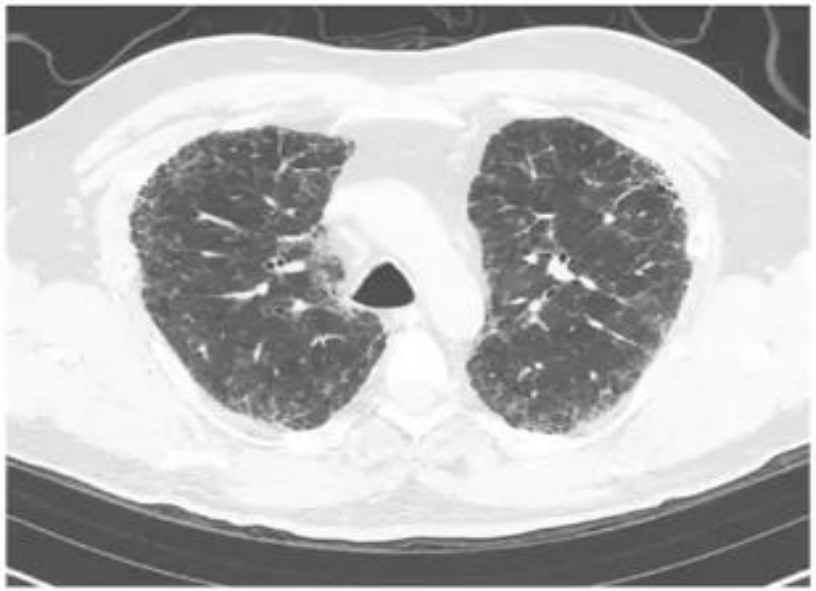
New GERD recommendations

"We suggest not treating patients with IPF with antacid medication for the purpose of improving respiratory outcomes (conditional recommendation, very low-quality evidence)."

"Remarks: Antacid medication and other interventions may be appropriate for patients with both IPF and symptoms of gastroesophageal reflux disease (GERD) for the purpose of improving gastroesophageal reflux (GER)–related outcomes in accordance with GER-specific guidelines."

Raghu et al. AJRCCM 2022





Acute Exacerbation of ILD

Acute Exacerbation of ILD (AE-ILD)

- Pathologic pattern of acute lung injury
- Rates of acute exacerbation
  - ~10% in the first year in cohort studies
- Risk factors
  - Low FVC
  - ? Triggers (Similar acute lung injury – aspiration, infection, surgery…)
- High mortality
  - Respiratory failure requiring hospitalization; mortality 50%
  - **Refer early for lung transplantation evaluation**
- Patients need to know to call early with any worsening symptoms
  - Identify any treatable causes
  - ? Steroids/antimicrobial therapy

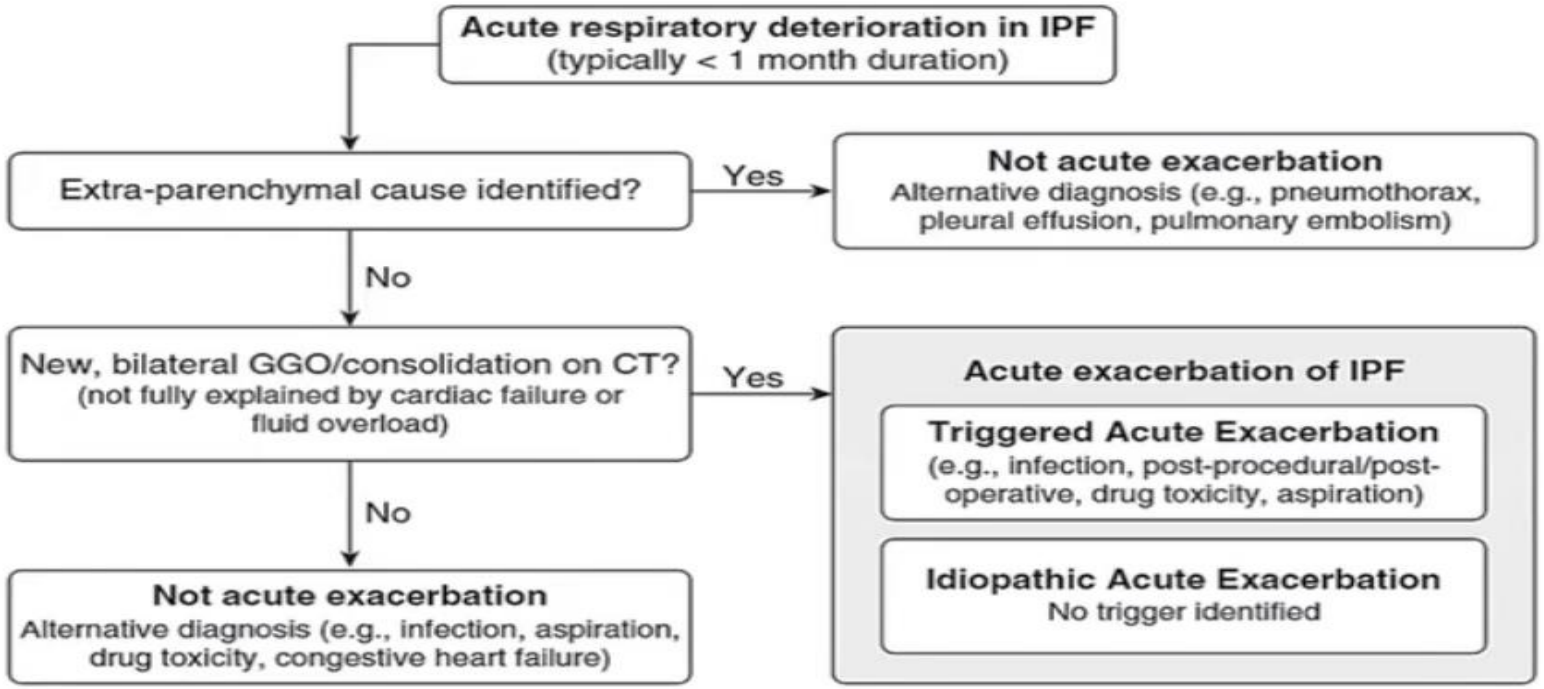
Collard HR, et al. *Am J Respir Crit Care Med*. 2016:194:265-275.

CONCISE CLINICAL REVIEW

Acute Exacerbation of Idiopathic Pulmonary Fibrosis

An International Working Group Report

Harold R. Collard[1], Christopher J. Ryerson[2], Tamera J. Corte[3], Gisli Jenkins[4], Yasuhiro Kondoh[5], David J. Lederer[6], Joyce S. Lee[7], Toby M. Maher[8,9], Athol U. Wells[9], Katerina M. Antoniou[10], Juergen Behr[11], Kevin K. Brown[12], Vincent Cottin[13], Kevin R. Flaherty[14], Junya Fukuoka[15], David M. Hansell[16], Takeshi Johkoh[17], Naftali Kaminski[18], Dong Soon Kim[19], Martin Kolb[20], David A. Lynch[21], Jeffrey L. Myers[22], Ganesh Raghu[23], Luca Richeldi[24], Hiroyuki Taniguchi[5], and Fernando J. Martinez[25]



Collard HR, et al. *Am J Respir Crit Care Med*. 2016:194:265-275.

Management of AE-ILD

- Identify early -patients report changes in symptoms
- Evaluations
  - Imaging +/- bronchoscopy/ sputum culture, BNP, ECHO, CT angiogram
- Acute setting treatment
  - Outpatient – corticosteroids 40 to 60mg +/- abx
  - Inpatient – Solumedrol 500 to 1000mg/d x 3d +/- abx
- Chronic/recurrent AE (AIP)
  - MMF, AZA, Cytoxan, transplant

Oxygen Therapy

- "Ensure oxygen saturations are > 90% at all times"
  - Rest, Ambulation, Exercise, Sleep
    - Obstructive Sleep Apnea (OSA) is common in IPF
    - Patients may not present with typical symptoms
    - Untreated OSA may be associated with worse prognosis
      - Mortality & Clinical Progression
  - While this is a "Strong Recommendation," limited data
    - No proven survival benefit
    - Evidence does exist that it may improve exercise capacity/reduces dyspnea
    - At present,
      - Ongoing studies
      - Calls for more research

Raghu G, et al. Am J Respir Crit Care Med. 2011;183:788-824.
Bosi M, et al. Lung. 2017 Jul 3.

Lung Transplantation

- The **only therapy** that prolongs survival in IPF
- IPF is now the **number one** diagnosis for transplant
- Five-year survival is ~ 50%
- Many centers are transplanting older patients (>65)

Primary Transplants, January 1992 – June 2017 Diagnosis by Age/Organ Group

Diagnosis	N	%
Cystic Fibrosis	9330	15.68
Chronic Obstructive Pulmonary Disease	22397	37.64
Idiopathic Pulmonary Fibrosis	15033	25.27
Other	12736	21.41
All	60680	100

Slides from ISHLT Registries. Available at: [redacted].
King TE Jr, et al. Lancet. 2011;378:1949-1961.

Lung Transplantation

- When to refer for transplant?
  - At the time of diagnosis
    - **Evaluation** (due to unpredictable course)
  - As disease progresses
    - Listing (based on Lung Allocation Score)

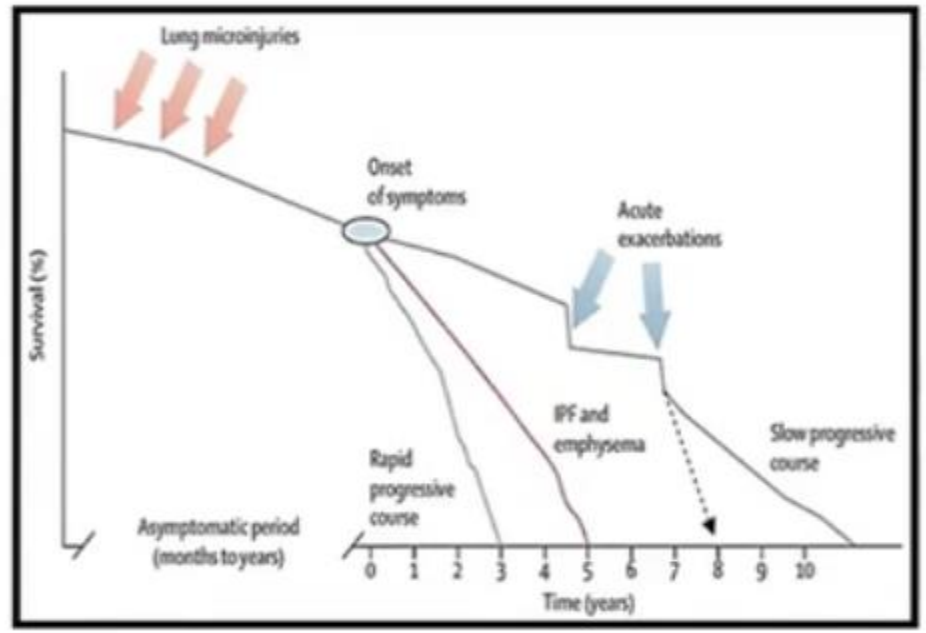


TABLE 1 Criteria for referral and listing for lung transplantation in patients with interstitial lung disease (ILD)

Timing of referral[#]	Timing of listing
Histopathological UIP	Hospitalisation for respiratory decline, pneumothorax or acute exacerbation
Radiographic probable or definite UIP pattern	Desaturation to <88% on 6MWT or >50 m decline in 6MWD over 6 months
FVC <80% or D_{LCO} <40% pred	Pulmonary hypertension on right heart catheterisation or echocardiography
Relative decline in pulmonary function over the past 2 years: FVC ⩾10% or D_{LCO} ⩾15% or FVC ⩾5% with symptomatic or radiographic progression	Absolute decline in pulmonary function over the past 6 months despite appropriate treatment: FVC >10% or D_{LCO} >10% or FVC >5% with radiographic progression
Any resting or exertional oxygen requirement	
For inflammatory ILDs, disease progression despite treatment	

Referral or listing should be considered if meeting any one criterion. UIP: usual interstitial pneumonia; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-min walk test; 6MWD: 6-min walk distance. [#]: earlier referral is recommended for patients with connective tissue disease or familial idiopathic pulmonary fibrosis to address potential extrapulmonary manifestations. Reproduced and modified from [13] with permission.

TABLE 2 Risk factors for adverse post-transplant outcomes in candidates for lung transplantation

General	High or substantially increased risk	Absolute contraindications
Age 65–70 years	Age >70 years	Lack of patient willingness or acceptance of transplant
GFR 40–60 mL·min^{-1}·1.73 m^{-2}	Severe CAD requiring CABG at transplant	Malignancy with high risk of death or recurrence
CAD including prior CABG	LV ejection fraction <40%	GFR <40 mL·min^{-1}·1.73 m^{-2} unless being considered for multi-organ transplant
LV ejection fraction 40–50%	Significant cerebrovascular disease	Acute coronary syndrome within 30 days (excluding demand ischaemia)
Peripheral vascular disease	Severe oesophageal dysmotility	Stroke within 30 days
Connective tissue disease	Untreatable haematological disorders (bleeding diathesis, thrombophilia, severe bone marrow dysfunction)	Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant
Severe GOR	BMI ⩾35 kg·m^{-2}	Acute liver failure
Oesophageal dysmotility	BMI <16 kg·m^{-2}	Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery
Bone marrow dysfunction	Limited functional status with poor rehabilitation potential	Active extrapulmonary infection including septic shock
Osteoporosis	Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence	Active tuberculosis infection
BMI 30–34.9 kg·m^{-2}	Unreliable support system	HIV infection with detectable viral load
BMI 16–17 kg·m^{-2}	Lack of understanding of disease and/or transplant despite teaching	Severely limited functional status with poor rehabilitation potential
Frailty	*Mycobacterium abscessus* infection	Progressive cognitive impairment
Hypoalbuminaemia	*Lomentospora prolificans* infection	Repeated episodes of nonadherence without evidence of improvement
Poorly controlled diabetes	*Burkholderia cenocepacia* or *gladioli* infection	Active substance use or dependence including current tobacco use, vaping, marijuana smoking or intravenous drug use
Edible marijuana	Hepatitis B or C infection with detectable viral load and liver fibrosis	Other severe uncontrolled medical condition expected to limit survival after transplant
Scedosporium apiospermum infection	Chest wall or spinal deformity expected to cause restriction after transplant	
HIV with undetectable viral load	Extracorporeal life support	
Previous thoracic surgery including pleurodesis	Re-transplantation for restrictive CLAD, antibody-mediated rejection or within 1 year following initial lung transplant	
Mechanical ventilation		
Re-transplantation		

Kada bi pacijentima sa PPF bilo potrebno upućivanje na program transplantacije pluća?

- Rano upućivanje na transplantaciju pluća u PPF, kao što je preporučeno u IPF-u Centri za transplantaciju radije procjenjuju pacijente *prije nego što je bolest u završnoj fazi!!!!*

- Vrijeme *uvrštavanja na listu* za transplantaciju mora se pažljivo procijeniti- *očekivani tok bolesti* i *rizike* povezane sa transplantacijom

- Ranije upućivanje pruža mogućnosti za rješavanje problema sa:
  - indeksom tjelesne mase (BMI),
  - liječenje/prevencija osteoporoze,
  - izbjegavanje dekondicioniranja i
  - omogućavanjem formiranja odnosa - osoblje transplantacijskog tima i pacijent

Hvala za pažnju!