Impacts and Management of Comorbidities in IPF

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인제대학교 부산백병원 호흡기.알레르기내과

이 현 경

What are comorbidities ?

Comorbidities are medical conditions that coexist alongside a primary diagnosis and affect your health, including your treatment and outlook.

https://my.clevelandclinic.org/health/articles/comorbidities

Why should we care about comorbidities ?

개별질환만 있을 때 보다 환자에게 **더 큰 영향** 을 줄 수 있다

환자의 **삶의 질** 에 더 큰 영향을 줄 수 있다

장기적인 **예후**에 영향을 줄 수 있다

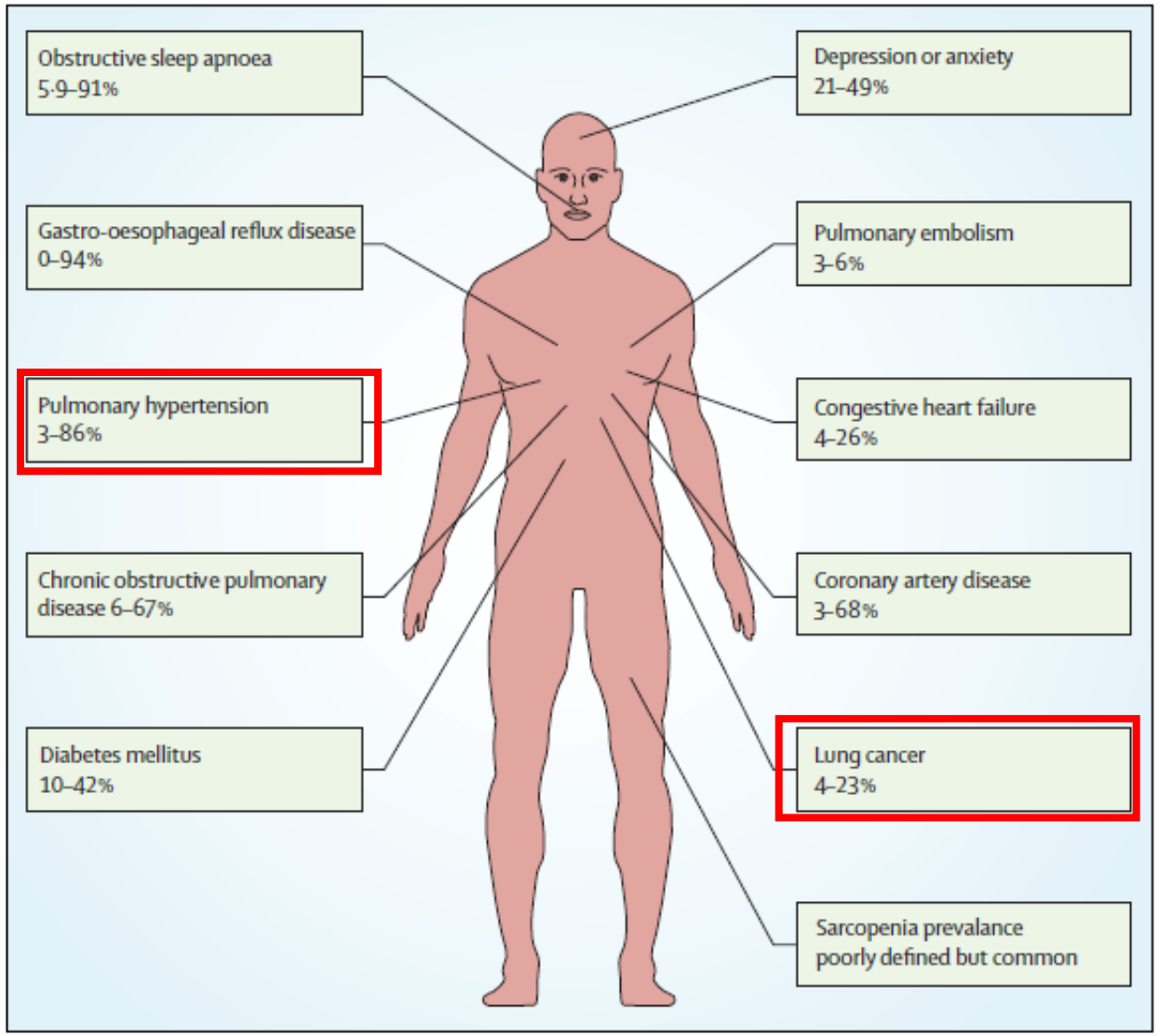
치료가 복잡해 질 수 있고, 질환끼리 영향을 줄 수 있고 한가지 질환에 대한 치료가 다른 질환을 악화시킬 수 있다

https://my.clevelandclinic.org/health/articles/comorbidities

Key Questions of today's lecture

- IPF환자에서 흔한 동반질환의 종류는?
- 동반질환의 유병율, 발생율은 ?
- 동반질환 발생의 기전은?
- IPF환자에서 동반질환이 환자에게 미치는 영향은 ?
  - ✓ 삶의 질
  - ✓ 생존 및 사망
- 동반질환을 어떻게 관리할 것인가 (조기발견, 치료) ?

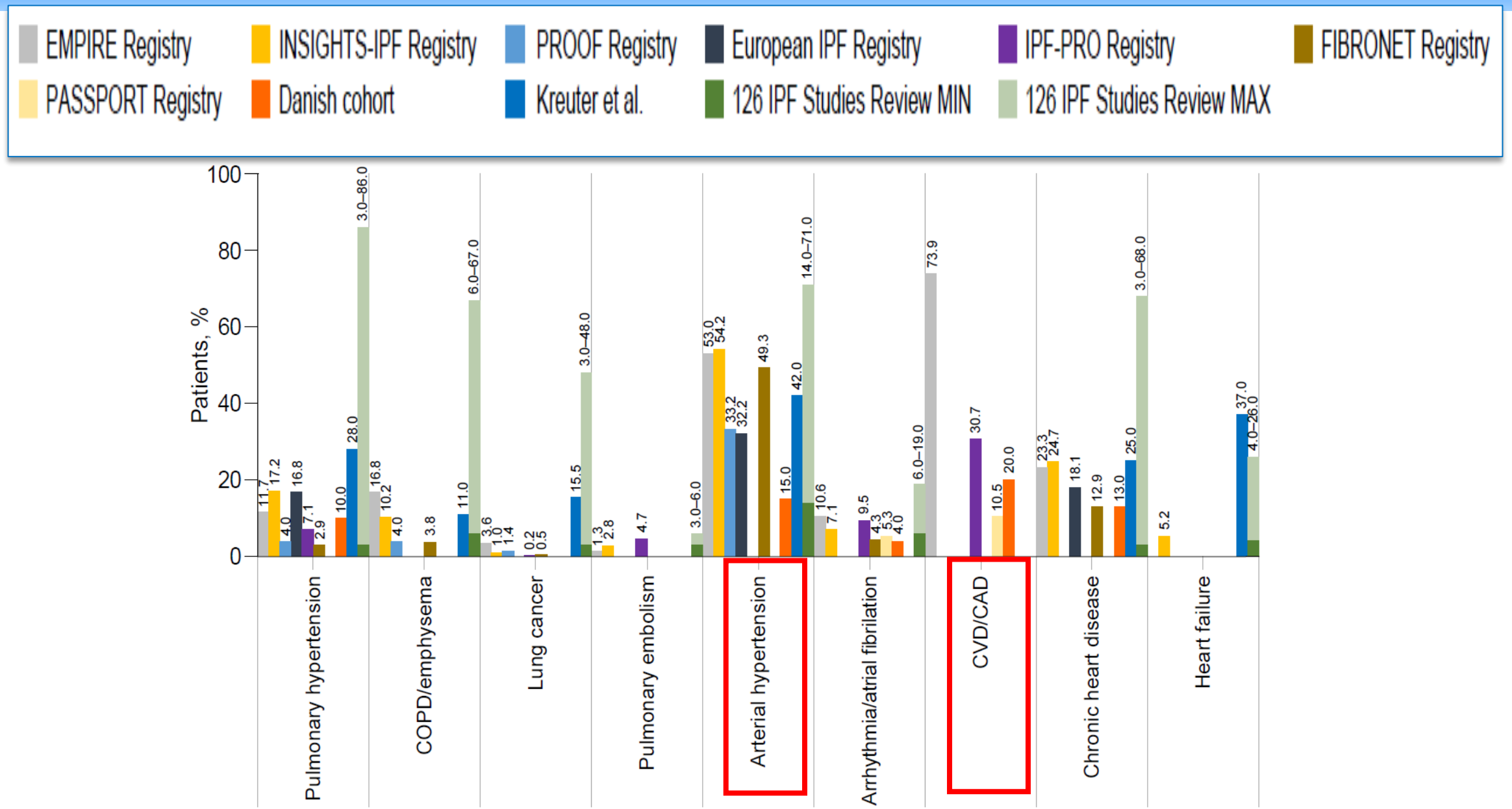
Prevalence of Comorbidities in IPF : highly Variable



- Study design
- Definition of cormorbidities
- Length of study period
- Sample size

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Comparison of Comorbidities among studies (1)



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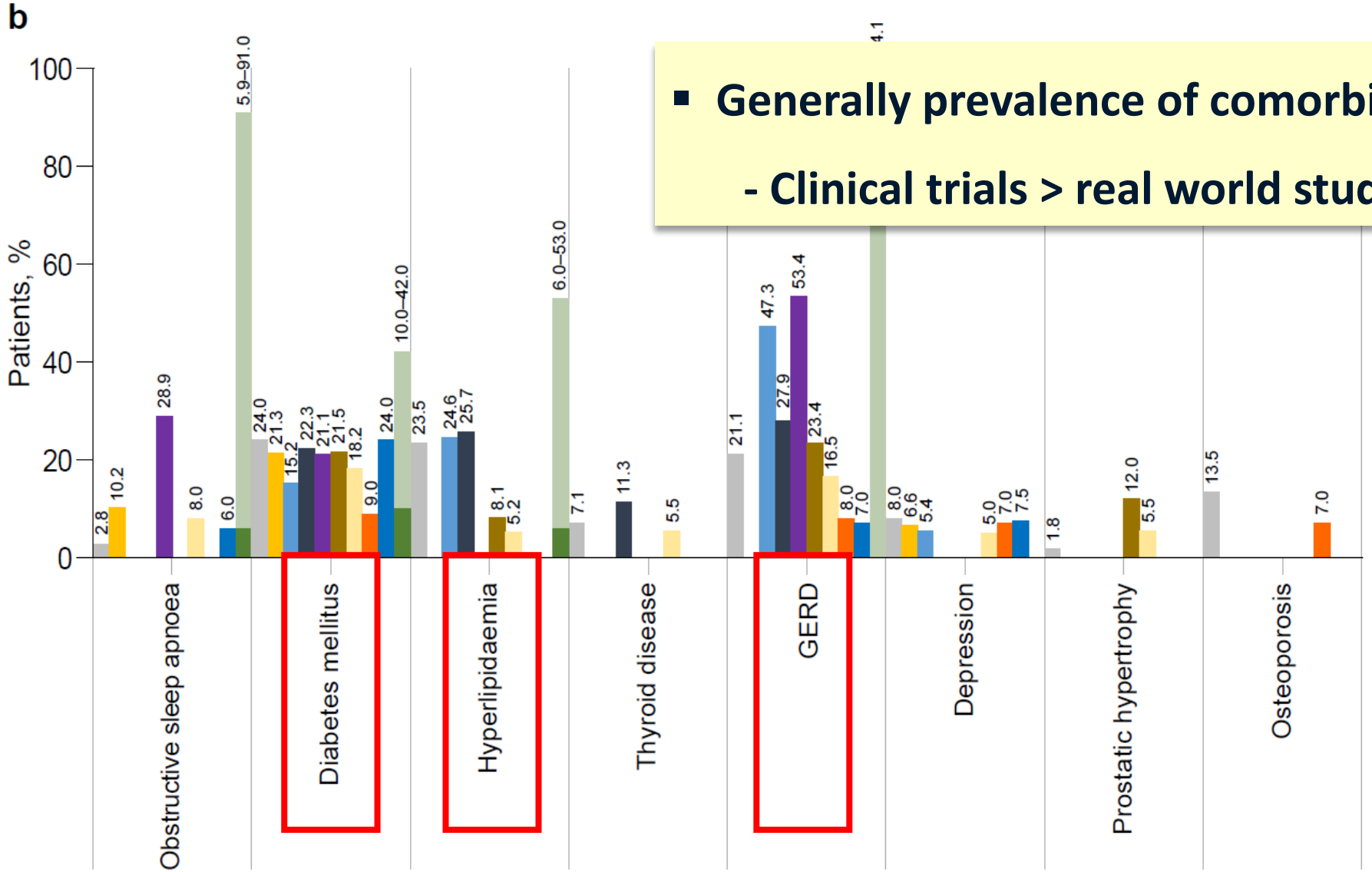
Comparison of Comorbidities among studies (2)



- **Generally prevalence of comorbidities**
  - **Clinical trials > real world studies**

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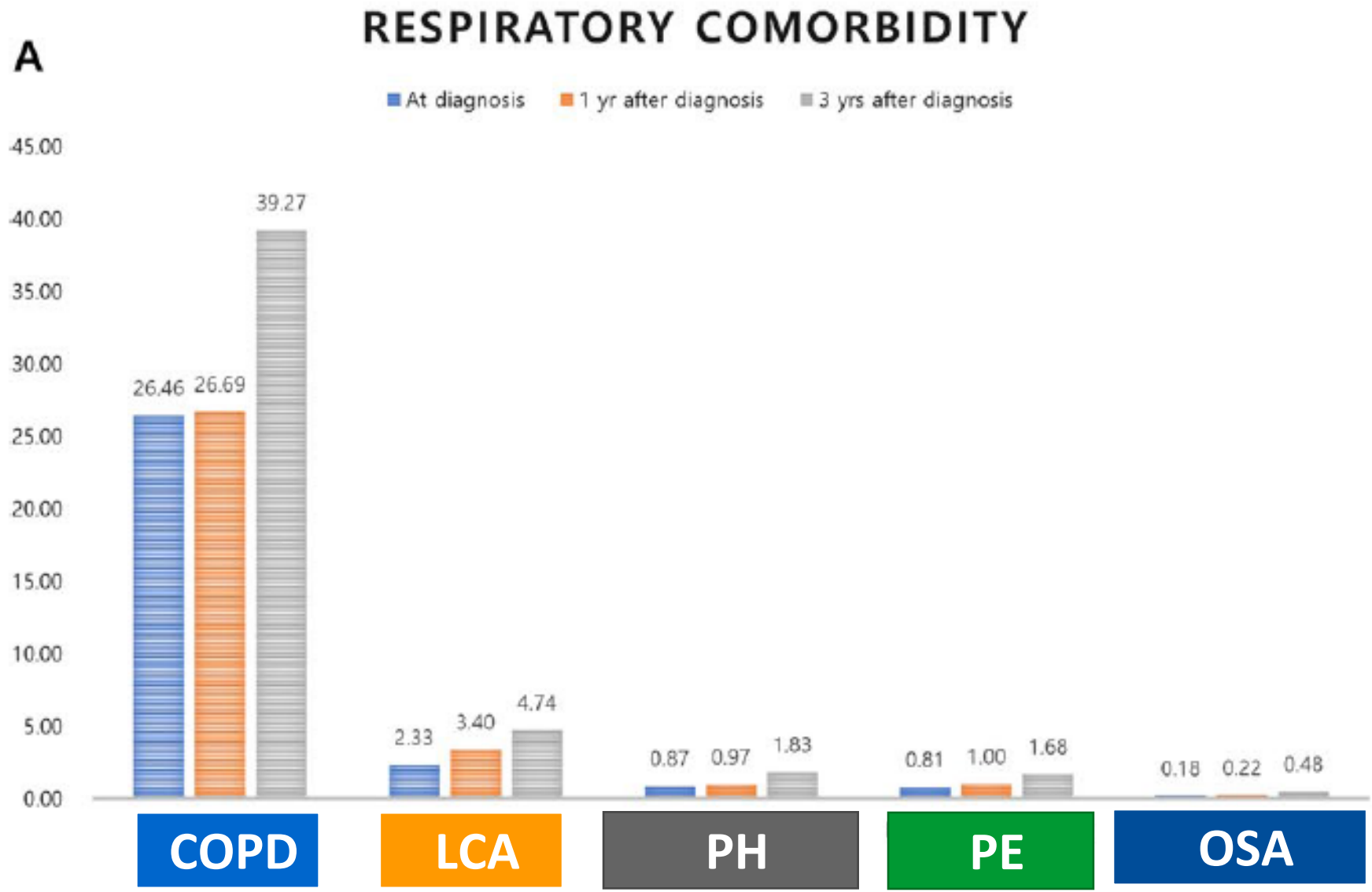
Prevalence of Comorbidities in IPF : Korean Nation Wide Cohort

HIRA data : 2011-2019

- **J84 + Rare Intractable Disease coded for IPF**



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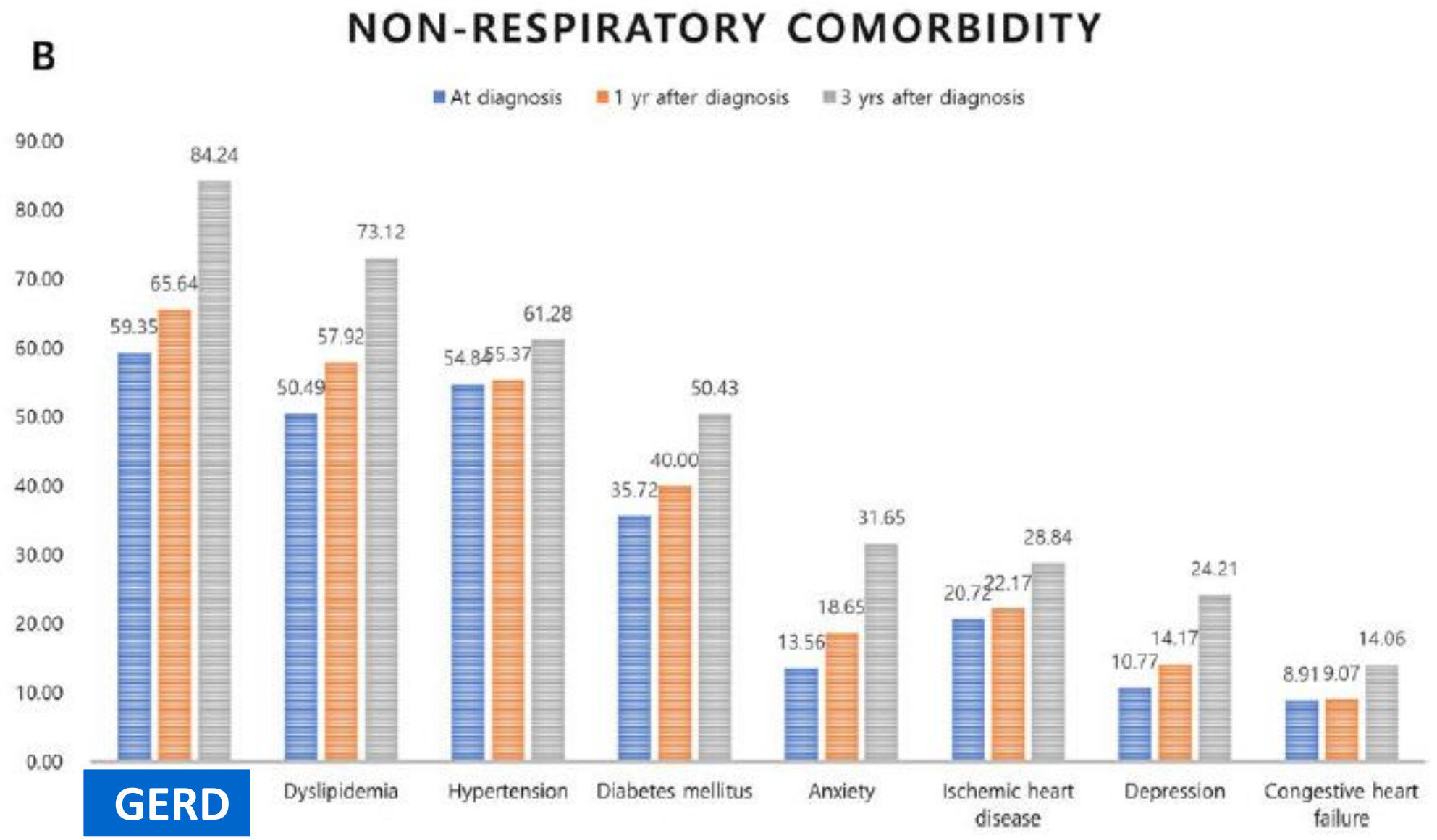
Prevalence of Comorbidities in IPF : Korean Nation Wide Cohort



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Medical Resource Utilization and Comorbidities : Korean Nation Wide Cohort

	Within 90 days				Within 365 days			
	Total (n = 21,111)	CCI 0–3 (n = 11,618)	CCI over 4 (n = 9493)	*p* value	Total (n = 21,111)	CCI 0–3 (n = 11,618)	CCI over 4 (n = 9493)	*p* value
Patients who visited outpatient clinics	18,042 (85.46%)	10,395 (89.47%)	7647 (80.55%)	< 0.001	18,170 (86.07%)	10,462 (90.05%)	7708 (81.20%)	< 0.001
Patients admitted to hospitals	4156 (19.69%)	1771 (15.24%)	2385 (25.12%)	< 0.001	5806 (27.50%)	2693 (23.18%)	3113 (32.79%)	< 0.001
Total medical costs (KRW1000)	86.0 [25.0–303.0]	79.2 [24.5–234.0]	97.0 [25.59 –585.7]	< 0.001	314.0 [63.0– 1321.0]	303.1 [65.5– 961.3]	332.7 [59.7– 1963.9]	< 0.001

** CCI : Charlson comorbidity index*

Pirfenidone Use and Comorbidities: Korean Nation Wide Cohort

	Pirfenidone user (n = 5449)	Pirfenidone non-user (n = 7494)	*p* value
Sex			< 0.001
Men	4312 (79.13%)	5110 (68.19%)	
Women	1137 (20.87%)	2384 (31.81%)	
Age			< 0.001
Older age (≥ 70 years)	2300 (42.21%)	2591 (34.57%)	
Younger age (< 70 years)	3149 (57.79%)	4903 (65.43%)	
Respiratory diseases			
COPD	1893 (34.74%)	2671 (35.64%)	0.289
Lung cancer	217 (3.98%)	243 (3.24%)	0.025
Pulmonary embolism	72 (1.32%)	150 (2.00%)	0.003
Pulmonary hypertension	45 (0.83%)	133 (1.77%)	< 0.001
Obstructive sleep apnoea	29 (0.53%)	24 (0.32%)	0.062
Non-respiratory diseases			
GERD	4272 (78.40%)	5581 (74.47%)	< 0.001
Dyslipidaemia	3715 (68.18%)	4944 (65.97%)	0.008
Hypertension	3193 (58.60%)	4603 (61.42%)	0.001
Diabetes mellitus	2460 (45.15%)	3495 (46.64%)	0.093
Ischaemic heart disease	1456 (26.72%)	1989 (26.54%)	0.820
Anxiety	934 (17.14%)	1601 (21.36%)	< 0.001
Depression	734 (13.47%)	1228 (16.39%)	< 0.001
Congestive heart failure	726 (13.32%)	1283 (17.12%)	< 0.001

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Suggested Mechanisms of Comorbidities in IPF

Shared underlying Risk Factors

- **Smoking**
  - Lung ca/COPD
  - CVD
- **Aging (TERT/TERC/Telomere shortening)**
  - Lung ca
  - emphysema

Medications used for IPF Tx

Diabetes (steroid)

IPF itself : Hypoxia

PH

Chr. Inflamm. through repetitive microaspiration : GERD-IPF

Hyperglycemia-ass. Pulmonary inflammation : Diabetes - IPF

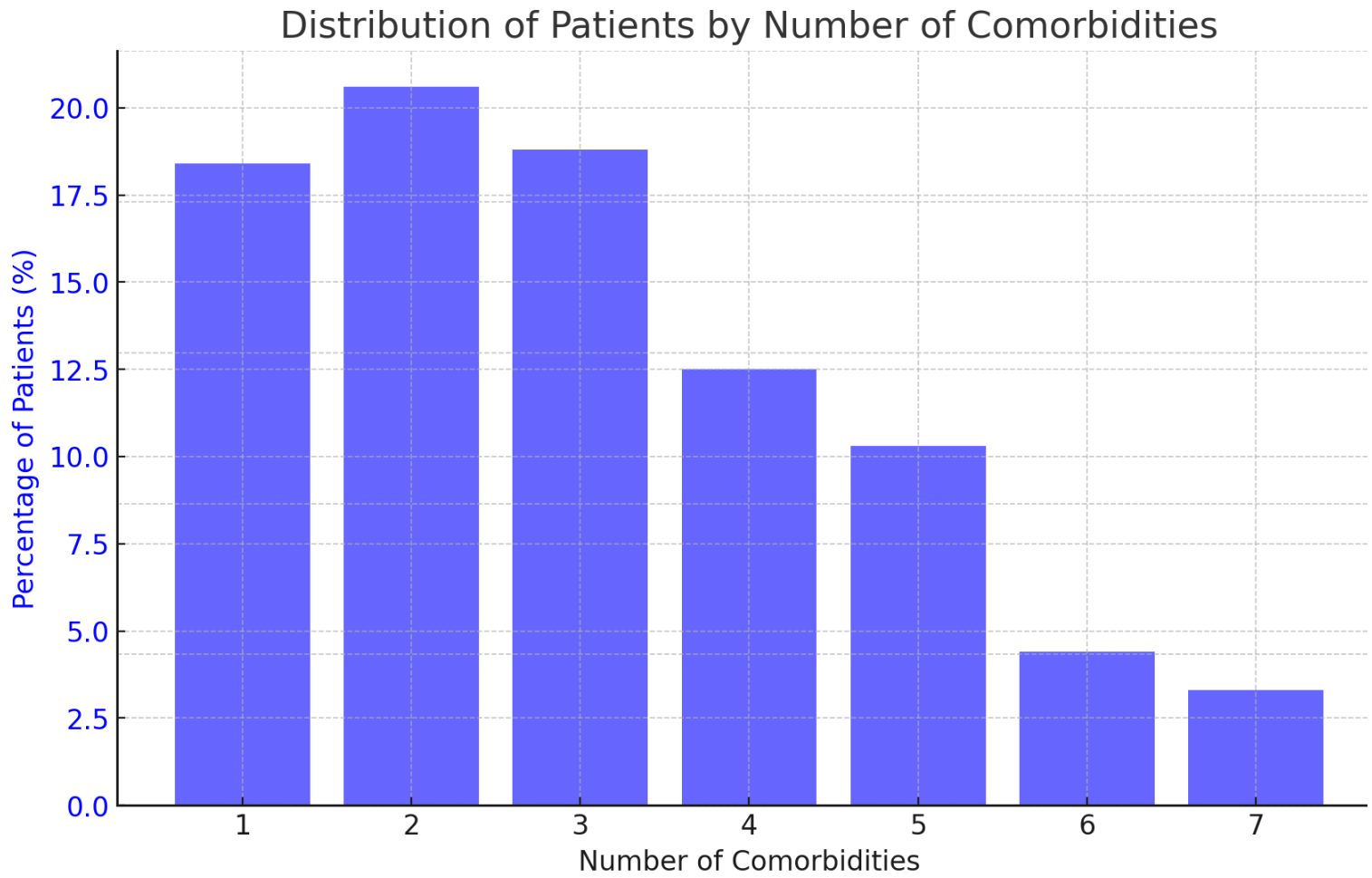
IPF development/progression

Distribution of Comorbidities in IPF patients

German tertiary referral center for ILD

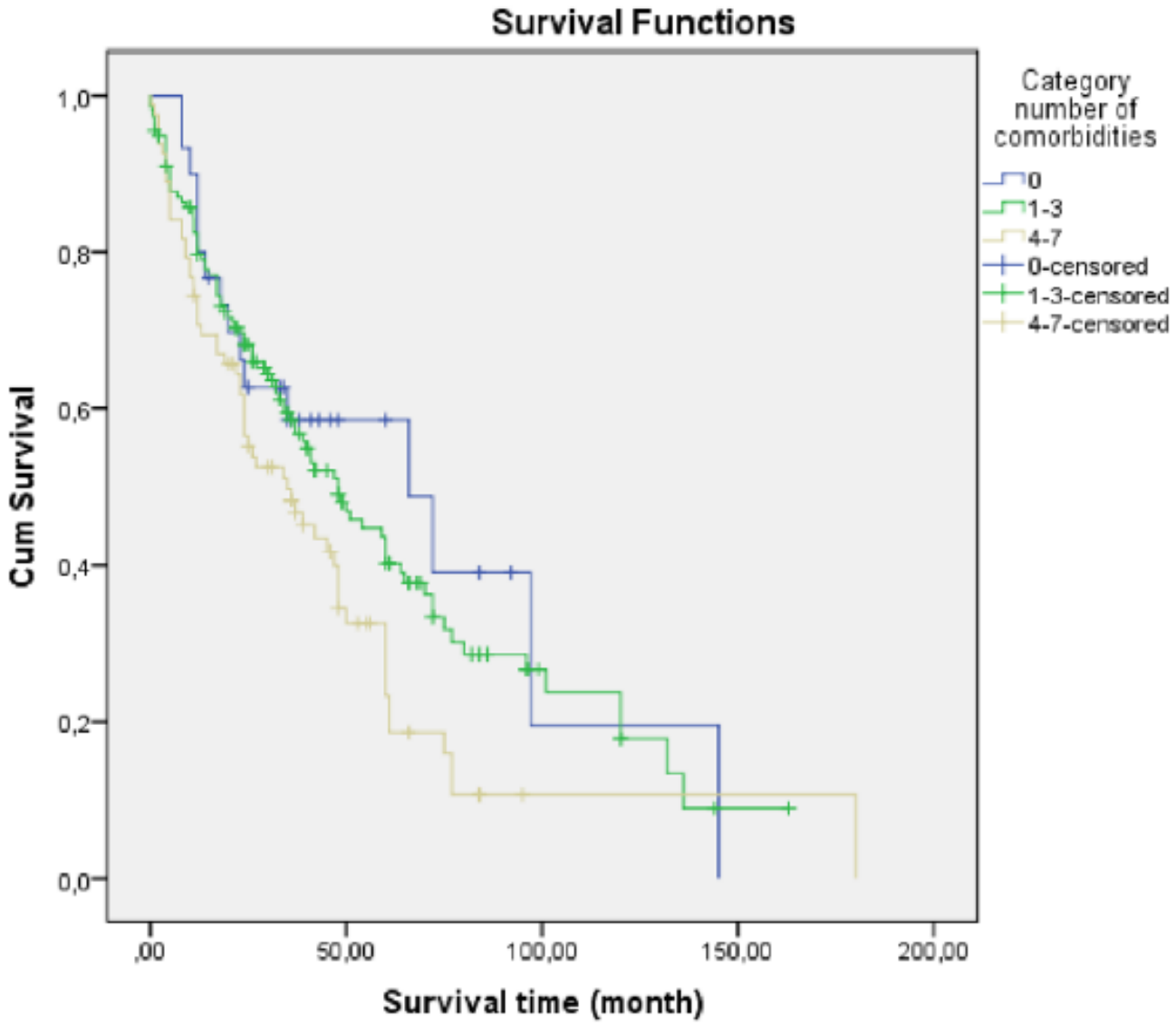
- **Study period : 2004.1-2012.4**
- **272 patients were included.**

- **Proportions of no comorbidities : only 11.4%**



Kreuter M, et al. PLoS ONE 11(3): e0151425. doi:10.1371/journal.pone.0151425

Numbers of Comorbidities and Mortality



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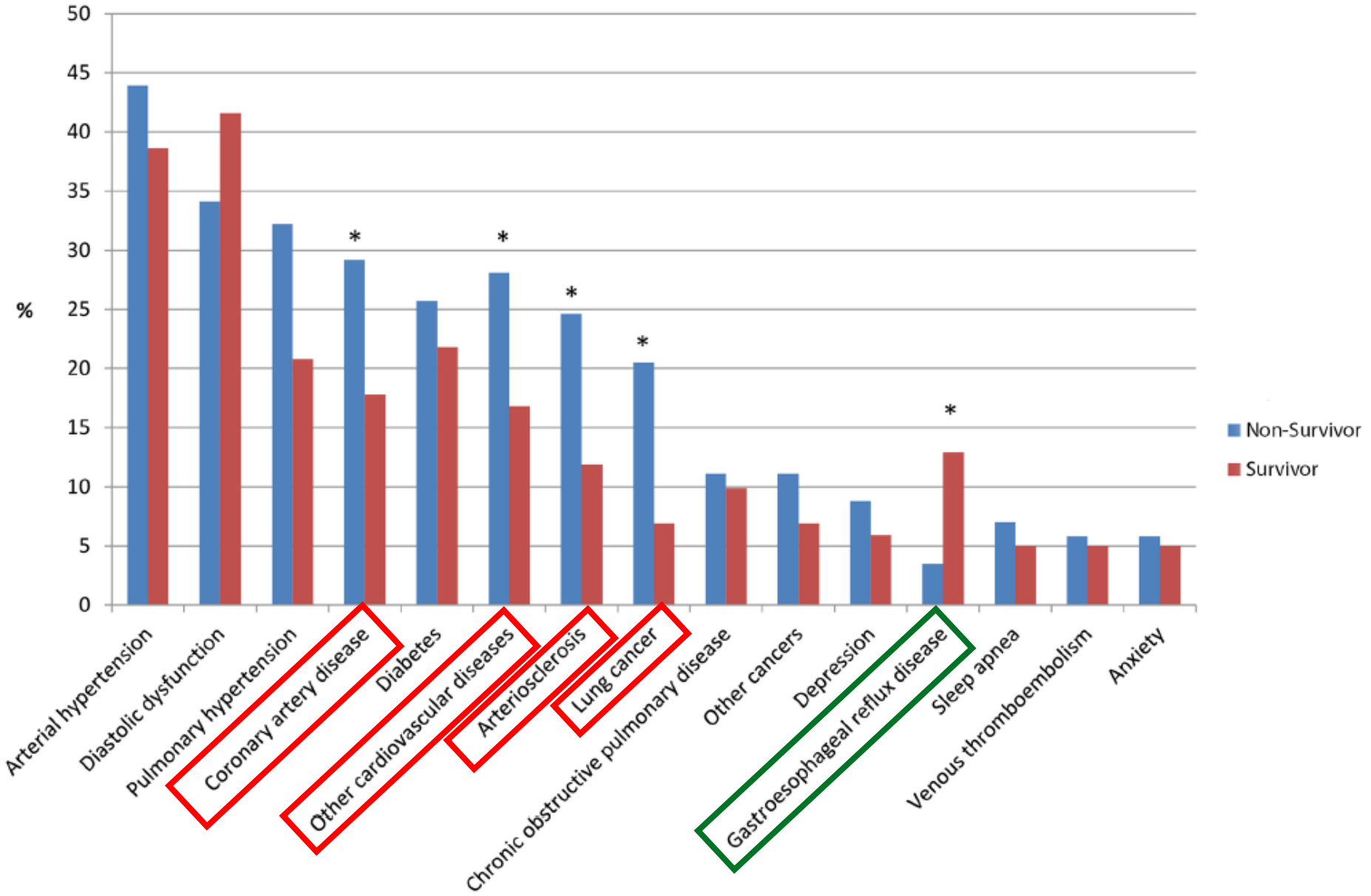
Prevalence of Comorbidities and Survival status



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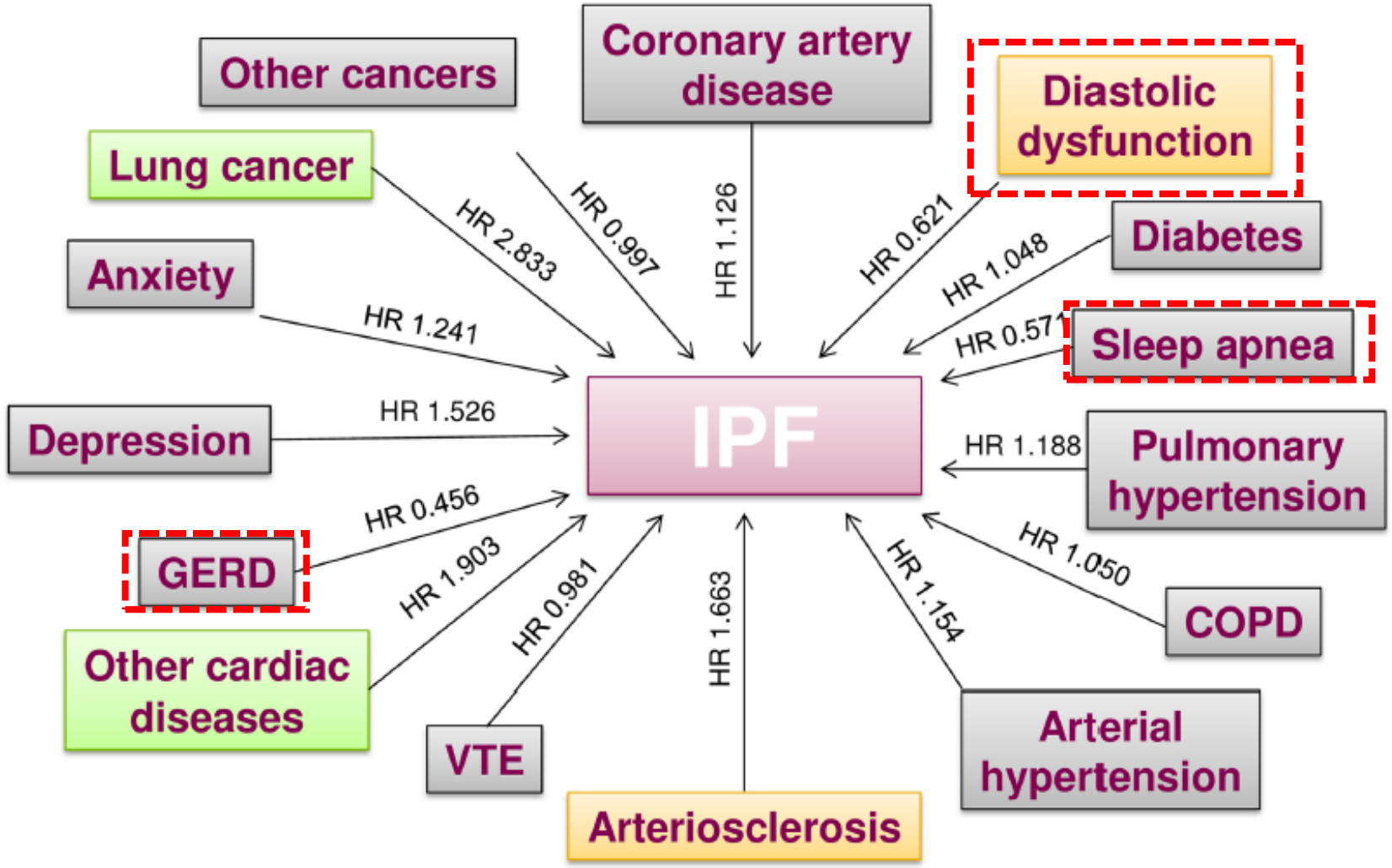
Impact of IPF and Comorbidities on Mortality



Kreuter M, et al. PLoS ONE 11(3): e0151425. doi:10.1371/journal.pone.0151425

Prediction Model for Survival in IPF with *Comorbidities* vs GAP

	Derivation cohort	Validation cohort	p-value
Patients n	476	461	
Age years	68.08±8.41	70.20±8.63	0.0002
Male	366 (76.73)	344 (74.46)	0.41
FVC % pred	75.24±19.85	70.04±17.67	<0.001
*D*LCO % pred	47.58±18.30	47.70±17.85	0.91
Atrial arrhythmias	33 (6.92)	27 (5.84)	0.51
GORD	117 (24.53)	150 (32.47)	0.007
Lung cancer	60 (12.58)	9 (1.95)	<0.001
Pulmonary hypertension	128 (26.83)	53 (11.47)	0.001
Valvular heart disease	30 (6.29)	24 (5.19)	0.47
Cerebrovascular disease	68 (14.26)	25 (5.41)	<0.001
Diabetes mellitus	114 (23.90)	73 (15.80)	0.002
Systemic hypertension	227 (47.59)	172 (37.23)	0.001
Depression	32 (6.71)	40 (8.68)	0.25
Transplanted	6 (1.26)	60 (12.99)	<0.001
Deceased	272 (57.02)	190 (41.13)	<0.001
Median follow-up time years	2.9	2.4	0.95
Median transplant-free survival years	3.7	4.6	0.001

Data are presented as mean±SD or n (%), unless otherwise stated. FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; GORD: gastro-oesophageal reflux disease.

Torrisi SE, et al. Eur Respir J 2019;53: 1801587

The TORVAN index calculation and Staging system

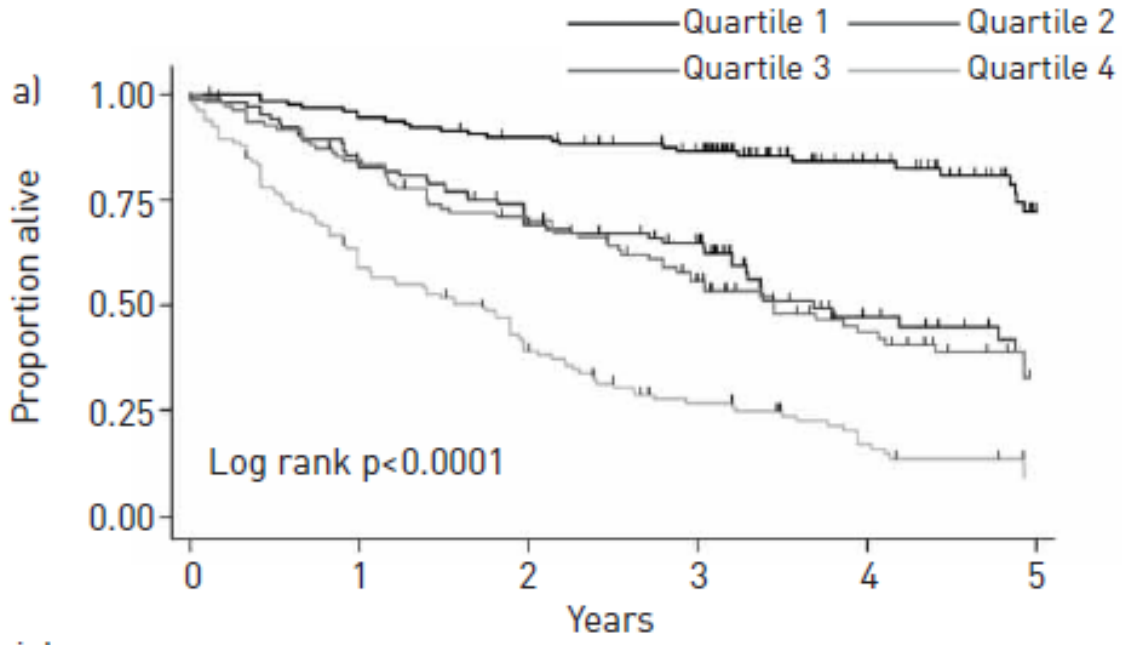
Predictors	Points (sparse model)	Points (full model)
Age years		
⩽55	0	0
56–70	6	6
>70	9	8
FVC % pred		
>80	0	0
61–80	1	1
⩽60	6	6
***D*Lco % pred**		
>60	0	0
31–60	6	6
⩽30	8	7
Unable to perform	9	9
Diabetes mellitus	1	2
Systemic hypertension	/	1
GORD	1 (absence)	2 (absence)
Pulmonary hypertension	2	2
Major depressive disorder	1	3
Lung cancer	6	6
Valvular heart disease	5	6
Atrial arrhythmias	6	6
Points (both for sparse and full models)	<14 / 14–16	17–22 / ⩾23
TORVAN stage	I / II	III / IV

- **Not selected : Sex, CAD, VTE, Peripheral vascular disease, emphysema, sleep apnea, dyslipidemia, kidney and liver failure, hypo/hyperthyroidism**

Torrisi SE, et al. Eur Respir J 2019;53: 1801587

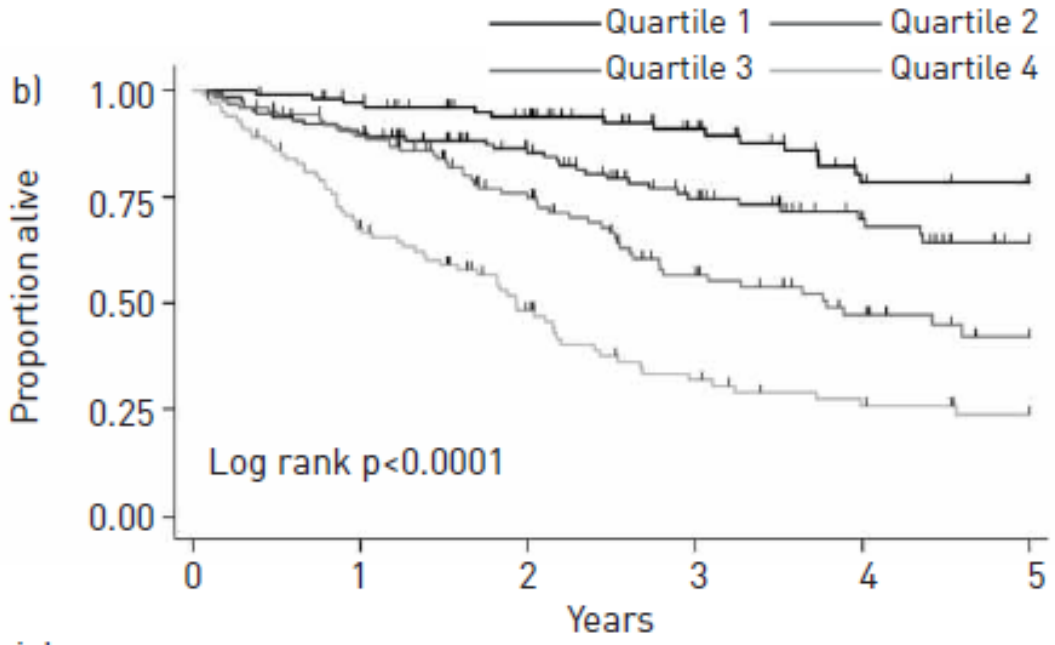
Transplant-free survival according to The TORVAN stage

Derivation cohort



At risk n						
Quartile 1	129	121	113	100	56	30
Quartile 2	105	86	68	56	21	13
Quartile 3	109	89	72	50	29	15
Quartile 4	133	76	46	28	15	6

Validation cohort



At risk n						
Quartile 1	106	95	79	57	40	35
Quartile 2	129	111	89	57	39	25
Quartile 3	125	104	71	41	26	13
Quartile 4	101	64	38	23	15	11

Torrisi SE, et al. Eur Respir J 2019;53: 1801587

When comorbidities included in survival prediction of IPF …

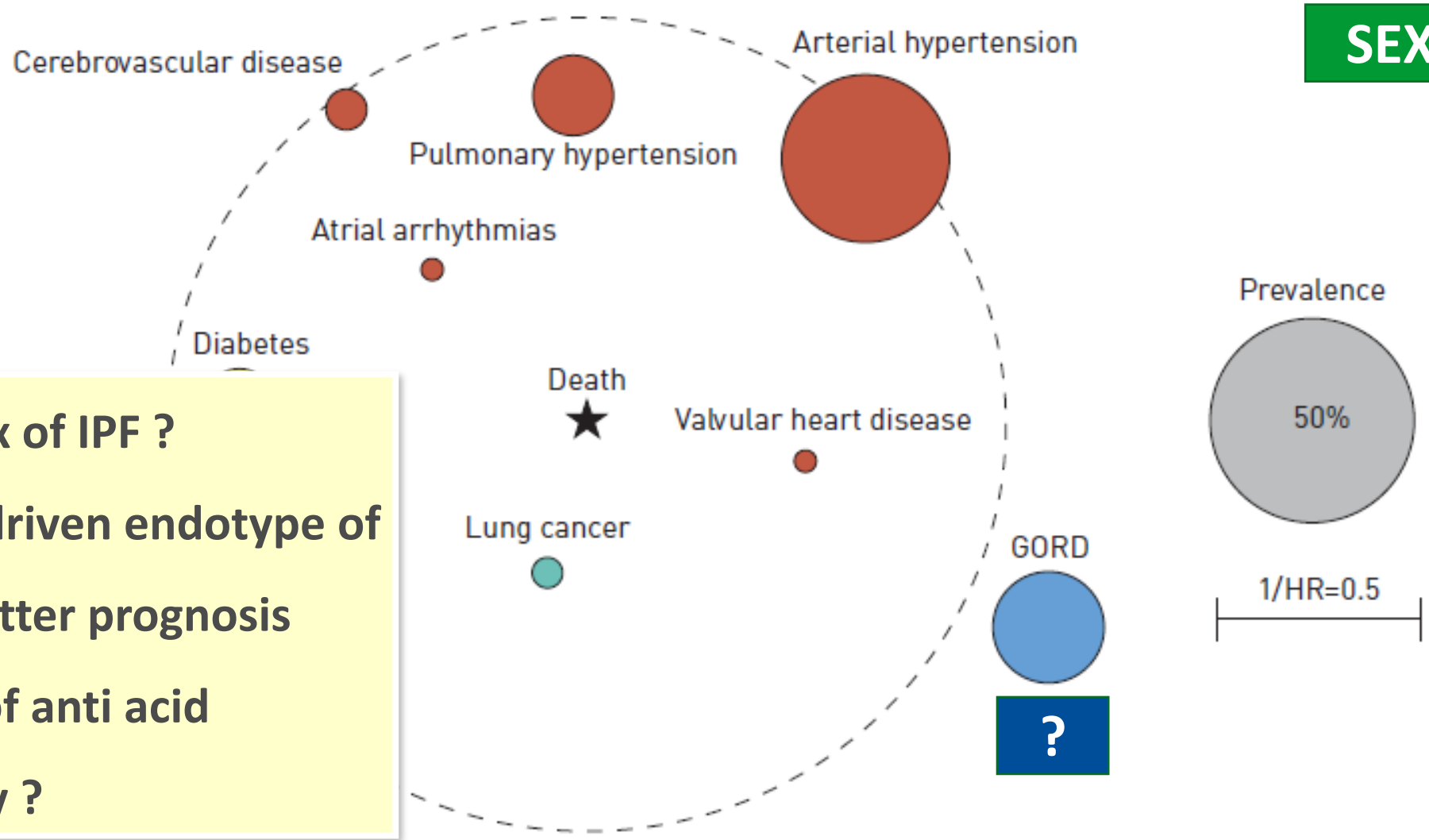
Improves prediction of survival **beyond basic demographic and physiological information (i.e. the GAP model)**

these tended to be comorbidities expected to influence short-term mortality

Patient sex becomes a less important prognostic indicator in the context of comorbidities.

Torrisi SE, et al. Eur Respir J 2019;53: 1801587

Comorbidome of IPF



1) Early dx of IPF ?
2) GERD-driven endotype of IPF : better prognosis
3) Effect of anti acid therapy ?

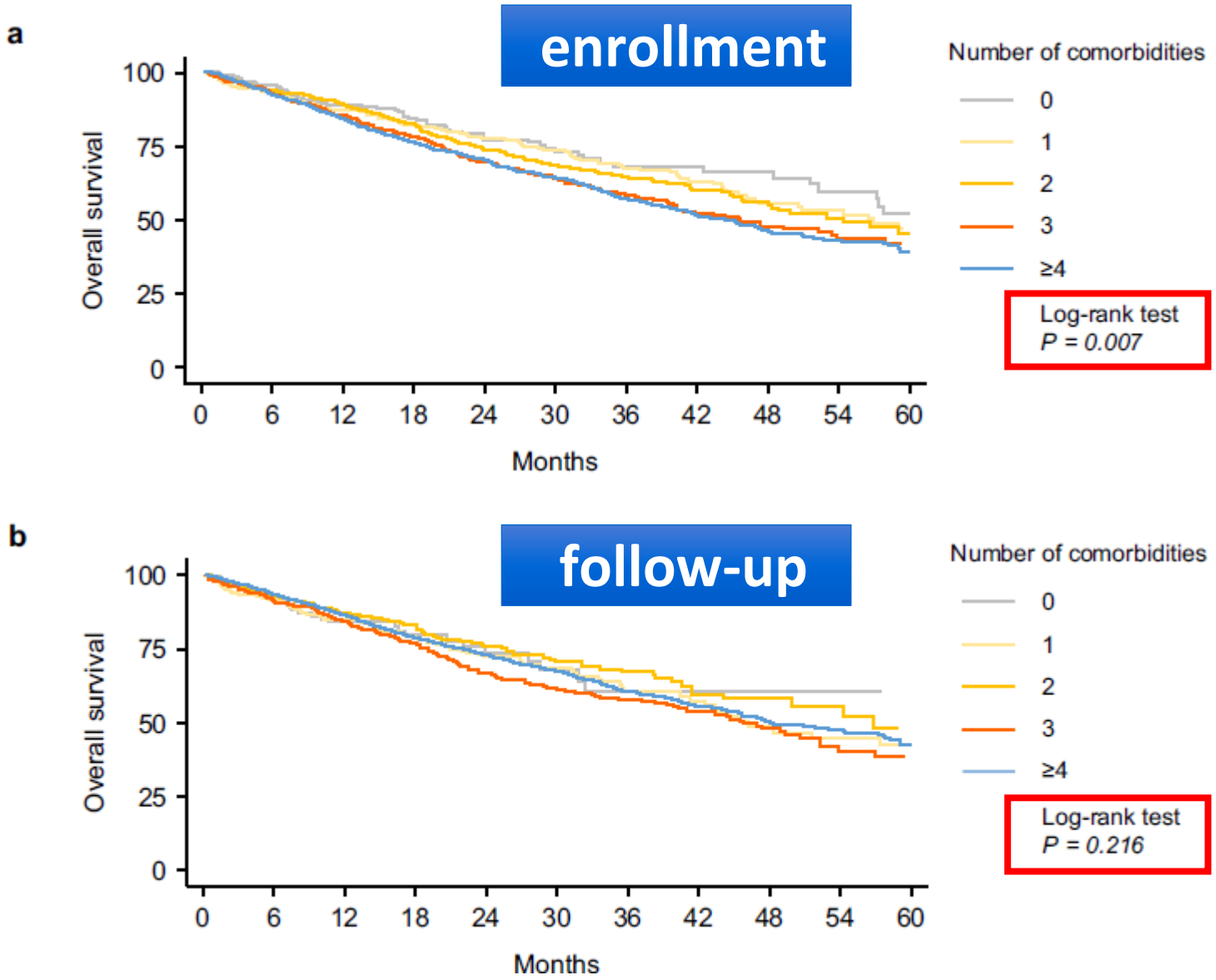
Torrisi SE, et al. Eur Respir J 2019;53: 1801587

Comorbidities and Survival of IPF patients : EMPIRE Registry

The EMPIRE Registry

- 11 Central and Eastern European countries established in Sep. 2014
- 3580 patients (2014.9 ~ 2020.5)

- Comorbidity related death was evidenced in at least 26.1% of cases.



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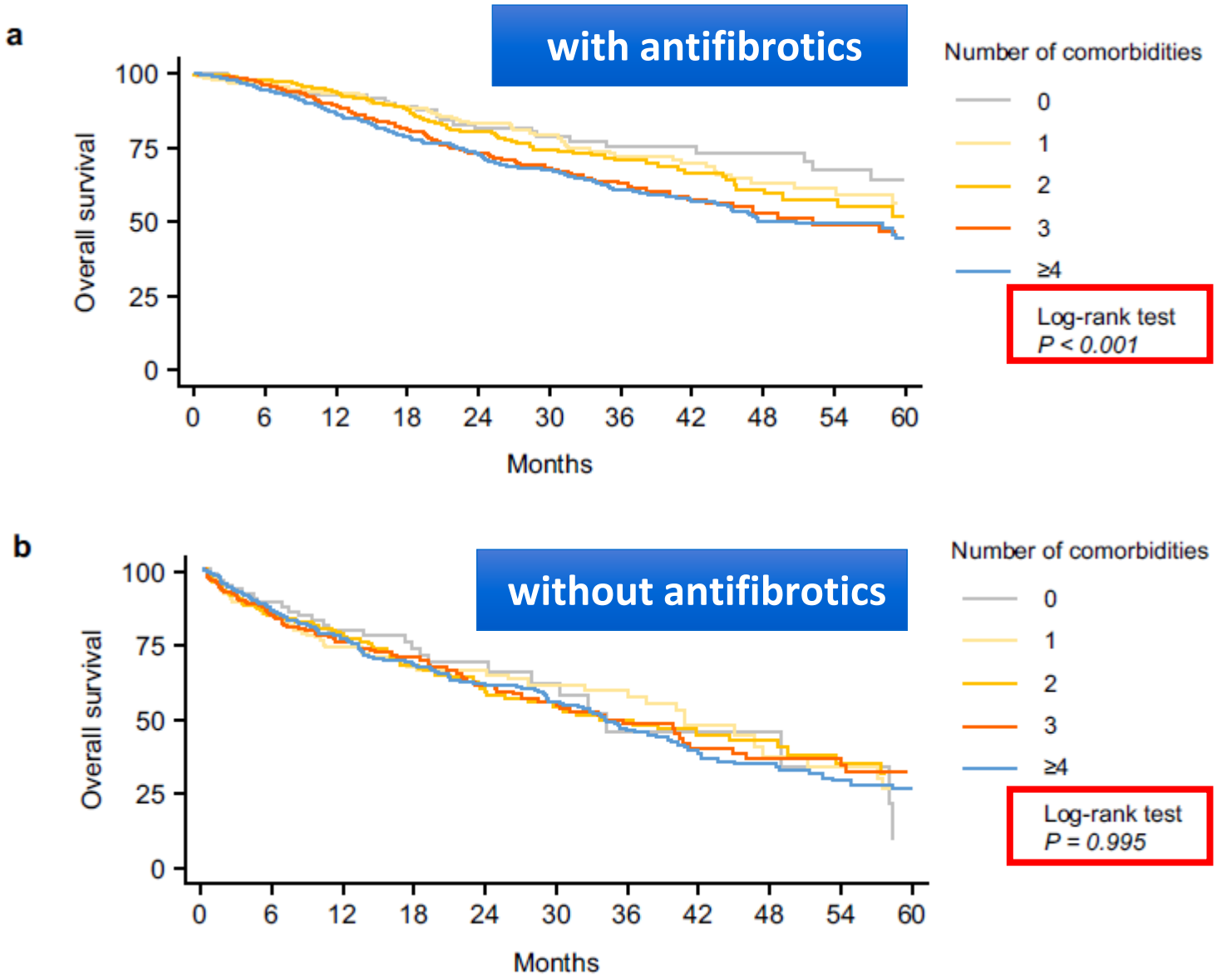
Comorbidities and Survival of IPF patients : EMPIRE Registry

- **Antifibrotic treatment and Survival**



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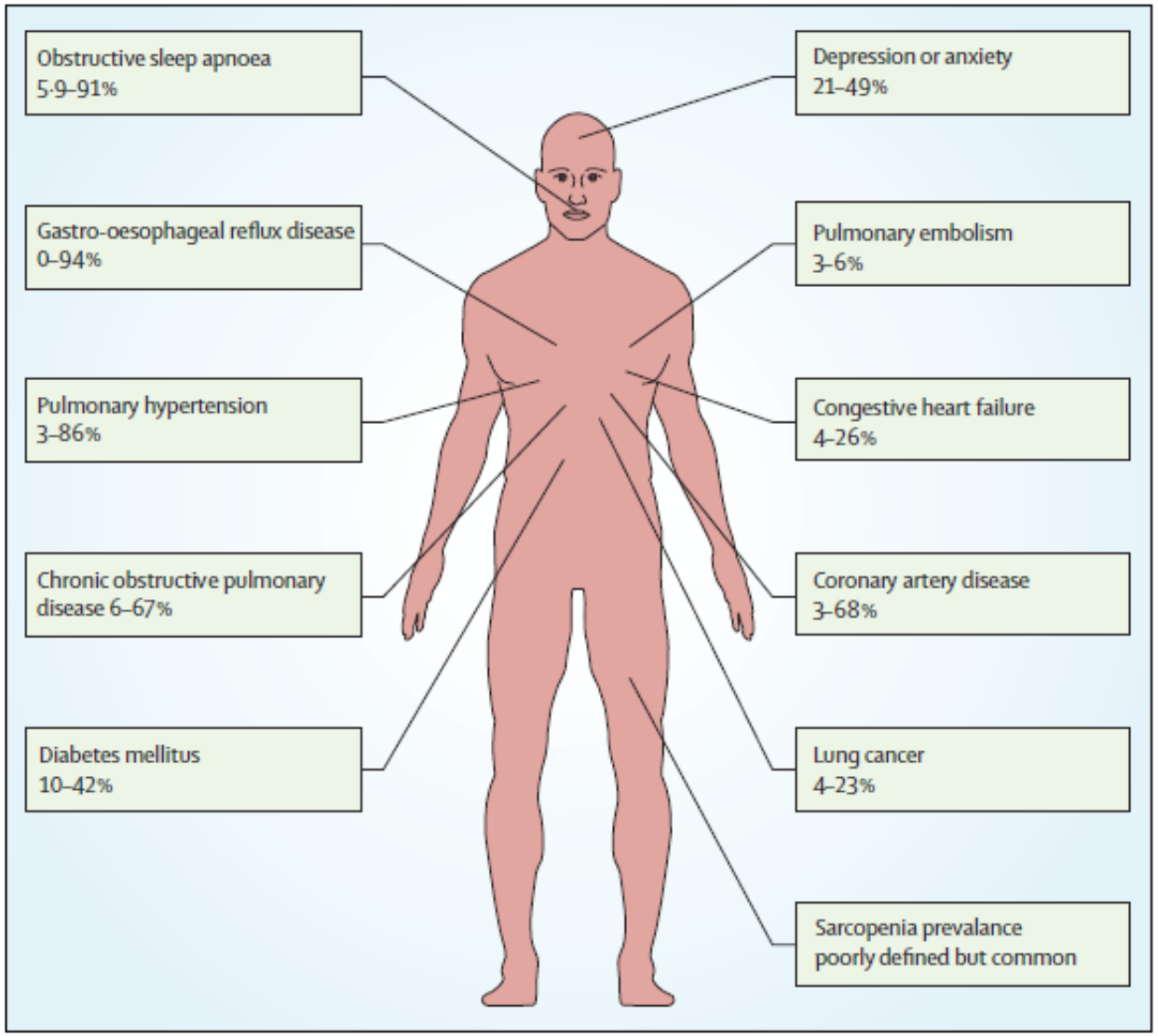
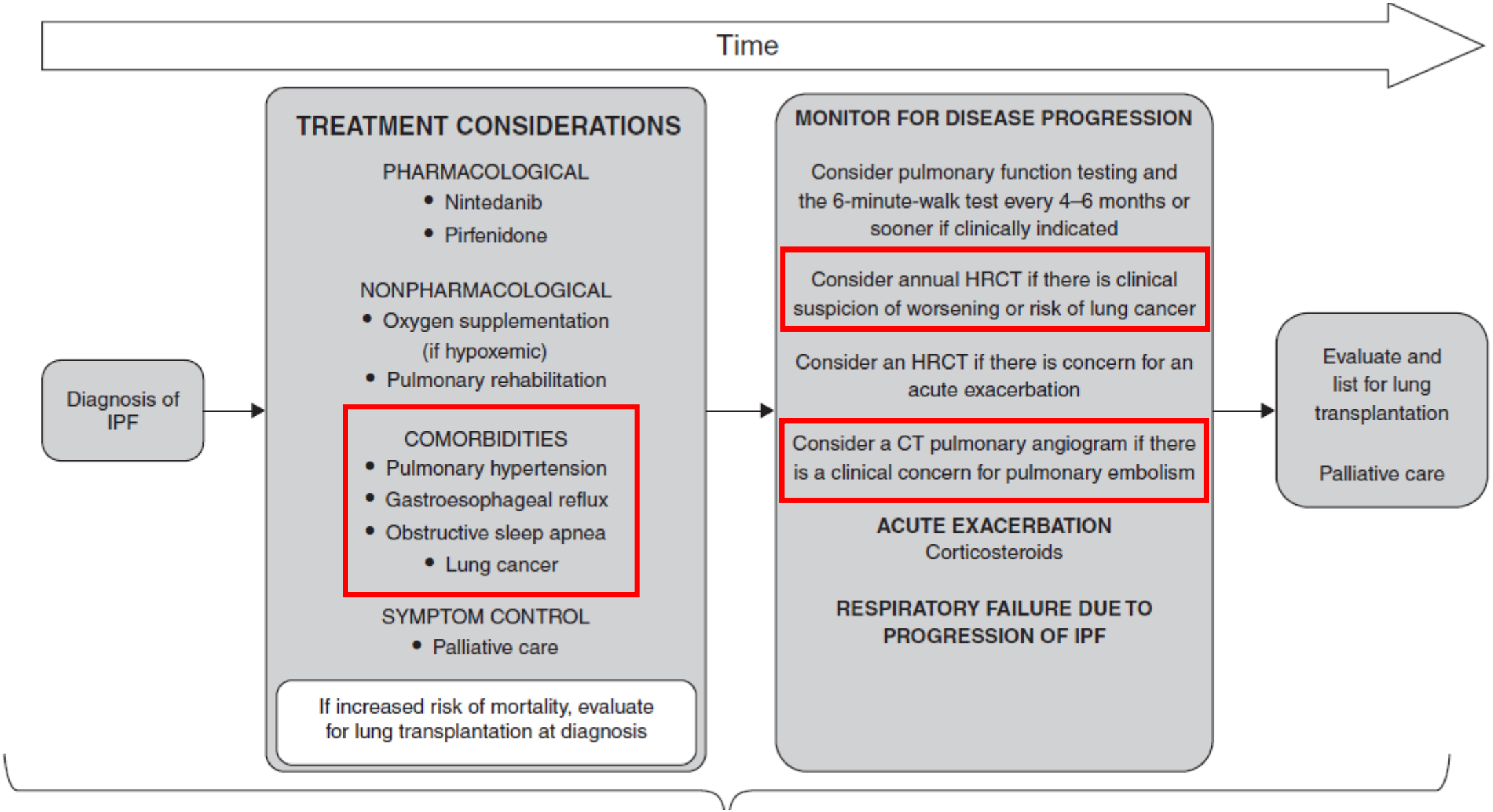
Management of Comorbidities in IPF

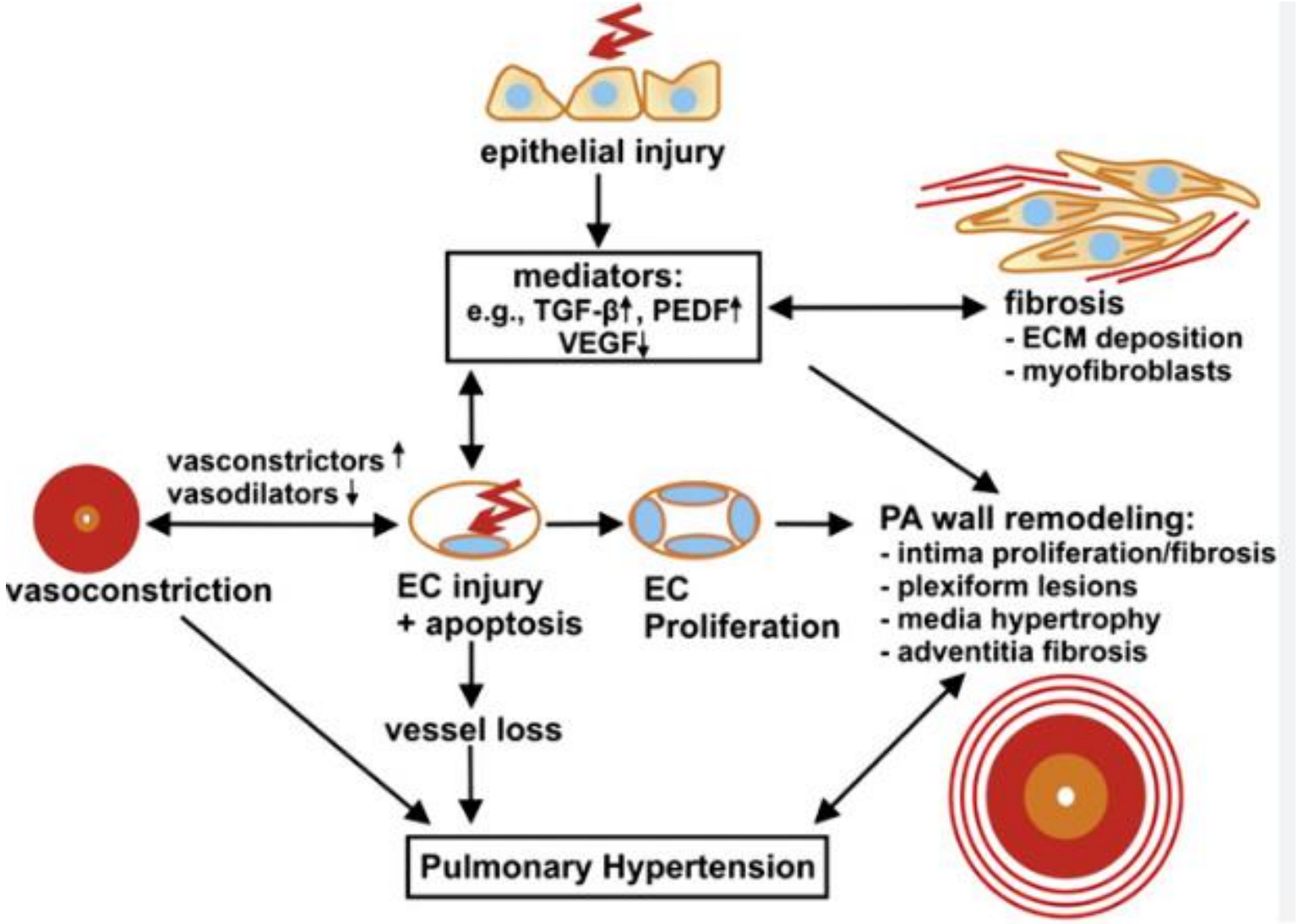


King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Management of Comorbidities of IPF : Recommended by ATS



Pulmonary hypertension : Mechanisms are complex



Farkas L, et al. Am J Respir Cell Mol biol. 25; 2010:1-15

Pulmonary hypertension : Impact and Things to Consider

- Increased 1-year mortality : 28% vs 5.5 % (PH-IPF vs no PH-IPF) in RHC confirmed cases
- Even mild PH (PAP ≥ 25 mmHg) in IPF increased the risk of death
- Mean right atrial pressure > 15 mmHg is the condition which determine the timing of Lung transplant listing
- PH impaired QoL, lower exercise tolerance, and greater oxygen requirements
- Associated comorbidities of PH should be considered such as OSA, thromboembolic disease, or heart failure due to treatability of these conditions.
- Sildenafil (STEP-IPF) improved dyspnea, QoL, and oxygenation.
- Inhaled Treprostinil (INCREASE) increased the 6-min walk distance.

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

** RHC : right heart catheterization*

Pulmonary hypertension : Possible Markers

Clinical signs

- Presyncope or syncope
- Dyspnoea out of proportion to imaging and pulmonary function test findings

Pulmonary function test results

- Severely reduced DLCO (<30% predicted)

Exercise test results

- Markedly reduced distance
- Desaturation to <85%
- Impaired heart rate recovery

Laboratory markers

- Elevated brain natriuretic protein

Imaging

- Ratio of pulmonary artery to aorta >1 on chest CT

Echocardiography

- Elevated right ventricular systolic pressure
- Dilated right atrium or ventricle, or both
- Right ventricular dysfunction

DLCO=diffusing capacity of the lungs for carbon monoxide.

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Comorbidities of IPF : CPFE

- Older, male and a current or former smoker
- Frequently preserved lung volumes with a severely reduced DLCO
- Prevalence of lung cancer is higher than IPF or emphysema alone.
- PH is more prevalent and severe in CPFE. CPFE-PH has worse prognosis.
- Conflicting survival data of CPFE vs IPF
- Lack of CPFE specific clinical trials of anti-fibrotic drugs
- Bronchodilator therapy can be tried to symptom relieve.

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Comorbidities of IPF : Lung cancer

- Relative risk of developing lung cancer in IPF : 7 times higher
- Must carefully weight the risk and benefit of treatment due to treatment related morbidity and mortality.
- Treatment should be done after a clear discussion.
- The effects of antifibrotic drugs on the development of lung cancer in IPF remain to be established.

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

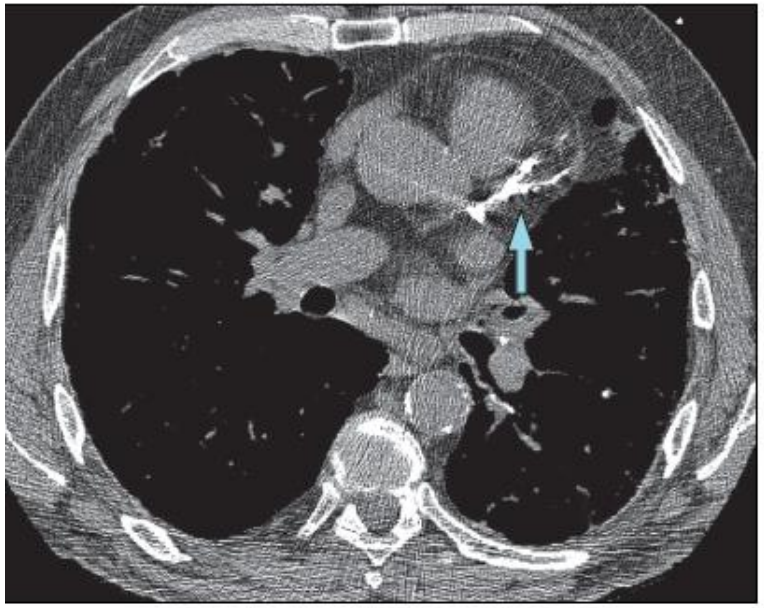
Comorbidities of IPF : GERD

- Updated ATS guideline in 2022 recommended not treating patients with IPF with antacid medication for the purpose of improving respiratory outcomes(conditional recommendation, very low quality evidence).
  - No benefit on disease progression, mortality, exacerbation, hospitalization, and lung function

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Comorbidities of IPF : Cardiac comorbidities

- Prevalence of coronary artery disease
  - IPF > COPD, Fibrotic lung disease > non-fibrotic lung disease
- 2nd most common cause of mortality in patients with IPF (10% of deaths)
- Screening of CAD : presence of mod-to-severe coronary a. calcification on **HRCT** had a sensitivity of 81% and specificity of 85% for CAD



King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Comorbidities of IPF : Venous thromboembolism (VTE)

- Relative risk for PE was 6.97 in a US insurance claims database.
- Incidence of IIP was higher among individuals with a history of VTE (Danish population study).
- VTE is responsible for 0·4–3% of deaths in the IPF population.
- Cause of increased VTE : decreased mobility, coagulation cascade activation (possibly)

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Comorbidities of IPF : Depression and anxiety

- Causes of psychological distress include dyspnea, loss of independence, feelings of social isolation, and inadequate sleep.
- Depression exacerbates the perception of respiratory symptoms
- All patients who present with IPF should be screened for these disorders.
- Cognitive and behavioral therapy antidepressant medication can be recommended.
- Sleep-disordered breathing should be screened.
- Pulmonary rehabilitation showed sustained improvement of depressive symptoms.

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Comorbidities of IPF : Deconditioning

- Decreased mobility in patients with IPF is attributable to IPF itself and peripheral muscle dysfunction as well.
- Studies have shown that patients with IPF have reduced strength, size, and endurance of their quadriceps.
- Pulmonary rehabilitation in IPF improved dyspnea, QoL, exercise capacity, and 6MWT.

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Comorbidities of IPF : Sleep-disordered breathing

- Given the high prevalence of sleep-disordered breathing, all patients who present with IPF should be considered for a sleep study.
- OSA should be corrected with CPAP.
- The presence of moderate-to-severe coronary artery calcifications on HRCT was strongly associated with severe OSA.
- CPAP improved activities of daily living, quality of sleep, QoL and decrease mortality in IPF in on study but needs to be explored further in prospective studies.

Sleep Breath 2015; 19: 385–391 ***King CS, Nathan SD. Lancet Respir Med* 2017;5: 72–84**

Comorbidities of IPF : Diabetes mellitus

- Increased prevalence of diabetes mellitus in patients with IPF compared with matched controls even after controlling for corticosteroid use.
- Effect of aggressive DM control to the outcome of IPF is unclear.

So Guideline based management is recommended.

King CS, Nathan SD. Lancet Respir Med 2017;5: 72–84

Under-recognized

- Comorbidities in IPF are **common** but may often be **under-recognized** in clinical practice

Awareness & Proactive identification

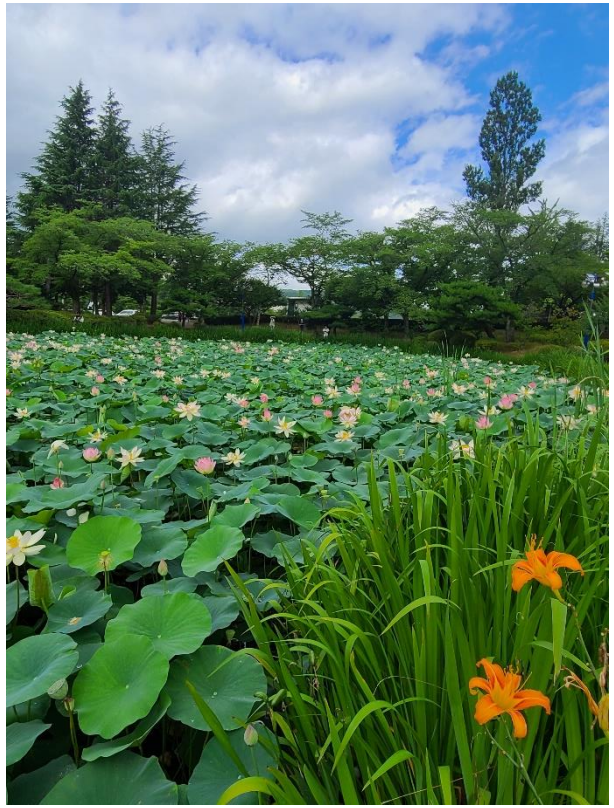
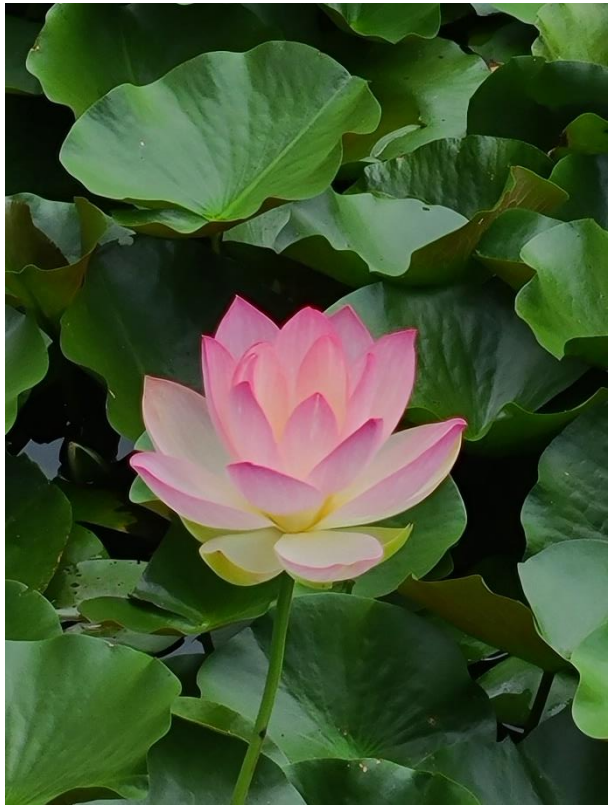
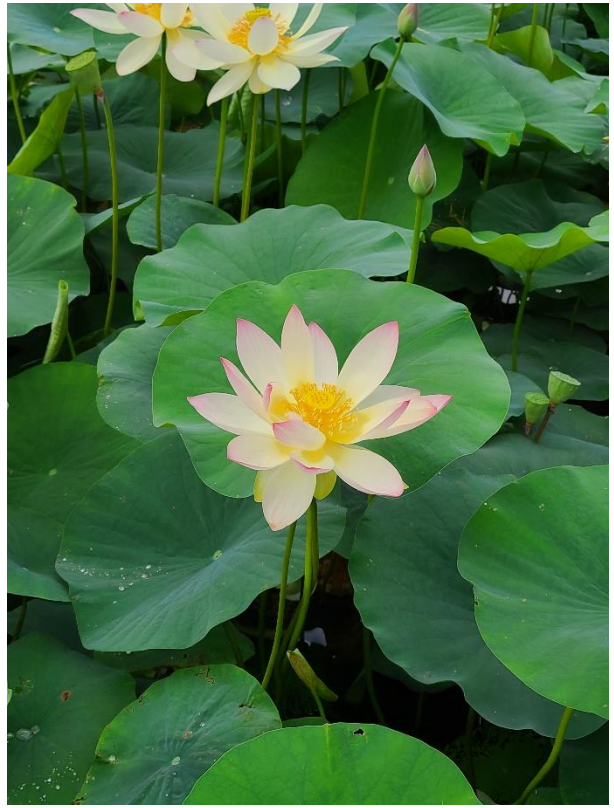
- **Raising awareness** of the impact that comorbidities can have on these patients would help to improve recognition and management in clinical practice.

- Optimizing **detection and management** of comorbidities would help to improve *outcomes* in patients with IPF

- with **improved survival** associated with antifibrotic treatment

Improve outcome (QoL)

Improve survival


Thank you for your kind attention.