ILD Collaborative

Project ECHO

Acute Exacerbations of ILD

Katy Black, MD

Division of Pulmonary and Critical Care Medicine

Massachusetts General Hospital

Disclosures

No financial disclosures.

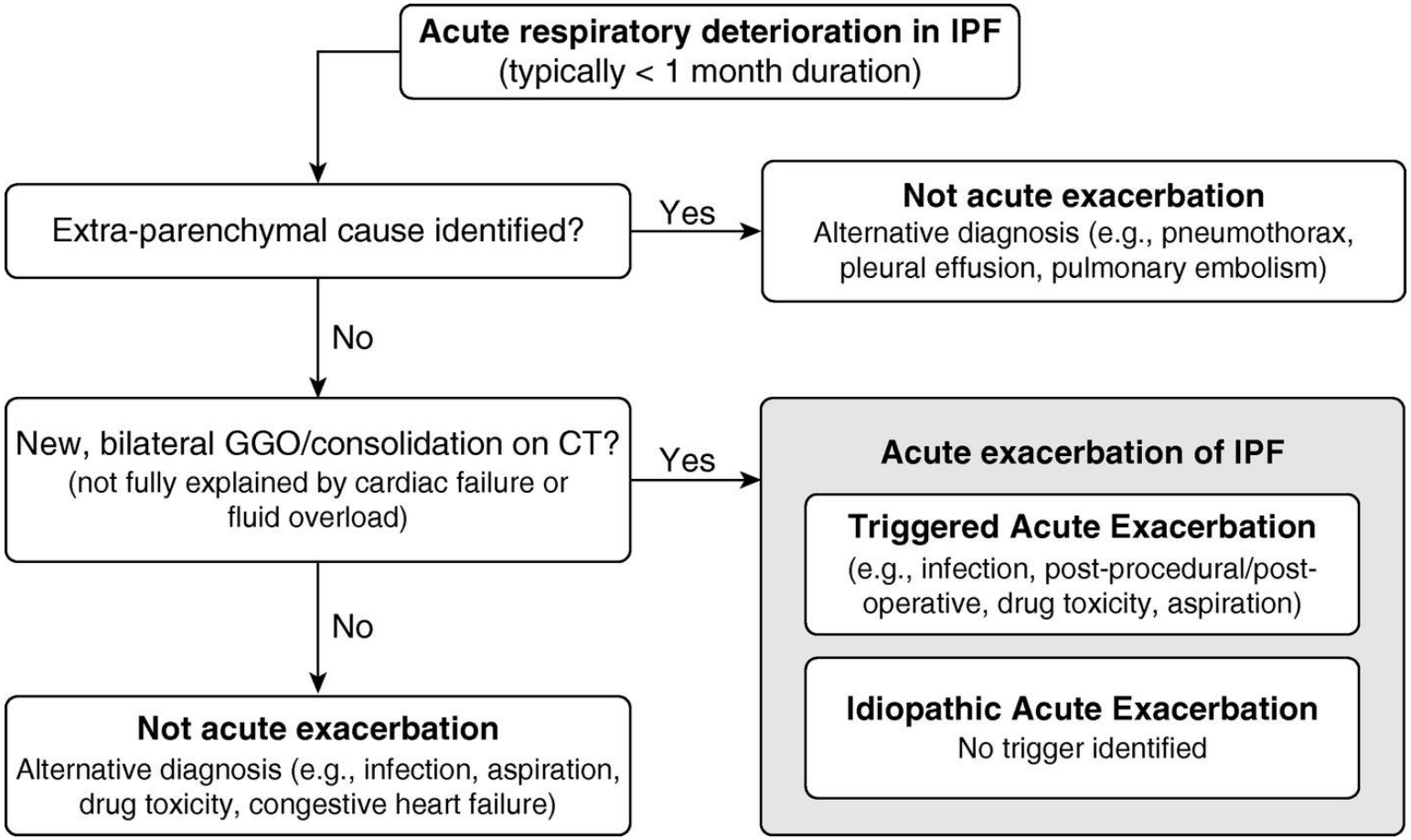
Minimal evidence-based guidance on this subject

Defining Acute Exacerbations of ILD

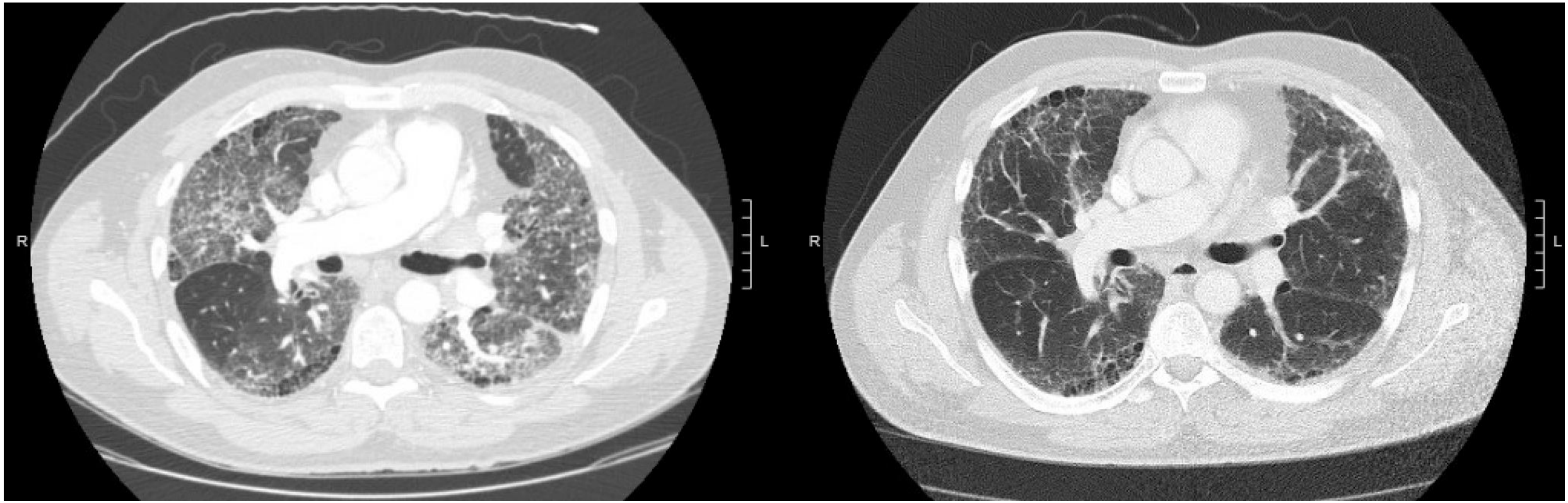
- Previous or concurrent diagnosis of ILD
- Acute worsening or development of dyspnea **within 1 month**
- CT with **new** bilateral ground-glass opacity and/or consolidation on a background pattern with usual interstitial pneumonia pattern
- Deterioration not fully explained by cardiac failure or fluid overload
- **Includes "triggered" exacerbations –i.e. infection**
- **Defined in IPF, now well-described in non IPF ILD**

Kondoh et al Chest 1993 Jun
Collard HR, ,Moore BB, Flaherty KR, 2007
Collard HR, Ryerson CJ, Corte TJ, et al. *Am J Respir Crit Care Med 2016*
Ryerson CJ, Cottin V, Brown KK, Collard HR. *Eur Respir J.* 2015
Biondini et al. *Expert Rev Respir Med* 2020

Diagnosis of AE-IPF



AED-ILD: Radiology

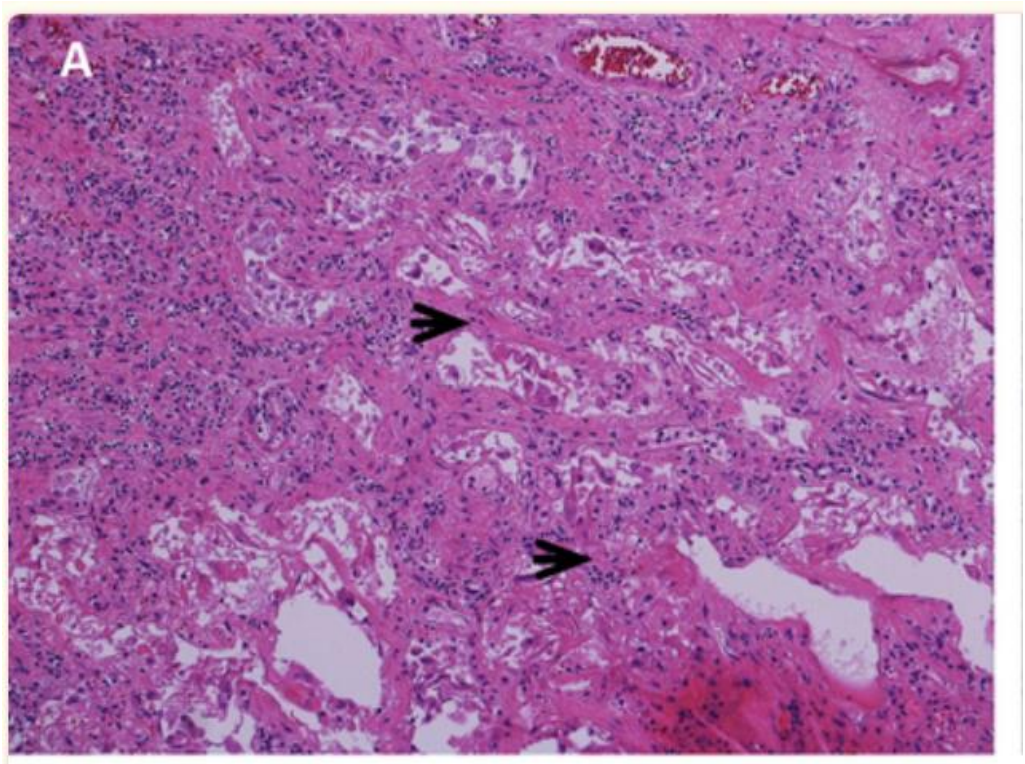


January – acutely worsened hypoxia
New ground glass

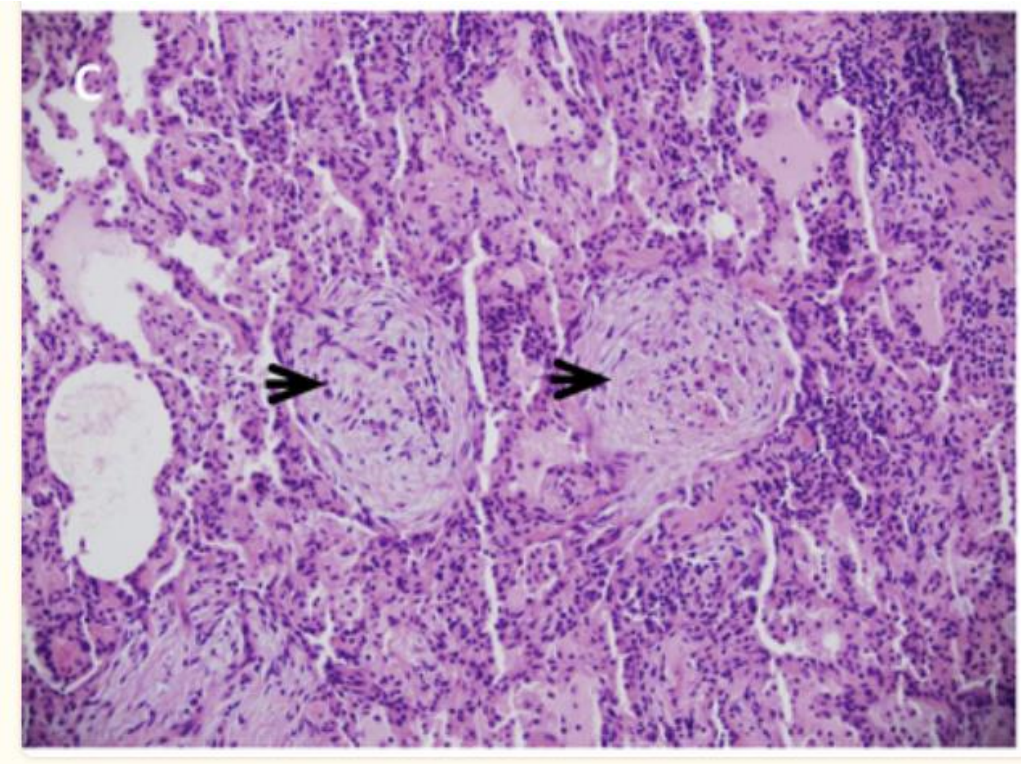
Prior November – stable exertional dyspnea
Reticular changes

AE-ILD: Pathology

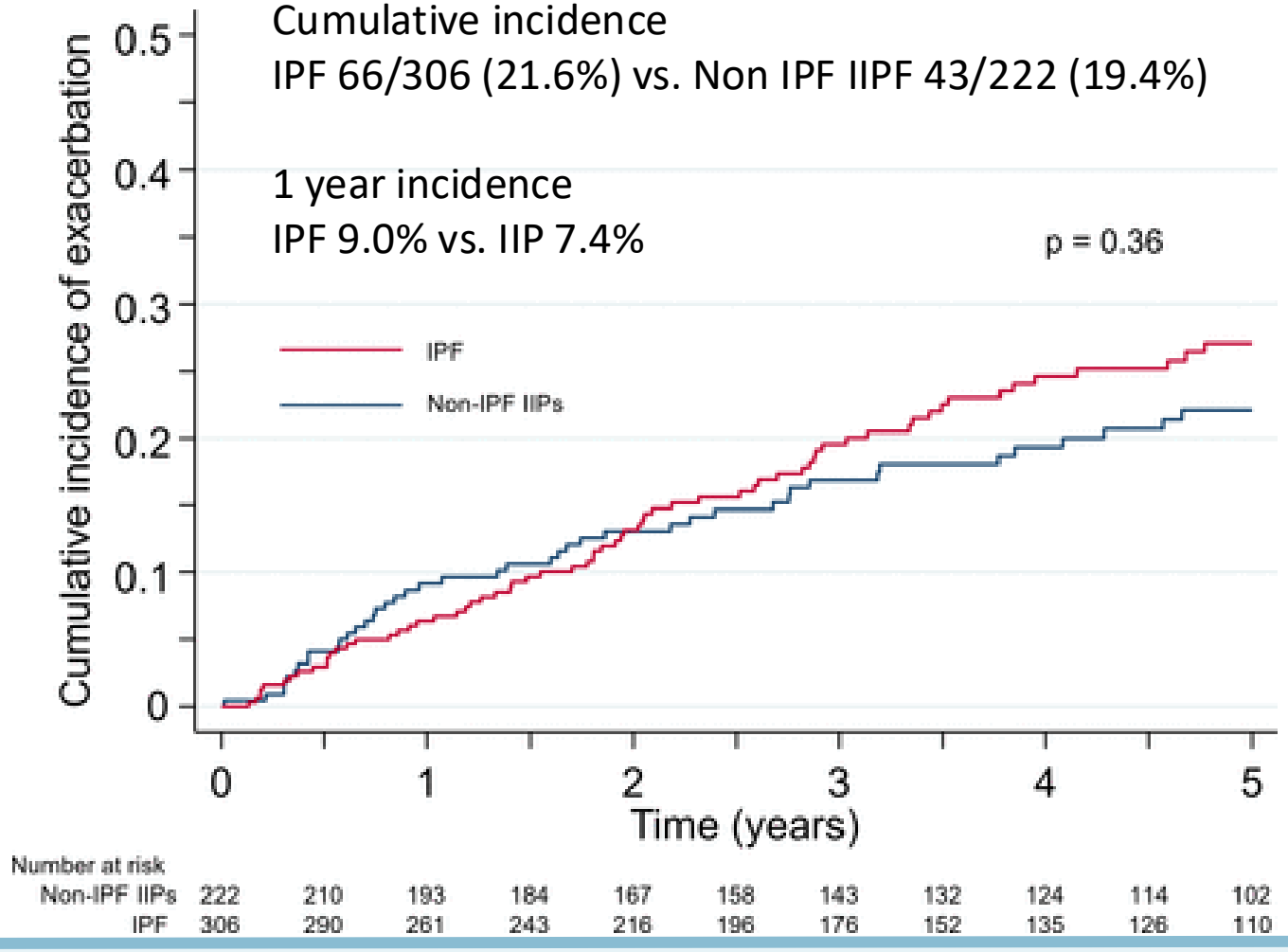
IPF with diffuse alveolar damage
Arrows showing hyaline membranes



Fibrotic NSIP with organizing pneumonia
Arrows on luminal fibroblastic plugs



Incidence of AE



133 non IPF patients

1 year AE incidence 12.5%

3 year 30.3%, 5 year 38.0%

Pooled studies in RA

1 year incidence 3-11%

5 year incidence 11-29%

Tsubouchi et al *BMJ Open Respiratory Research* 2023; Maosheng et al *BMC Pulmonary Medicine* 2023, Kim MJ Song JW *Res Research* 2024

Mortality of AE-ILD

INPULSIS study IPF

AE in 5.9% of patients over 52 weeks

30 day mortality

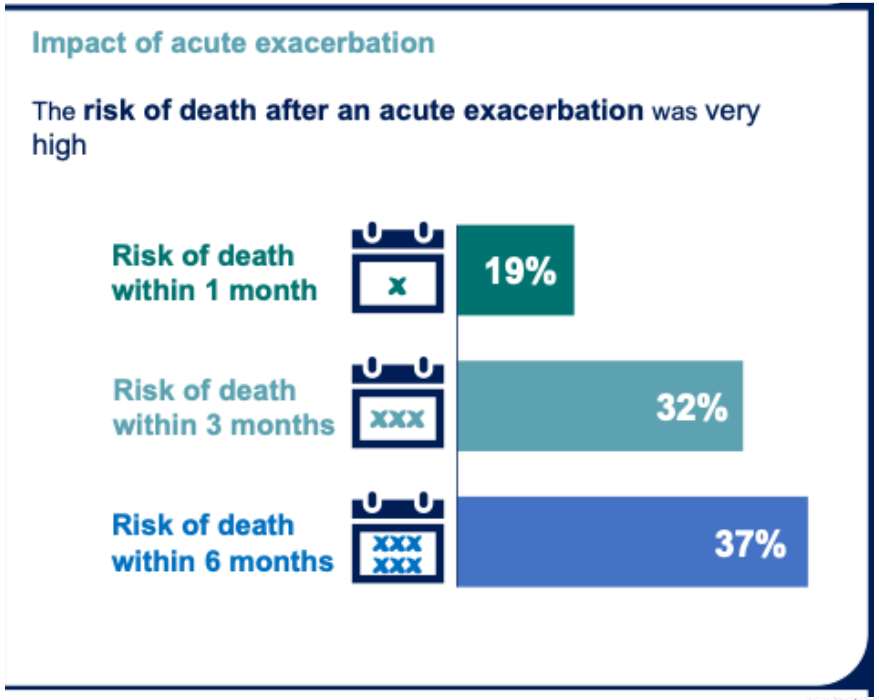
21% in nintedanib

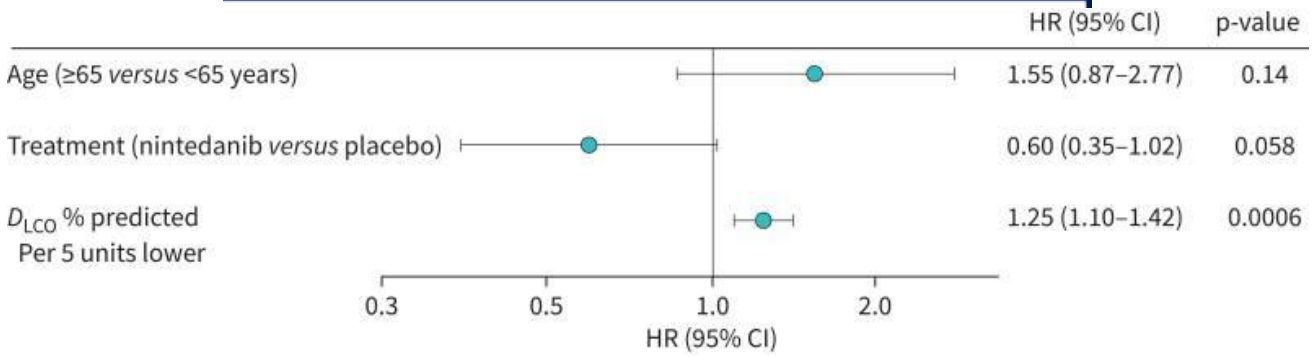
40% in placebo

INBUILD study PF-ILD for 19 months

AE in 8.7% of patients

30 day mortality 19%

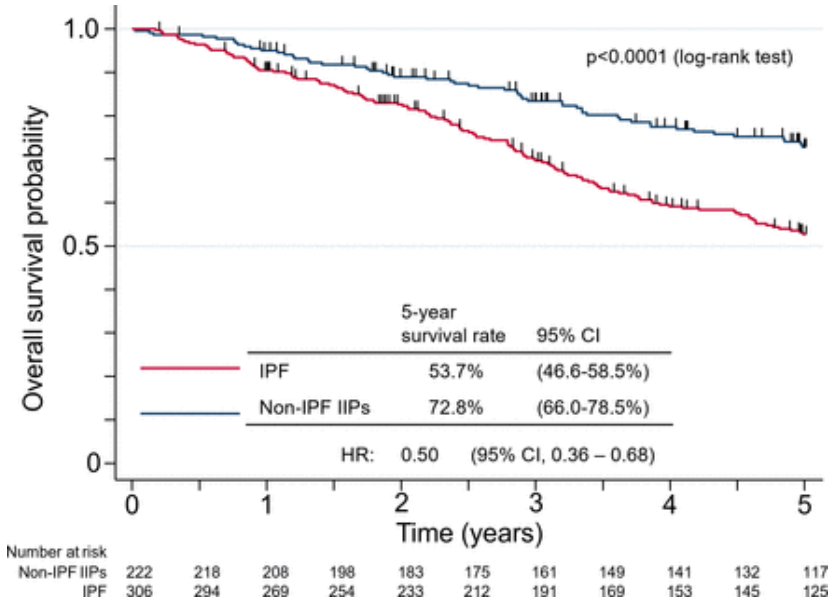


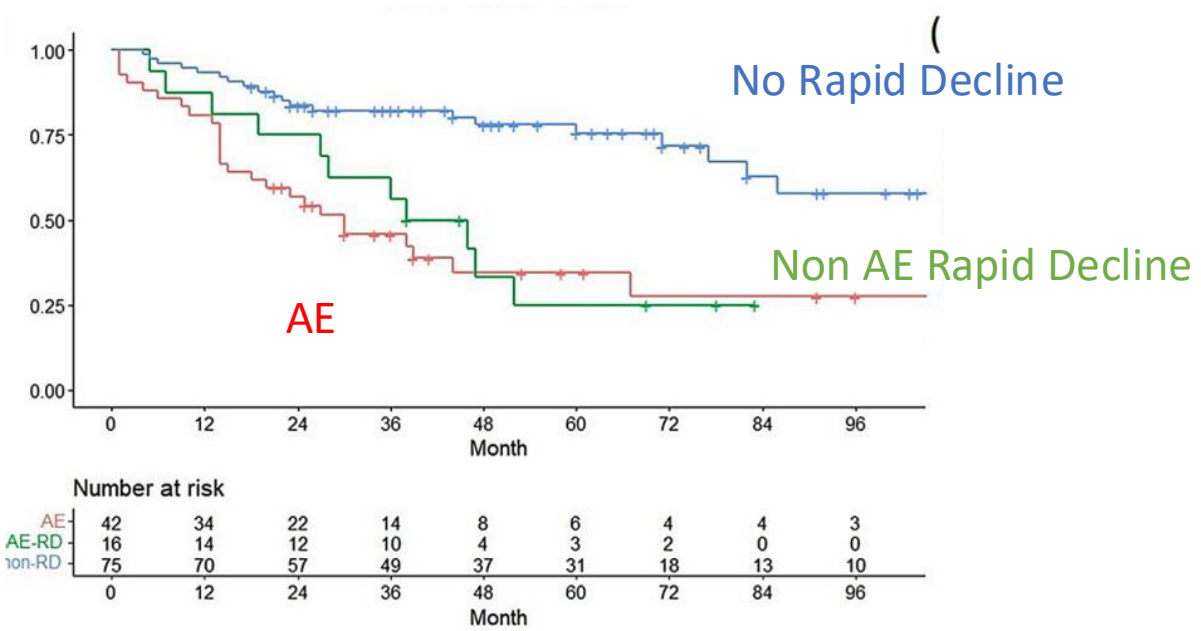


Kreuter M et al. *ERJ Open Res* 2024 Dec 2

Mortality after AE-ILD

Up to 46% of IPF deaths are preceded by acute exacerbation. Median survival after AE 3-4 months





5 year survival IPF 54% survival Non IPF-IIP 73% survival
23.5% of all IPF deaths were from AE; 24% of all of IIP
35% IPF 28% IIP died of chronic resp failure

Median survival of AE 30 months
Mortality 1 year 21%, 3 year 65% 5 year 82%
Post admission 36% at 30 days 41% 90 d

Collard HR, *Am J Respir Crit Care Med 2016*

Tsubouchi et al *BMJ Open Respiratory Research* 2023
Kim MJ Song JW *Res Research* 2024

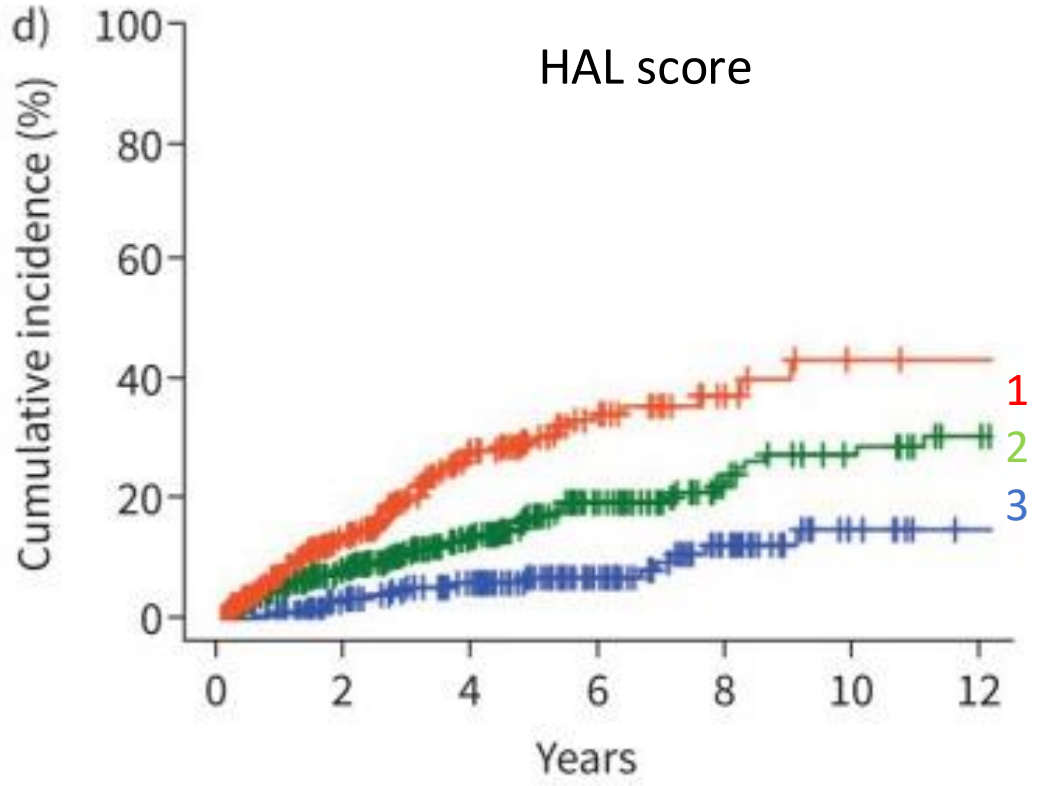
Risk factors for acute exacerbations

Baseline factors:

Lower FVC, DLCO, hypoxia

HAL score to predict AE

Honeycombing on HRCT, Age >75, Lactate dehydrogenase >222 U/L-1,

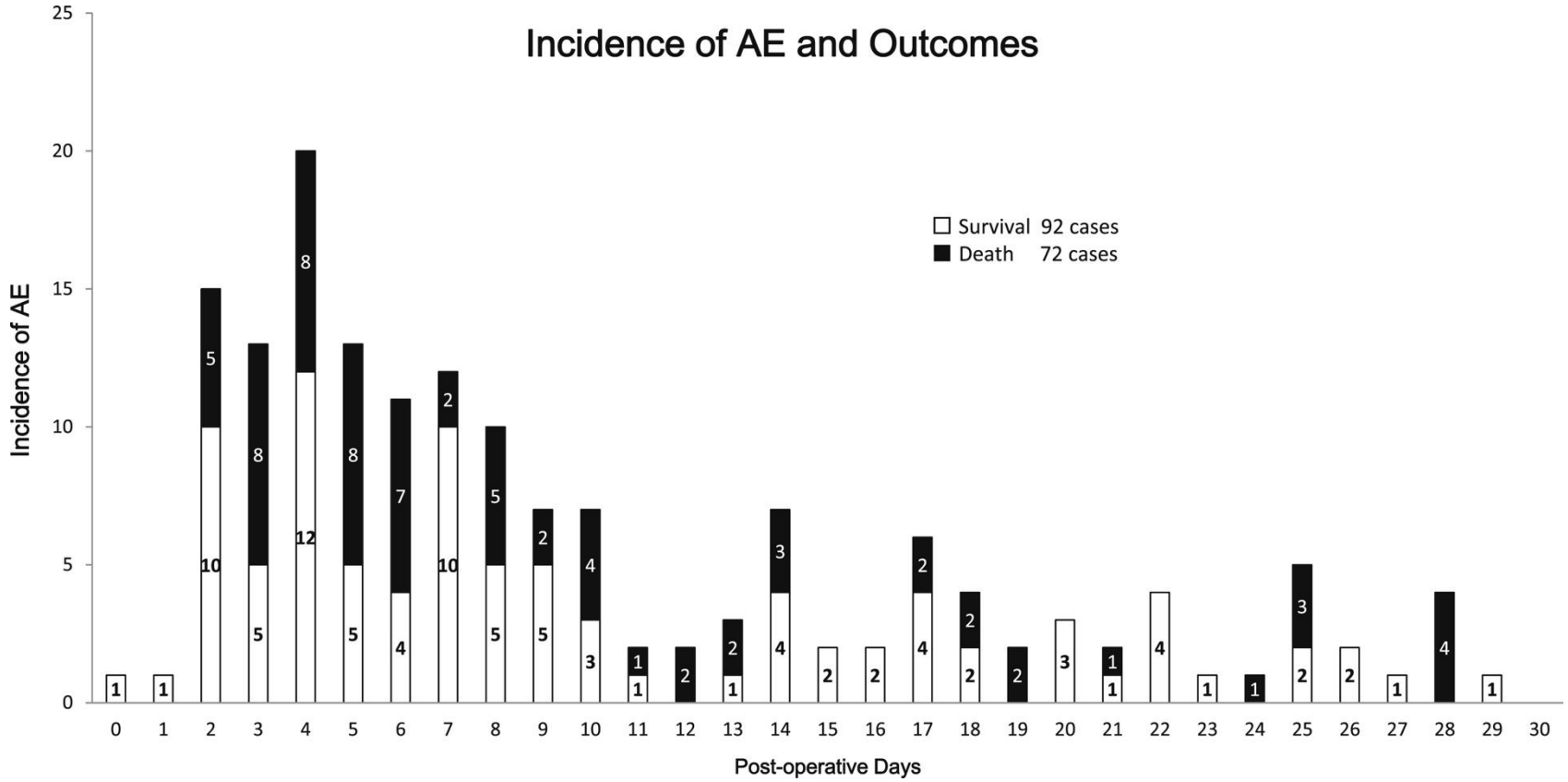


Score	Number at risk						
0	196	151	114	66	33	14	6
1	380	258	153	80	38	19	7
2	313	171	73	27	9	2	1

Karayama et al. *European Resp J* 2023
Kershaw ey al. *Resp Med* 2021

Surgery as trigger for AE-ILD

164 AE in 1762 ILD patients undergoing lung resection. 9% incidence overall



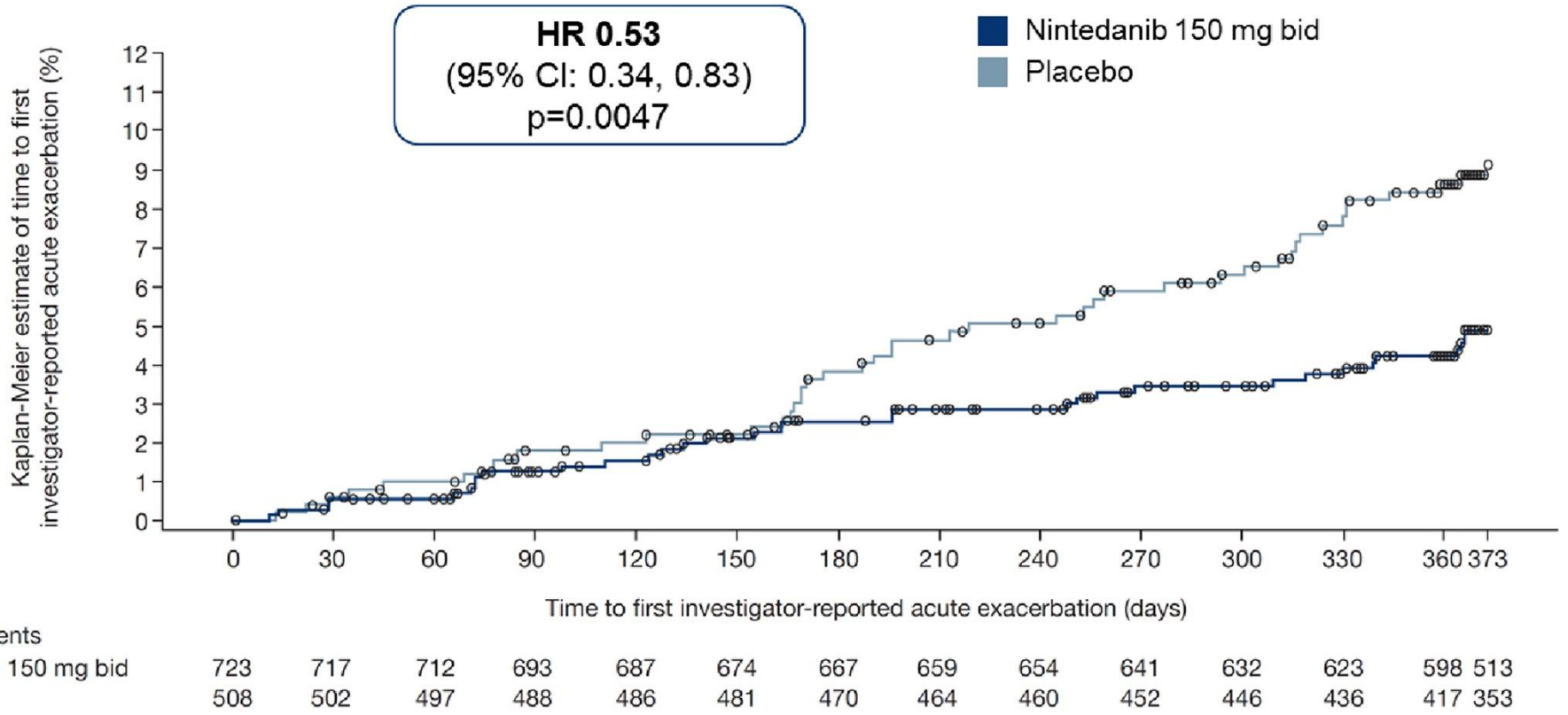
Sato et al *J Thorac Cardiovasc Surg* 2014

Possible Treatments for AE-ILD

- Antifibrotics –pirfenidone, nintedanib
- Corticosteroids
- Cyclophosphamide
- JAK inhibition
- Transplant

Nintedanib might reduce time to AE-IPF

Time to acute exacerbation of IPF



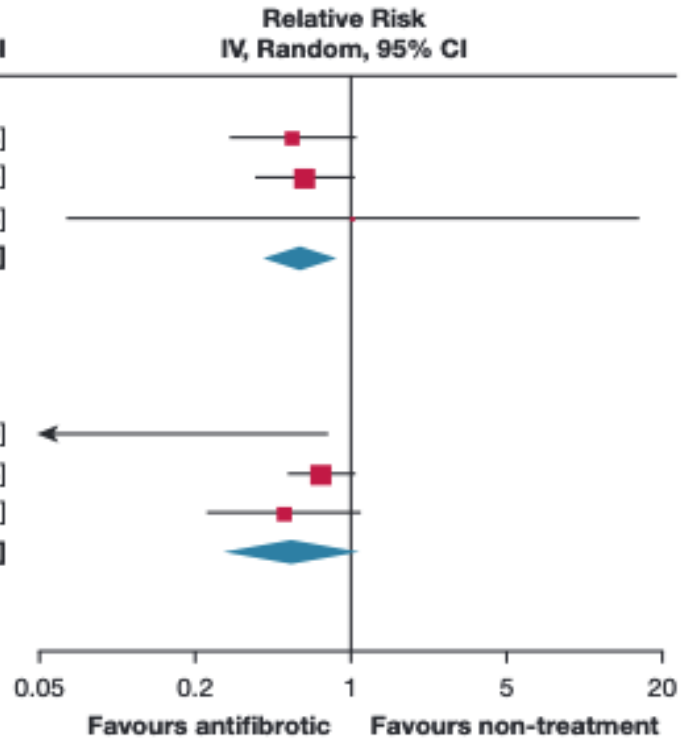
Meta analysis of data from TOMORROW and INPULSIS trials of nintedanib for IPF

Richeldi, Cottin… Brown et. al *Resp Med* 2016

Anti-fibrotic therapy might reduce AE

2022: Pooled analysis shows reduced relative risk in anti-fibrotic groups

Study or Subgroup	log[Relative Risk]	SE	Antifibrotic Total	Non-treatment Total	Weight	Relative Risk IV, Random, 95% CI
Nintedanib						
Richeldi 2011	−0.5621	0.3019	343	85	38.8%	0.57 [0.32, 1.03]
Richeldi 2014	−0.4427	0.2441	638	423	59.4%	0.64 [0.40, 1.04]
Lancaster 2020	0.0177	1.4016	56	57	1.8%	1.02 [0.07, 15.88]
Subtotal (95% CI)			**1,037**	**565**	**100.0%**	**0.62 [0.43, 0.89]**
Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 0.22$, $df = 2$ ($P = .89$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.56$ ($P = .01$)						
Pirfenidone						
Azuma 2005	−3.1048	1.463	72	35	5.1%	0.04 [0.00, 0.79]
Zurkova 2019	−0.2853	0.1611	383	218	57.9%	0.75 [0.55, 1.03]
Feng 2020	−0.635	0.3767	36	31	37.0%	0.53 [0.25, 1.11]
Subtotal (95% CI)			**491**	**284**	**100.0%**	**0.57 [0.29, 1.12]**
Heterogeneity: $Tau^2 = 0.18$; $\chi^2 = 4.27$, $df = 2$ ($P = .12$); $I^2 = 53\%$						
Test for overall effect: $Z = 1.62$ ($P = .10$)						
Test for subgroup differences: $\chi^2 = 0.04$, $df = 1$ ($P = .84$), $I^2 = 0\%$						



Note: 2024 Meta-analysis: No significant difference in incidence of AE in PF-ILD with antifibrotics

Petnak et al. *Chest* 2021 . Li. Xu et al. *Ther Adv Respir Dis* 2024 Urushiyama et al. *ERJ Open Res*. 2022

IVIG in AE-ILD: ongoing trial in Japn

Retrospective analysis of admissions with AE-ILD Japan 2018-May 2021

Treated with steroids + IVIG or steroids

41 IPF, 11 other - but CTD excluded

5 grams IVIG/day x 3-5 days

Better survival with IVIG

RCT ongoing; enrollment began 8/2022

jRCT1061220010

Retrospective analysis of 39 pts

All received Methylpred 0.5-1g x3 + taper

IVIG 1g/kg body weight over 3 days

10 pts died in patient 26%

13 died within 90 days (33%)

Higo et al. *Sarcoidosis Vasc Diffuse Lung Dis* 2022. Sotiropolou *Medicine (Kaunas)* 2025 Sep
https://rctportal.niph.go.jp/en/detail?trial_id=jRCT1061220010

Steroids might reduce or might worsen AE-ILD

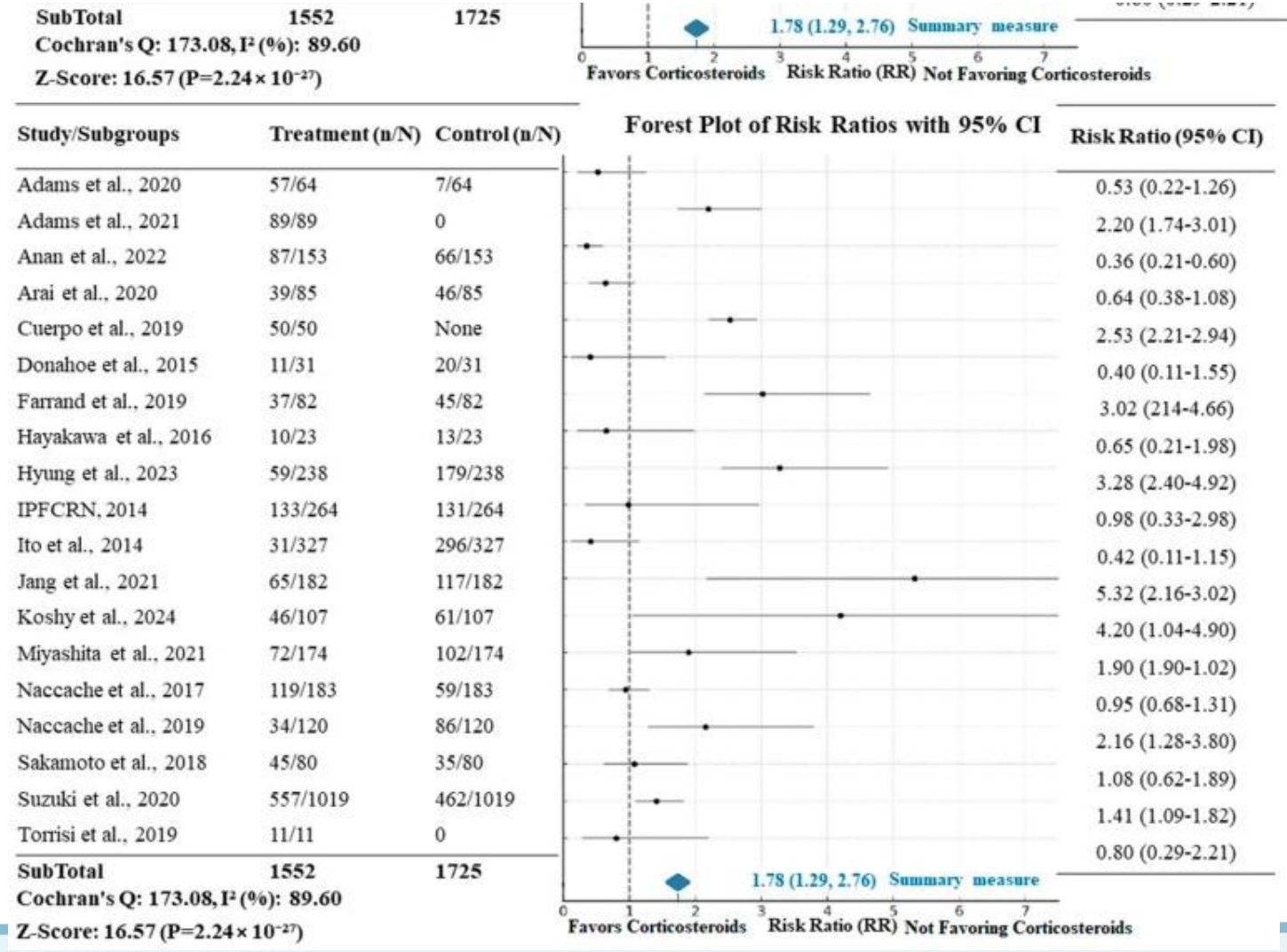
Mix of IPF and general ILD
1552 patients receiving steroid
1725 control

RR 1.78 for death in steroid group

Limited, only observational studies
No matching for disease severity

Conclusion – more studies needed

Increased risk of death with corticosteroids



Study/Subgroups	Treatment (n/N)	Control (n/N)	Risk Ratio (95% CI)
Adams et al., 2020	57/64	7/64	0.53 (0.22-1.26)
Adams et al., 2021	89/89	0	2.20 (1.74-3.01)
Anan et al., 2022	87/153	66/153	0.36 (0.21-0.60)
Arai et al., 2020	39/85	46/85	0.64 (0.38-1.08)
Cuerpo et al., 2019	50/50	None	2.53 (2.21-2.94)
Donahoe et al., 2015	11/31	20/31	0.40 (0.11-1.55)
Farrand et al., 2019	37/82	45/82	3.02 (214-4.66)
Hayakawa et al., 2016	10/23	13/23	0.65 (0.21-1.98)
Hyung et al., 2023	59/238	179/238	3.28 (2.40-4.92)
IPFCRN, 2014	133/264	131/264	0.98 (0.33-2.98)
Ito et al., 2014	31/327	296/327	0.42 (0.11-1.15)
Jang et al., 2021	65/182	117/182	5.32 (2.16-3.02)
Koshy et al., 2024	46/107	61/107	4.20 (1.04-4.90)
Miyashita et al., 2021	72/174	102/174	1.90 (1.90-1.02)
Naccache et al., 2017	119/183	59/183	0.95 (0.68-1.31)
Naccache et al., 2019	34/120	86/120	2.16 (1.28-3.80)
Sakamoto et al., 2018	45/80	35/80	1.08 (0.62-1.89)
Suzuki et al., 2020	557/1019	462/1019	1.41 (1.09-1.82)
Torrisi et al., 2019	11/11	0	0.80 (0.29-2.21)
SubTotal	1552	1725	

Cochran's Q: 173.08, I² (%): 89.60
Z-Score: 16.57 (P=2.24×10⁻²⁷)
1.78 (1.29, 2.76) Summary measure
Favors Corticosteroids Risk Ratio (RR) Not Favoring Corticosteroids

Mari et al. *Adv Respir Med* 2025 Mar 28;93(2):6.

Baricitinib for AE-ILD

Dual JAK 1/2 kinase inhibitor

Used for COVID

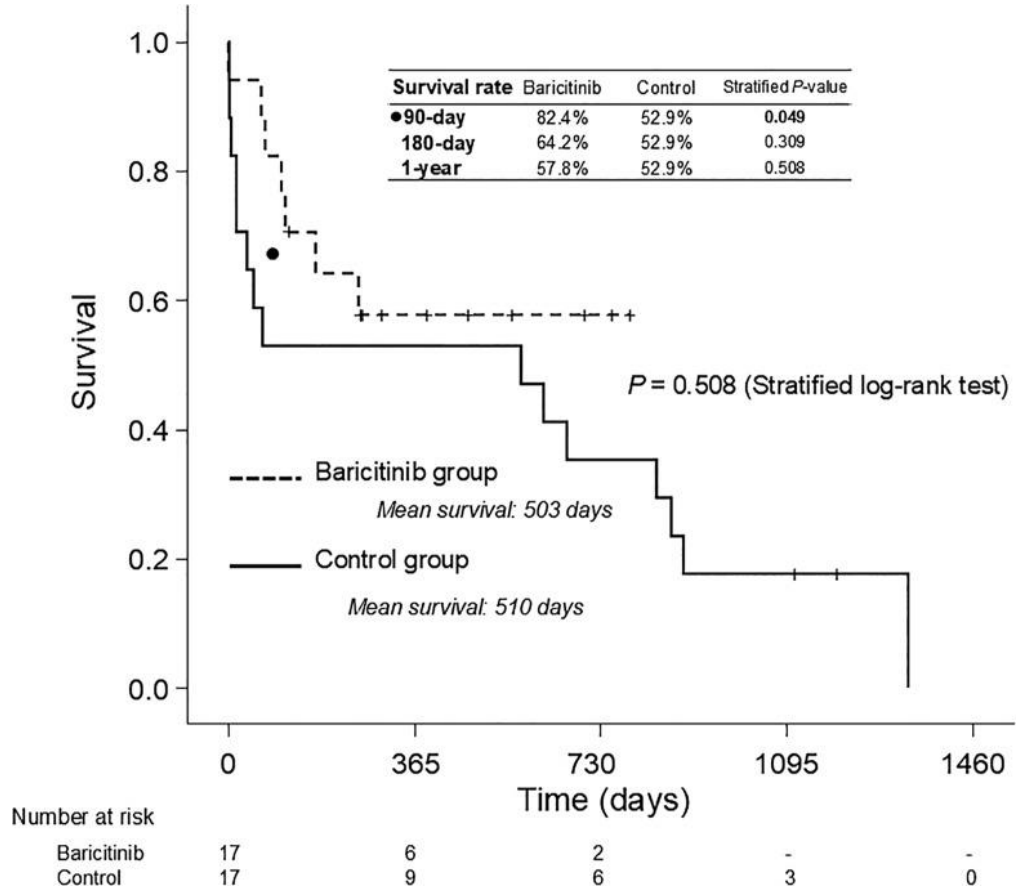
31 patients treated 2022-24

Compared to 28 historical controls 2021-2

No difference in survival.

Trend to improved 90 day survival

RCT needed



Yamakawa et al. *Respiration*. 2025 Jul 10;104(11):825–836.

Response to steroids in AE-ILD

89 patients in Toronto admitted with AE-ILD 2015-2019

Standardized protocol for AE-ILD

3 days 0.5-1g methylprednisolone

4 days 1mg/kg prednisone

Repeat CT scan day 7

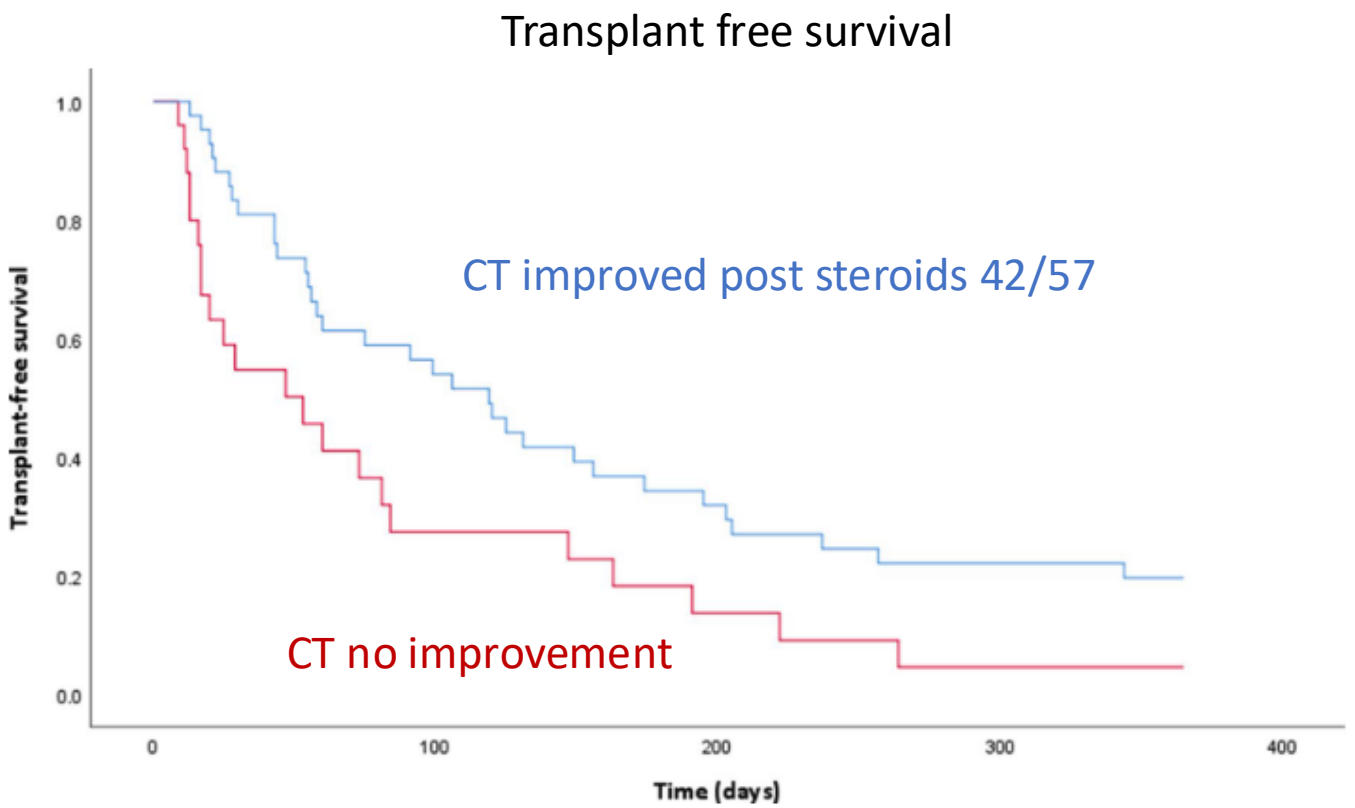
22 didn't get f/u scan

15 died or CMO

7 recovered

56 pts IPF

33 pts non-IPF



STRIVE-IPF Antibody reduction in AE-IPF

Treatment: Therapeutic plasma exchange, rituximab,
IVIG
Prednisone, antibiotics

Usual care: Prednisone, antibiotics

Exclusion: positive ANA, RF, CCP, anti SSA

51 patients have completed

- Prednisone = 60 x1, 20mg day 2-day 19;
  (100 mg solumedrol on d6, d15)
- Primary outcome: Six month survival
- Secondary outcome: O2 needs, 6MWD

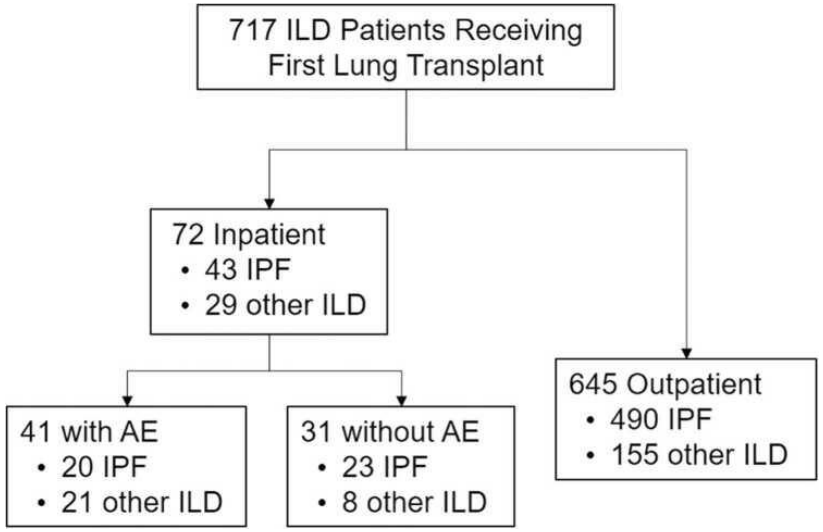


Recruiting centers:
U Alabama, Temple,
U Pitt, Baylor,
University of Utah,
Thomas Jefferson,
Loyola

NCT03286556

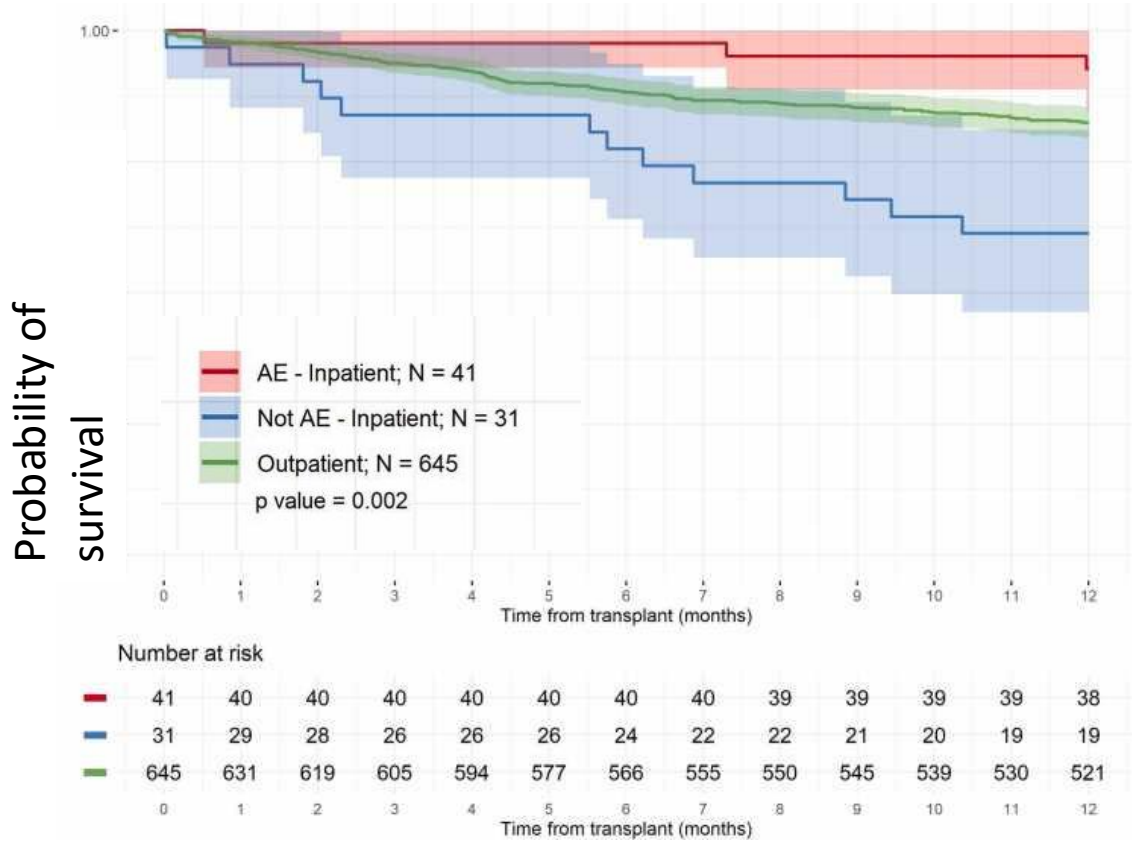
AE-ILD and survival post transplant

Duke 2005-2019



1 year survival 93% in AE-ILD
HR for death/retransplant
AE-ILD vs outpt 0.29 (0.09-1.00)
AE-ILD vs other inpt 0.16 (0.04-0.56)

IPF only no difference among groups



Months post transplant

Frailty, transplant, and survival after AE-ILD

89 patients admitted to U Toronto with AE-ILD 1/2015-10/2019

In hospital

22% mortality

19% of non-frail (11/58)

- 46 discharged home (79%), 1 to rehab (2%)

26% of frail (8/31)

- 20 discharged home (65%), 2 pall care, 1 rehab

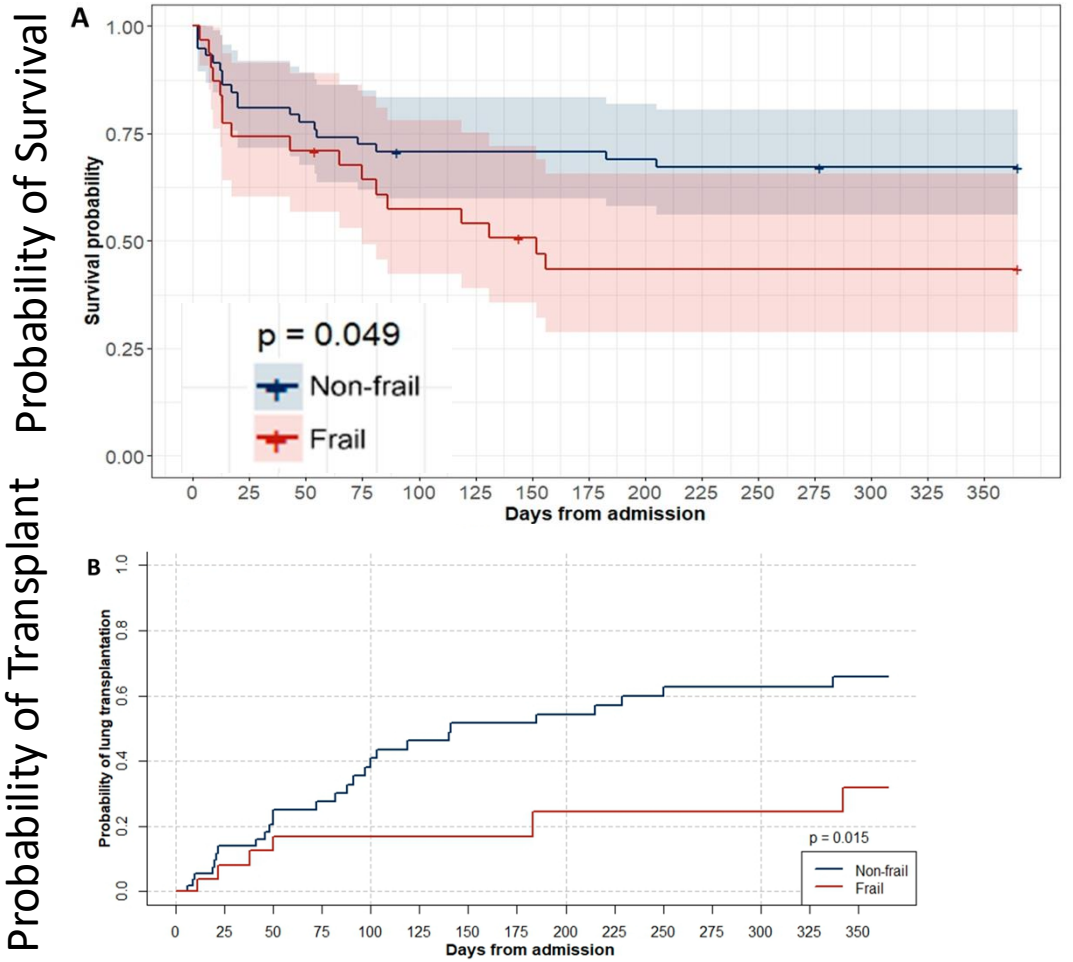
One year follow up

28% mortality

19% of non-frail (8/47); 55% lung transplant

43% of frail (9/23), 26 % lung transplant

Survival post admission



Von Hollebeke *Chron Respir Dis* 2024

Take home messages

- All fibrotic ILDs can have exacerbations
- Likely better outcome if steroid responsive
- Role of steroids in AE-IPF increasingly questioned
- Antifibrotics may reduce exacerbations; logistic challenges to inpatient initation
- Ongoing trials for IVIG and combined antibody reduction
- Consider transplant recognizing dangers of frailty
- Much more to be learned

References: general

- Kershaw et. al. Resp Med 2021 Characteristics and evaluation of acute exacerbations in chronic ILD Tsubouchi et al BMJ Open Resp Res 2023 Survival and acute exacerbations for patients with Ipf or non-IPF IIPs: 5 yr follow up analysis….
- Maosheng et al. Incidence, risk factors, and prognosis of acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis BMC Pulmonary Medicine 2023
- Dhanani & Gupta J Clin Med 2024 Management of Interstitial Lung Disease in the ICU: A Comprehensive Review PMID: 39597801

Additional slides

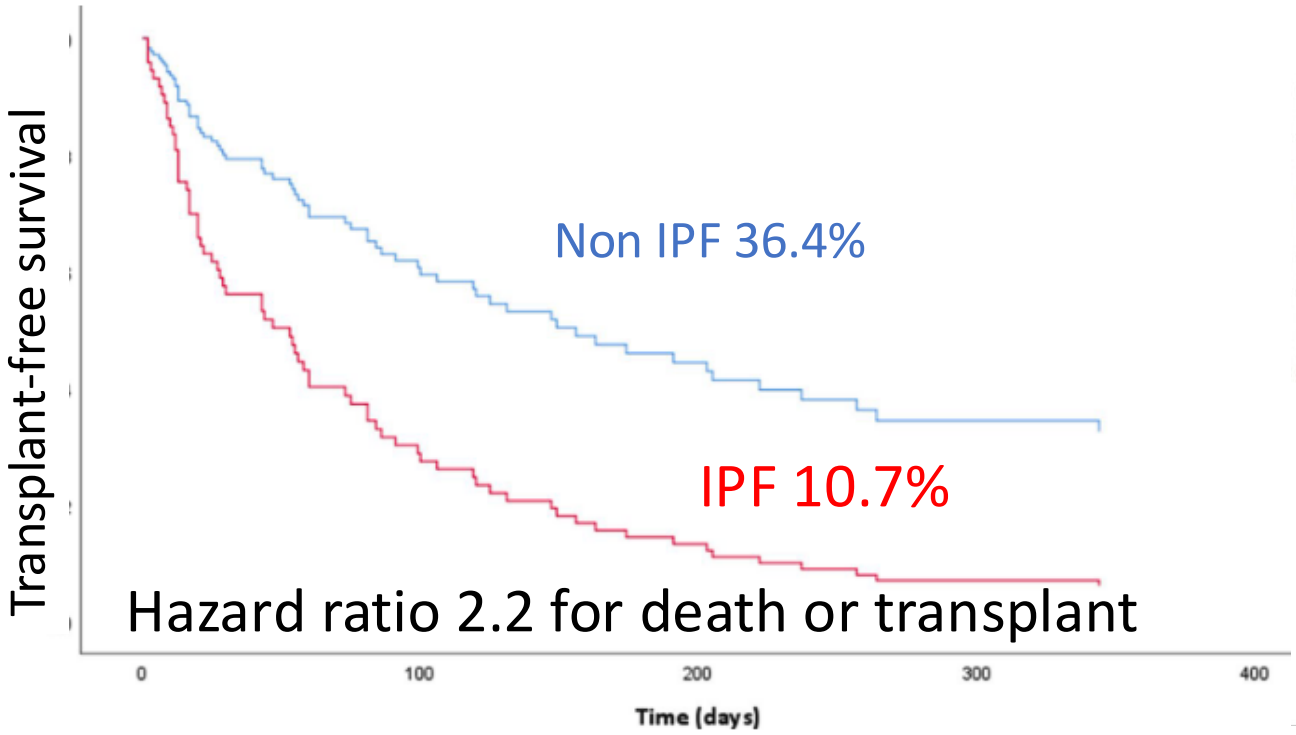
More data and selected references

References: Corticosteroids

- Srivali N, De Giacomi F, Moua T, et al. Corticosteroid therapy for treating acute exacerbation of interstitial lung diseases: a systematic review. *Thorax* 2025;80:140-149.
- Koshy et al *Respirology* June 2024 Steroid therapy in acute exacerbation of fibrotic interstitial lung disease
- Mari et al. *Adv Respir Med* 2025 Mar 28;93(2):6 The Impact of Corticosteroids on Mortality in Acute Exacerbations of Idiopathic Pulmonary Fibrosis: A Meta-Analysis

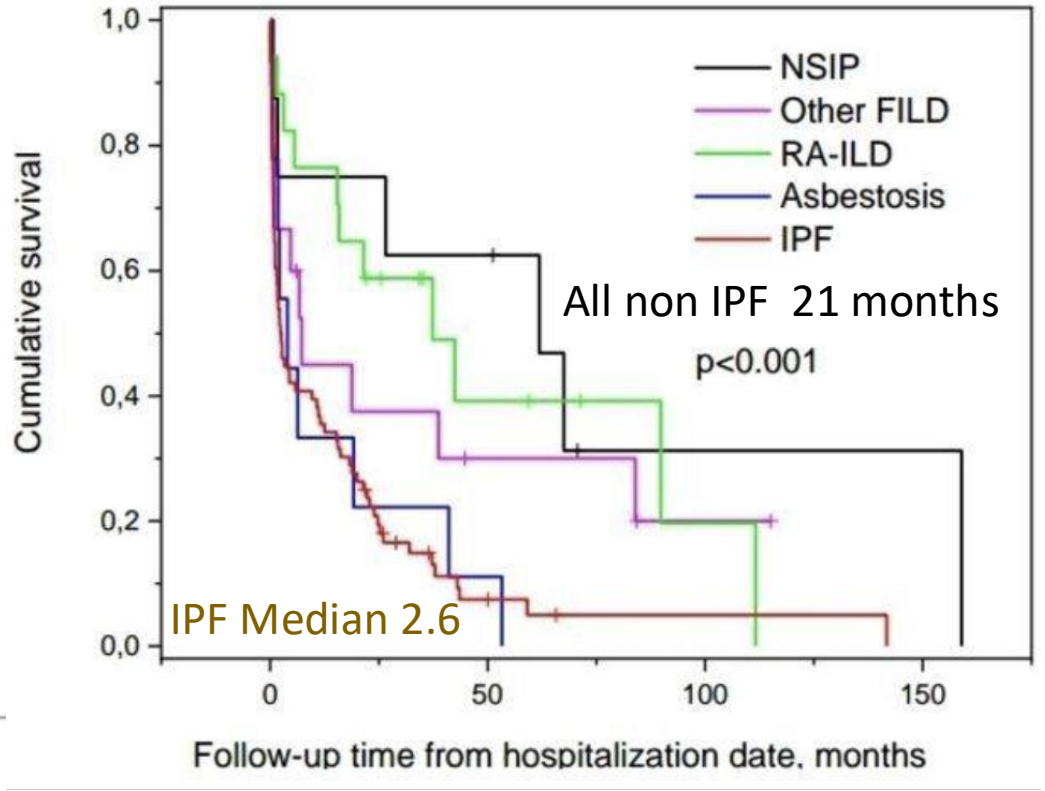
Better outcome after AE of non-IPF ILD

Toronto



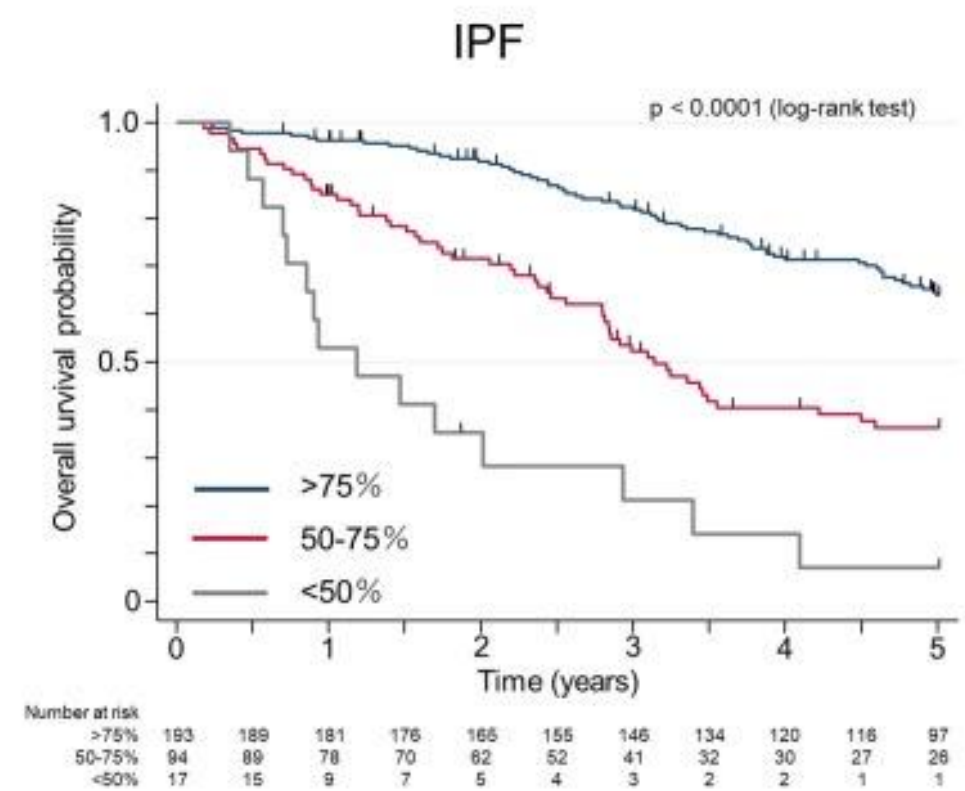
89 patients admitted with AE-ILD 2015-2019

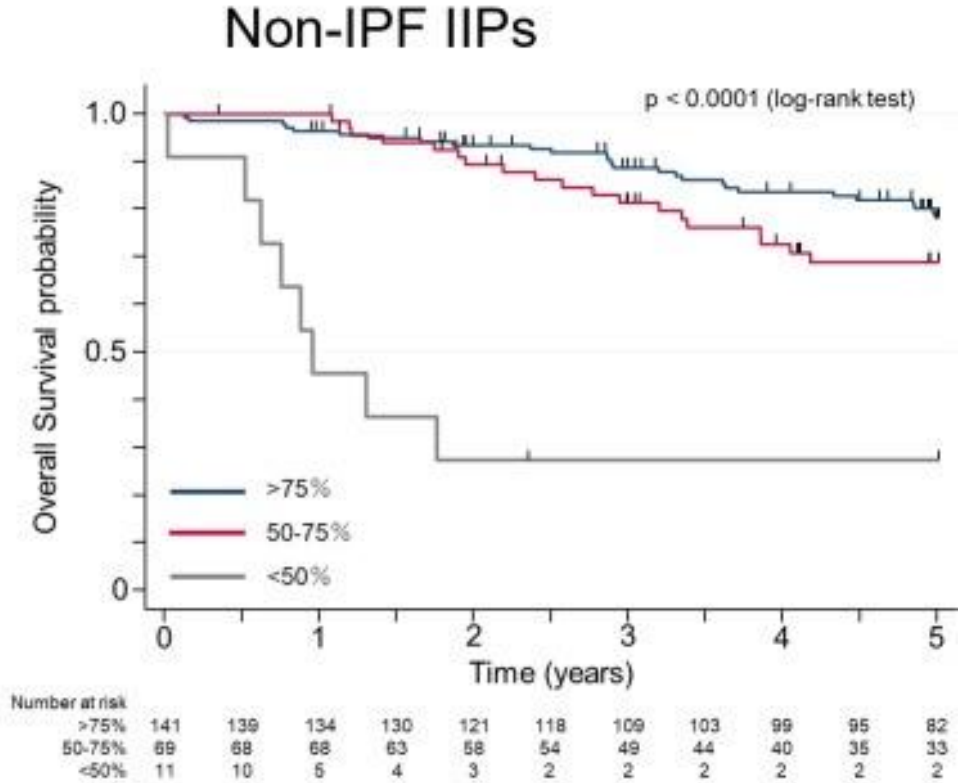
Finland



108 patients admitted with AE-ILD 2009-2017
Corticosteroids increased HR for death only in IPF

Risk for death of AE



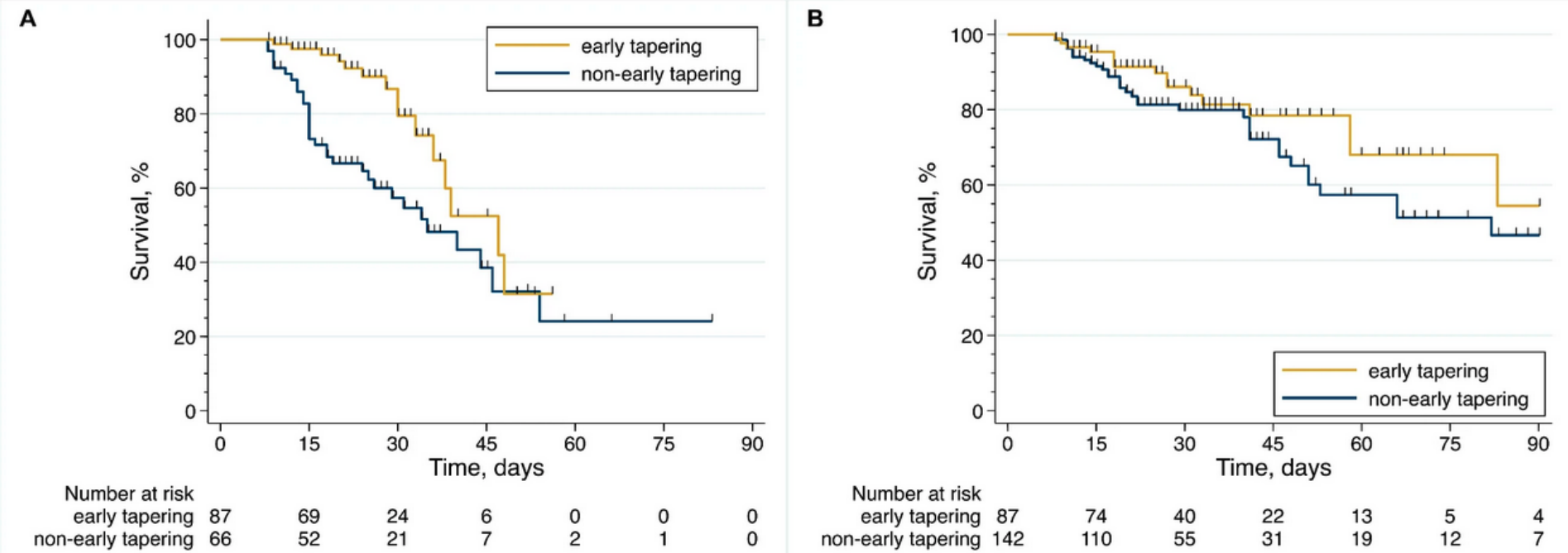


Tsubouchi et al *BMJ Open Respiratory Research* 2023

Corticosteroids in AE-ILD

Tapering of steroids within two weeks – did not include those who were only oulsed

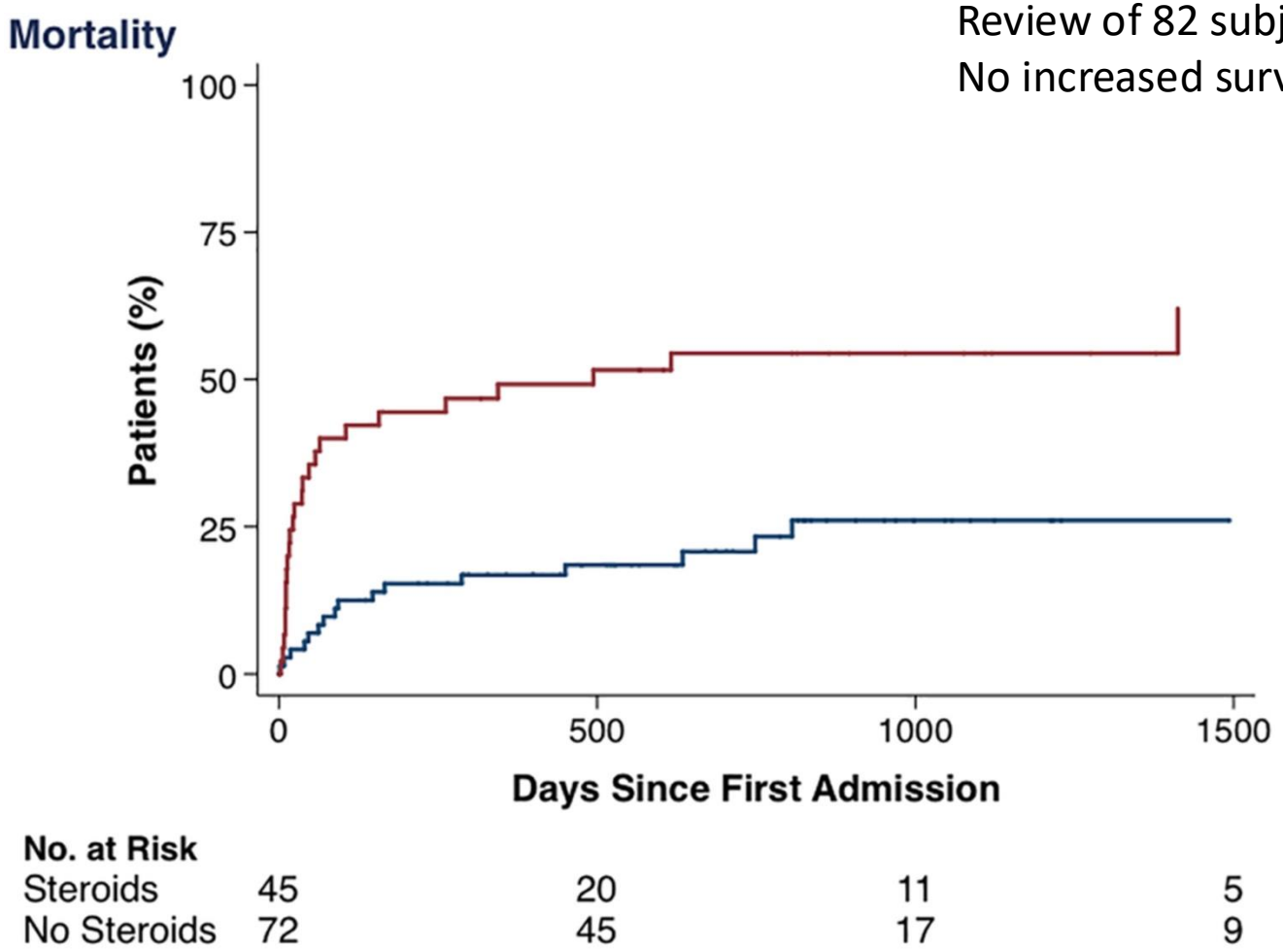
From: Early corticosteroid dose tapering in patients with acute exacerbation of idiopathic pulmonary fibrosis



Kaplan–Meier curves of AE-IPF patients with early or non-early tapering of corticosteroid dose. (**A**) Multi-center cohort. (**B**) Administrative cohort. AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis

Annan et al Respir Res 2022 Oct 26;23:291

Steroids have unclear benefit in AE-IPF



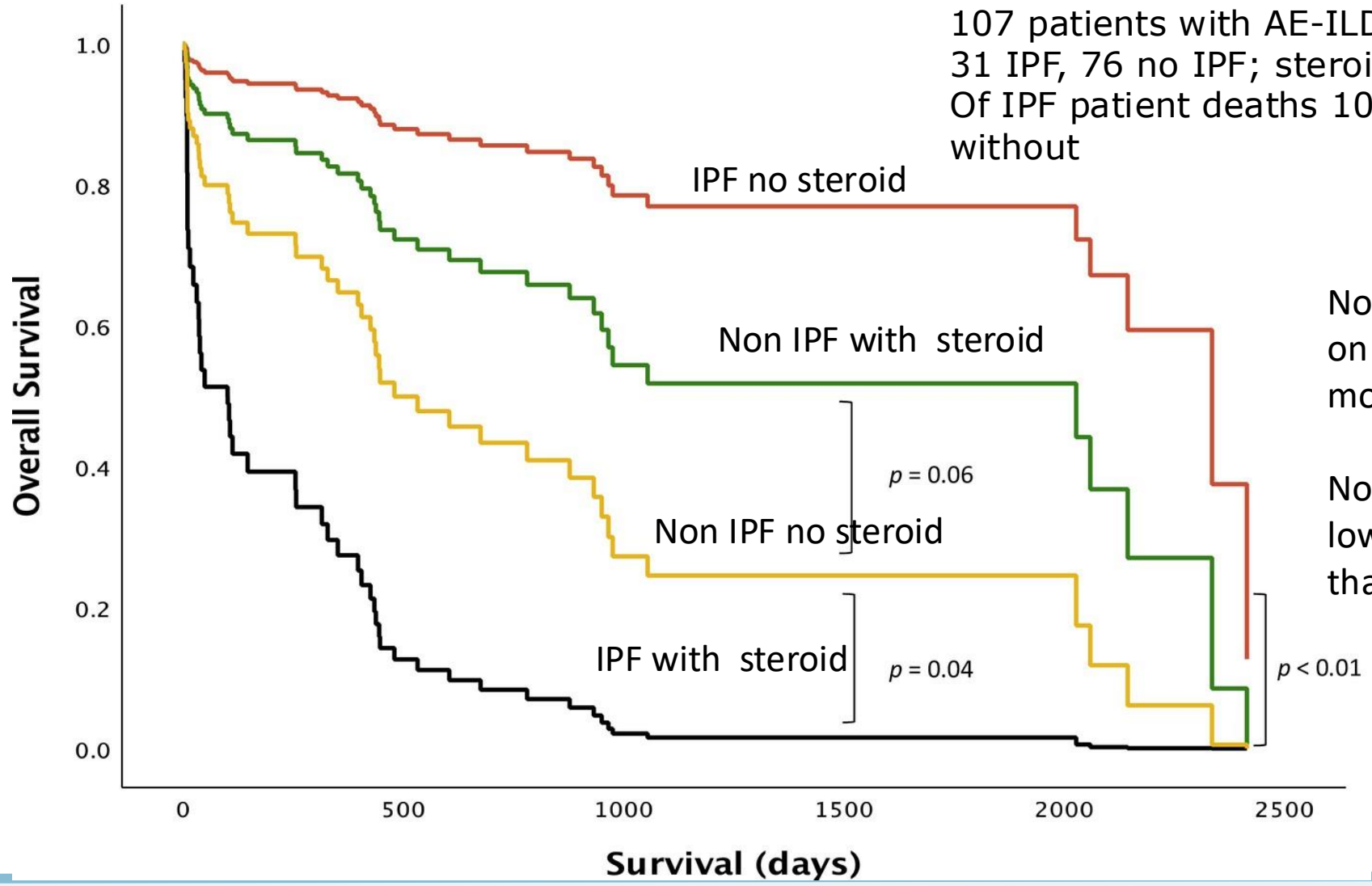
Review of 82 subjects with **AE-IPF** at USCF
No increased survival in patients given steroids

Steroids

No Steroids

Papiris et al *Front Pharmacol* 2022; Farrand, et al. *Respirology* 25, 629–635.

Survival with steroids in AE-ILD



107 patients with AE-ILD in Australia
31 IPF, 76 no IPF; steroids – 0.5 mg/kg x 3 days
Of IPF patient deaths 10/31 with steroid 4/31 without

No difference seen on IPF vs non IPF mortality

Non-IPF on steroids lower mortality risk than IPF on steroids

Kosky et al *Respirology* 2024

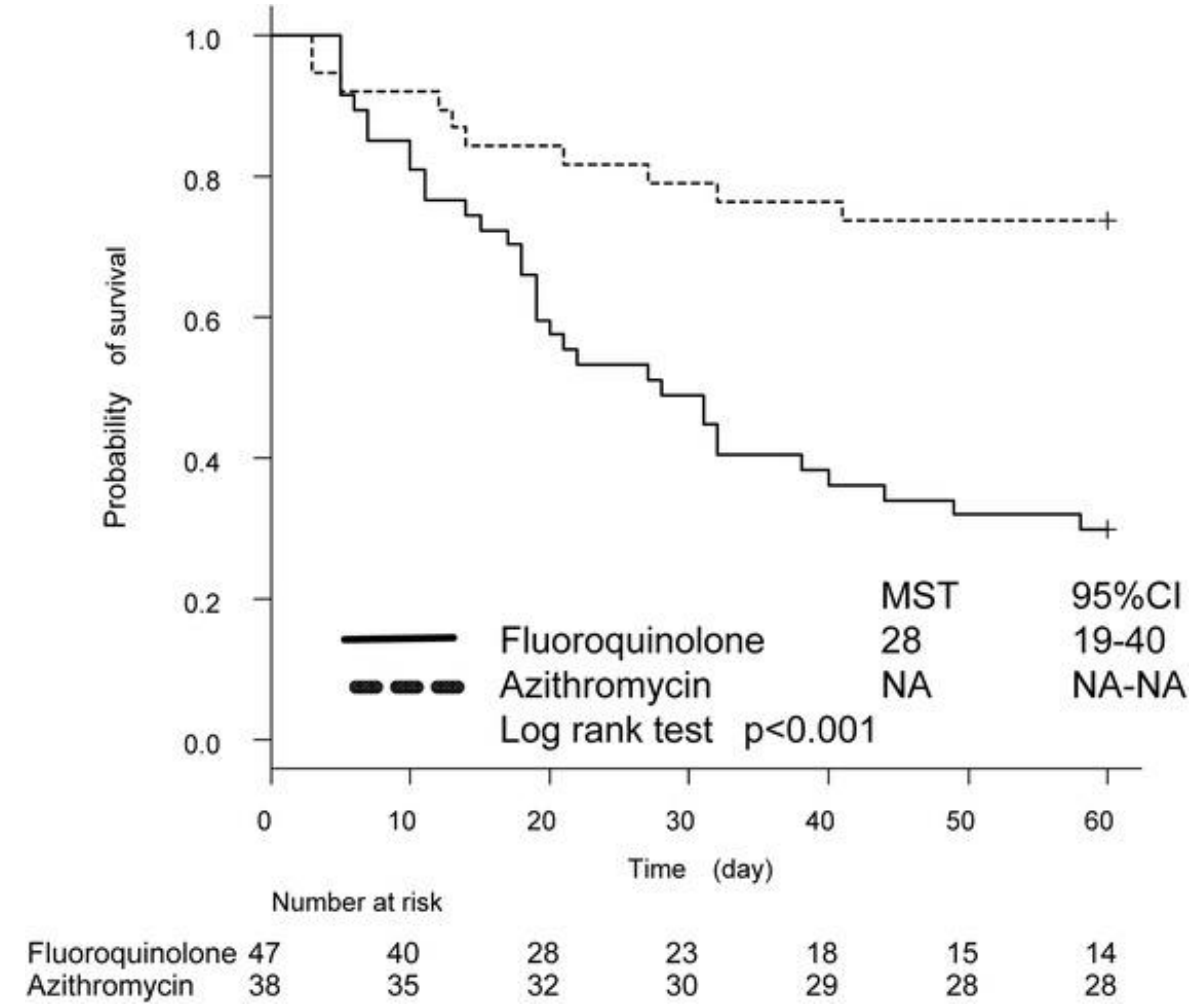
Azithromycin in AE-IPF

Single center retrospective study

Analysis of change in protocol from fluroquinolones pre 2012 to macrolides post 2012

Azithromycin IV 500mg x 5days

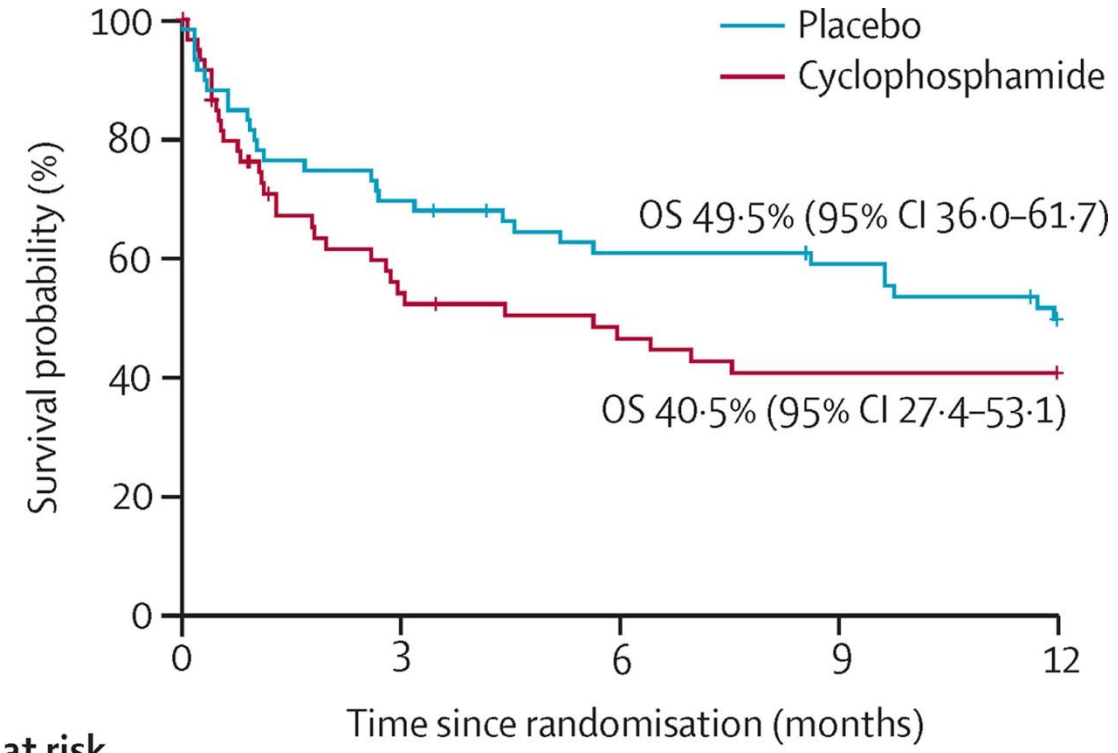
Substantially reduced mortality



No mortality benefit with cyclophosphamide

RCT of 120 patients

Trend to increased 3 month mortality

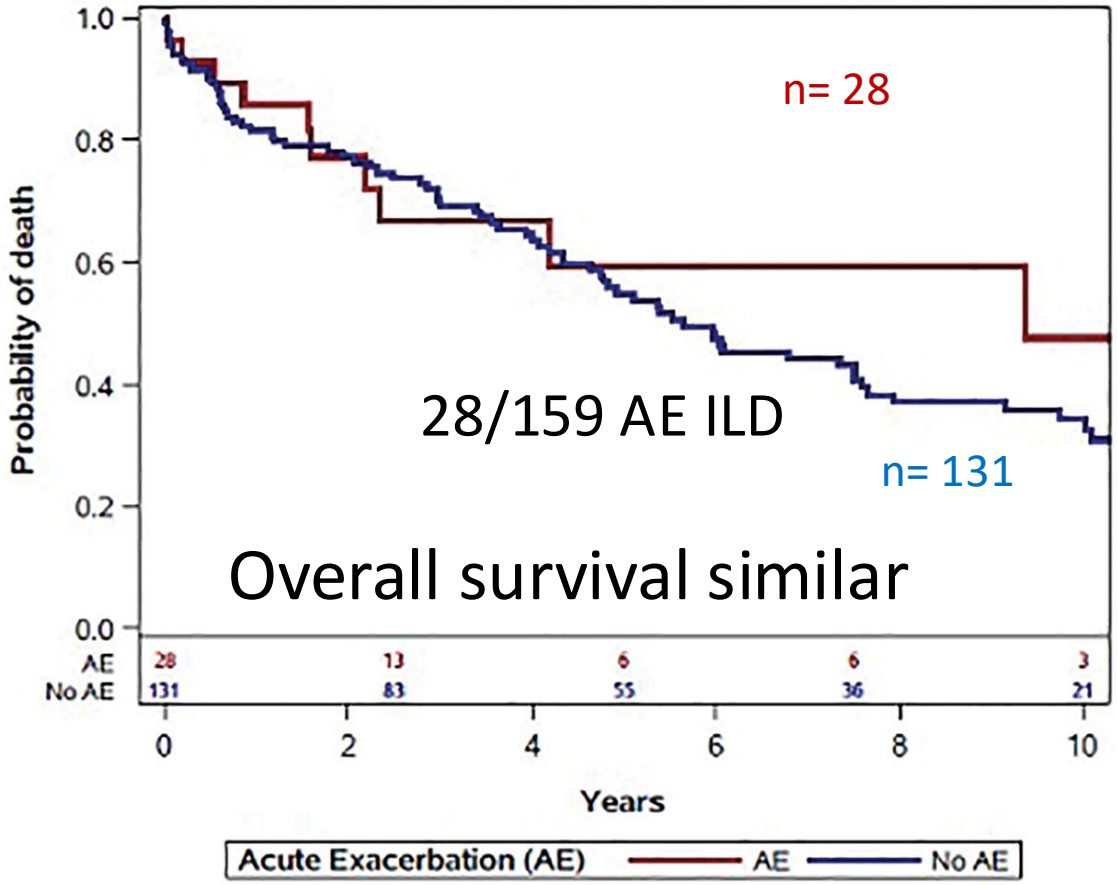


Number at risk (number censored)					
Placebo	59 (0)	41 (0)	34 (2)	32 (1)	26 (1)
Cyclophosphamide	60 (0)	29 (5)	24 (1)	21 (0)	21 (0)

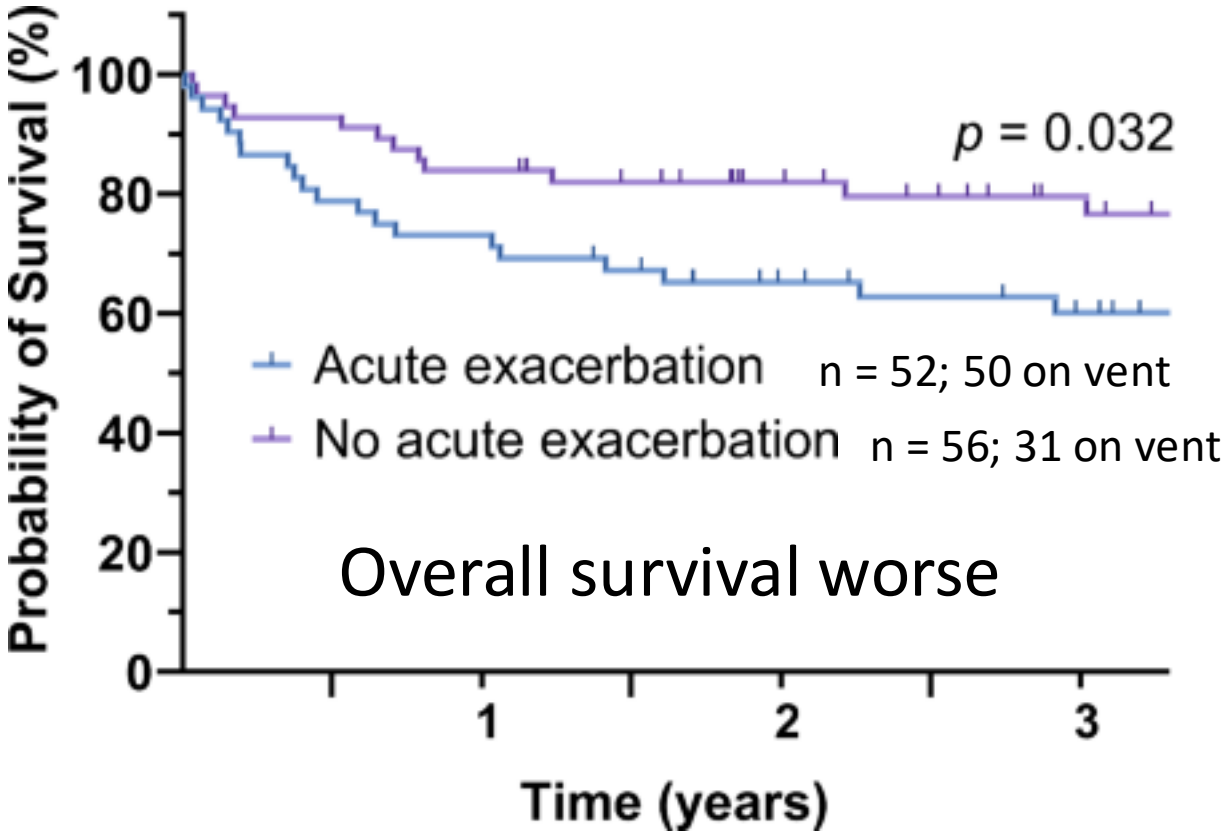
Naccache et al. *Lancet Resp* Med 2022

AE-ILD and survival post transplant

All 159 patients transplanted for IPF at Loyola
July 2005 - October 2020

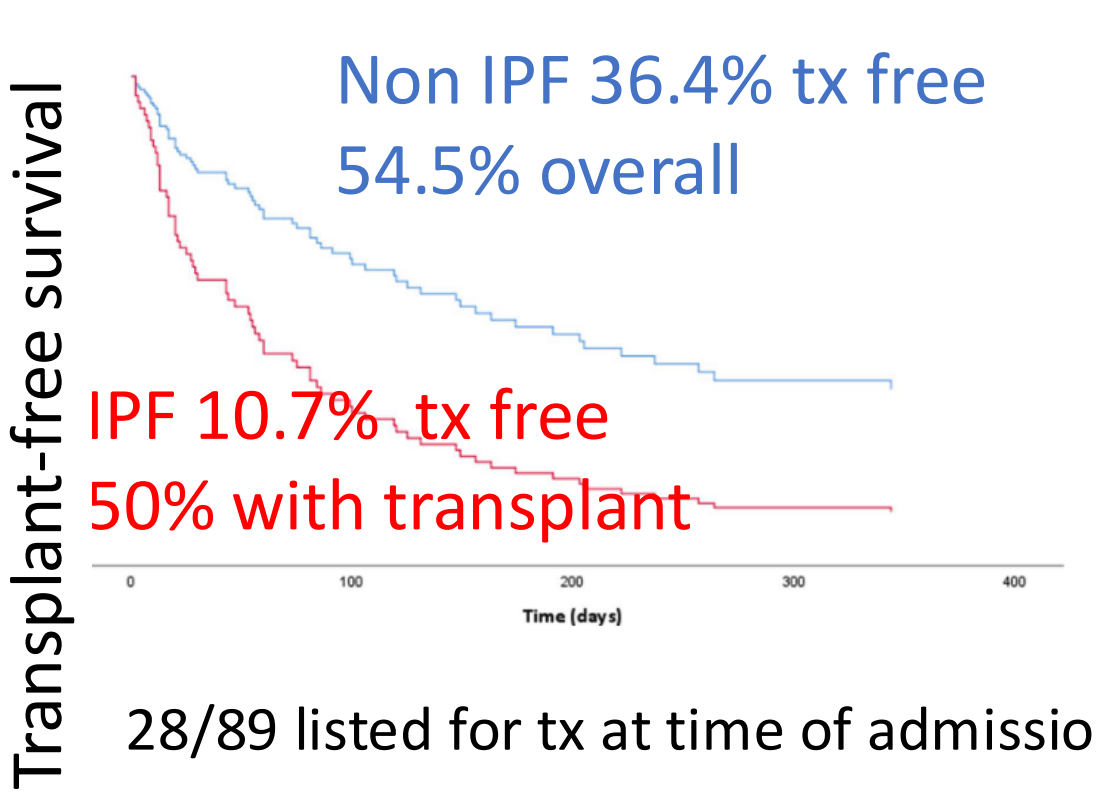


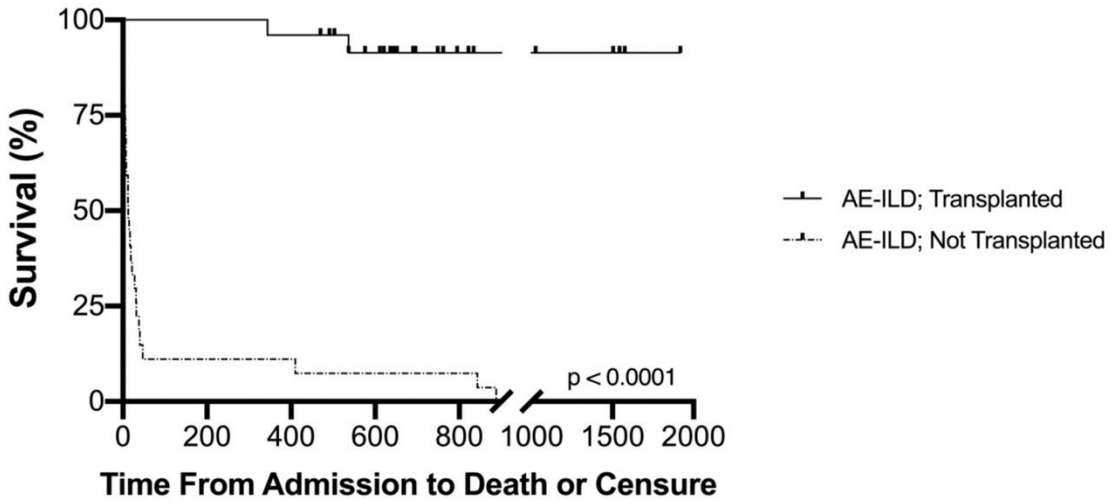
All 108 patients transplanted in S Korea
2008-2022 38 non IPF



Warrior et al. *Transplantation* 2024 Jan 31; Kim…Choi *Respir Res* 2023

Transplant as treatment for AE-ILD





28/89 listed for tx at time of admission (31.5%)

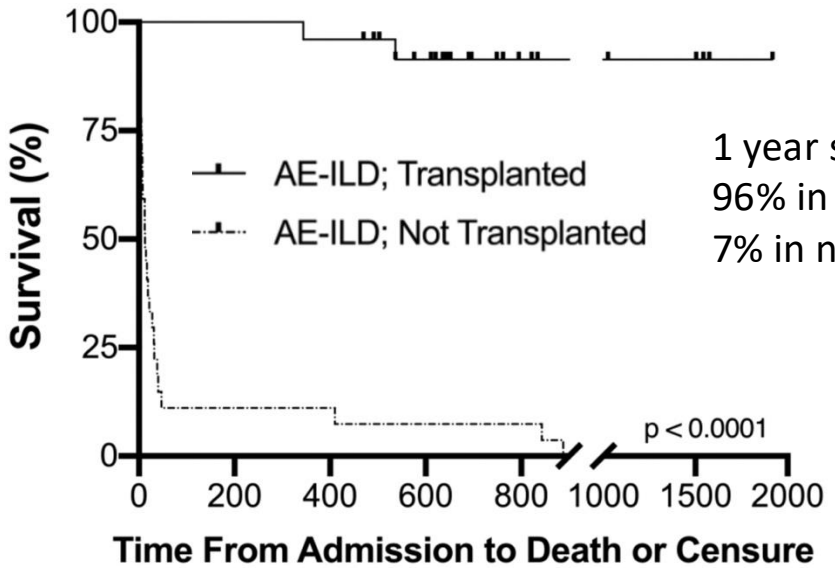
Hazard ratio 2.49

53 patients admitted to U Florida 2015-2018

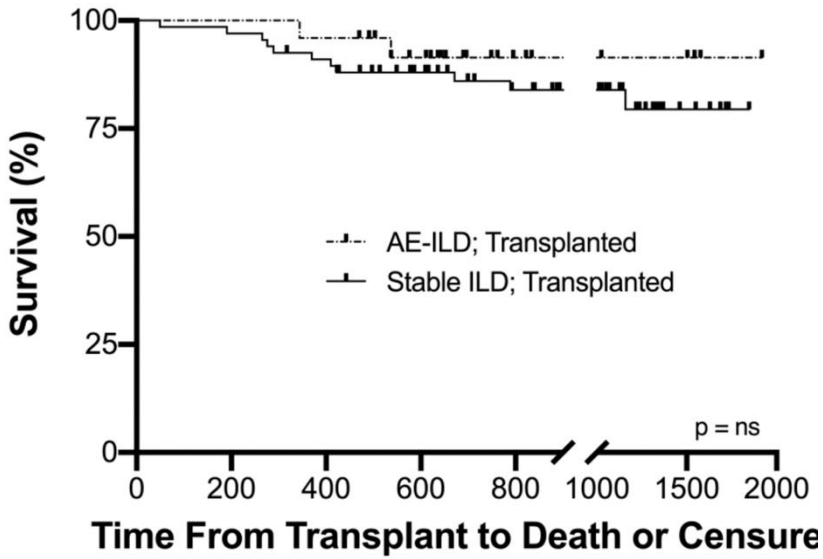
27 listed, 25 tranplanted

Time (days)

Transplant as treatment for AE-ILD



1 year survival
96% in transplanted
7% in non transplanted



53 patients admitted to U Florida 2015-2018

27 listed (9 prior to AE)

25 transplanted

Similar survival; rate of severe graft dysfunction compared to stable ILD pts (n=69) admitted for transplant