

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



AE-ILD observations



Definition of Acute Exacerbation

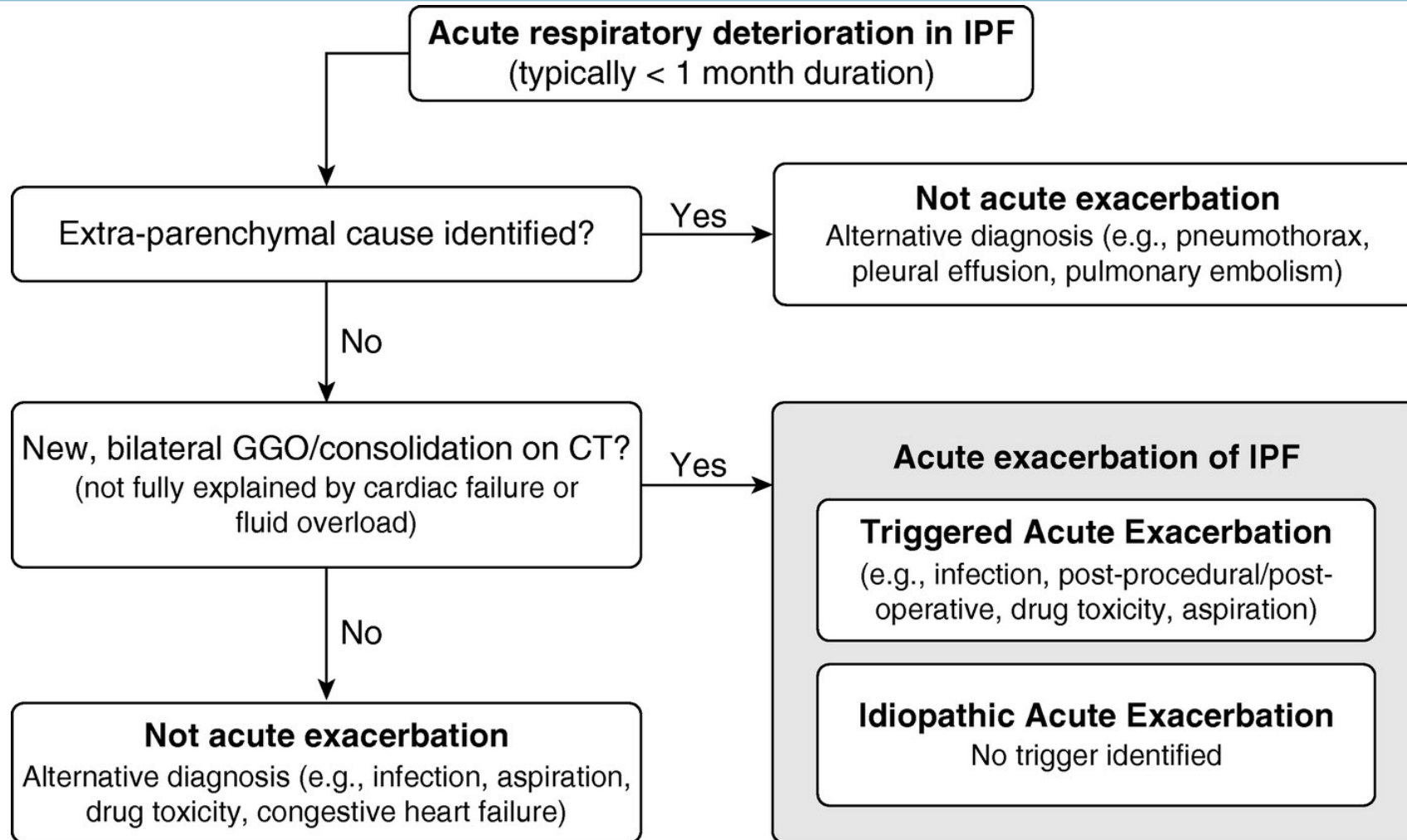
Defined in 2007

- Previous or concurrent diagnosis of IPF
- 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

Revised by 2016 ATS working group

- **Includes “triggered” exacerbations i.e. infection**

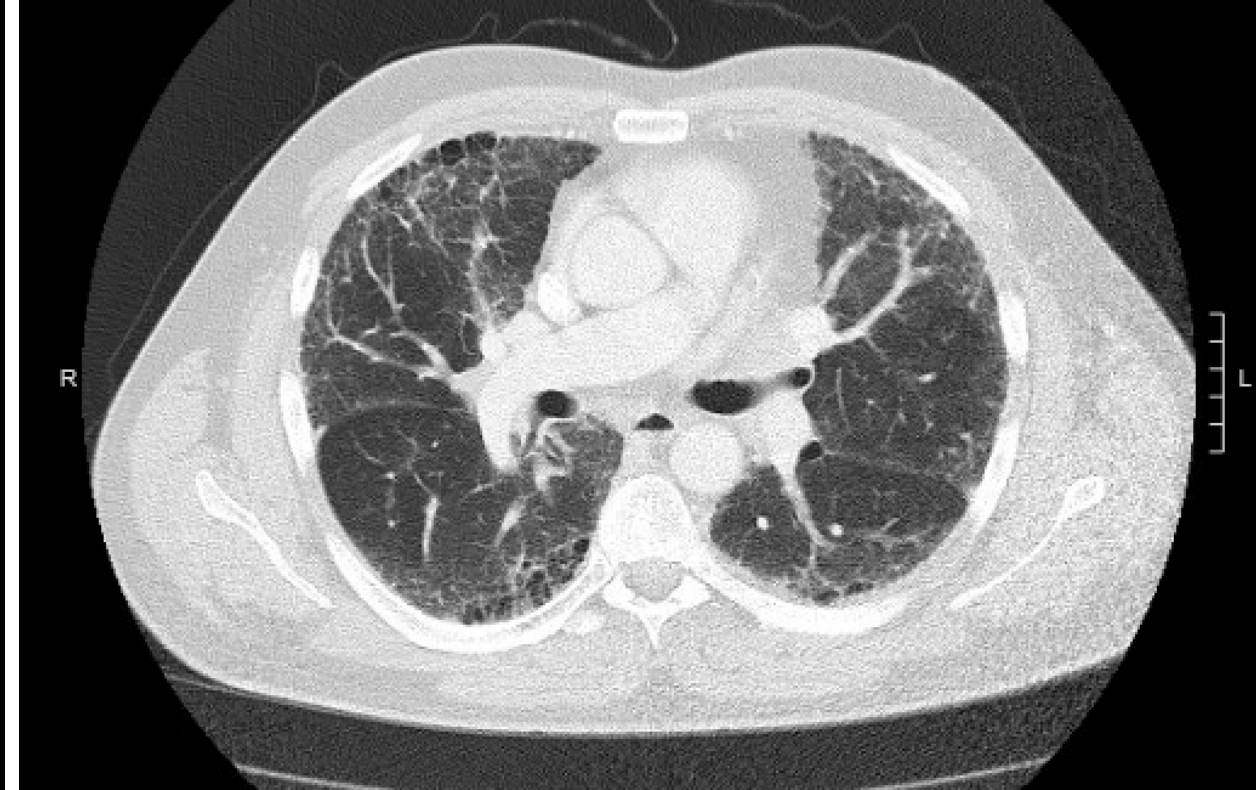
Diagnosis of AE-IPF



AED-ILD: Radiology



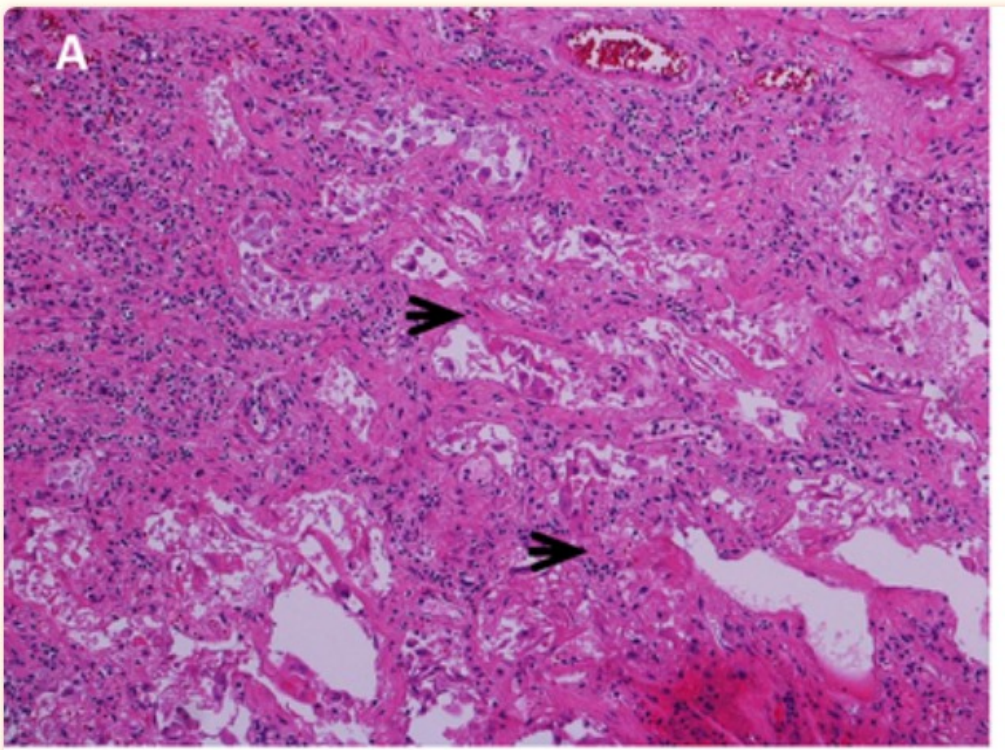
January – acutely worsened hypoxia



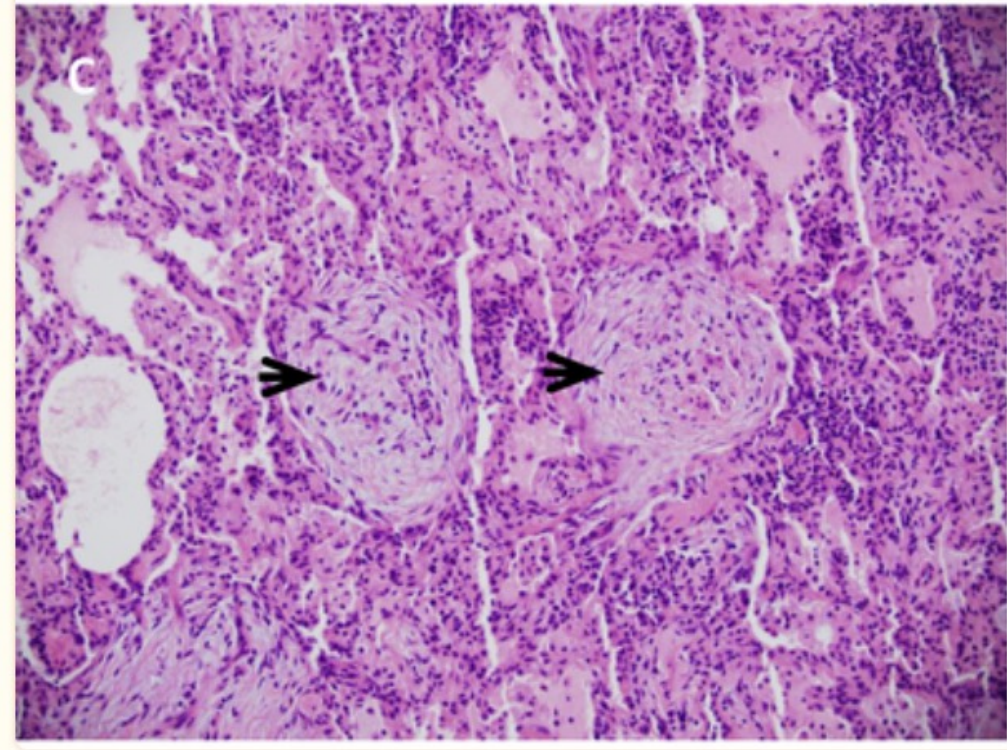
Prior November – stable exertional dyspnea

AE-ILD: Pathology

IPF with diffuse alveolar damage
Arrows showing hyaline membranes



Fibrotic NSIP with organizing pneumonia
Arrows on luminal fibroblastic plugs



Risks for acute exacerbations

Baseline risk:

Lower absolute FVC; recent fall in FVC, IPF

Japanese cohort 2011-2019 27% of 305 with IPF vs
18% of 149 RA-ILD

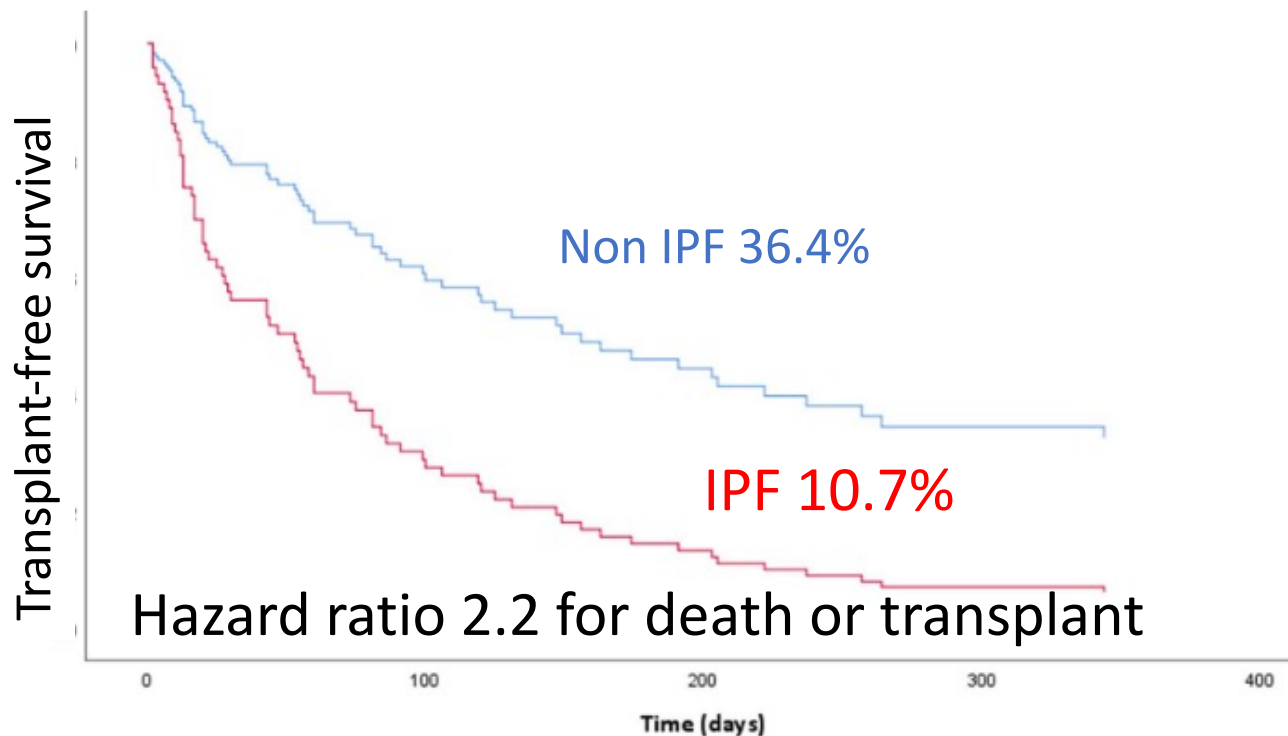
Potential triggers:

Infection, air pollution, micro-aspiration,
bronchoscopy, surgery

Worse prognosis: IPF, prior steroid use, home oxygen, need
for mechanical ventilation

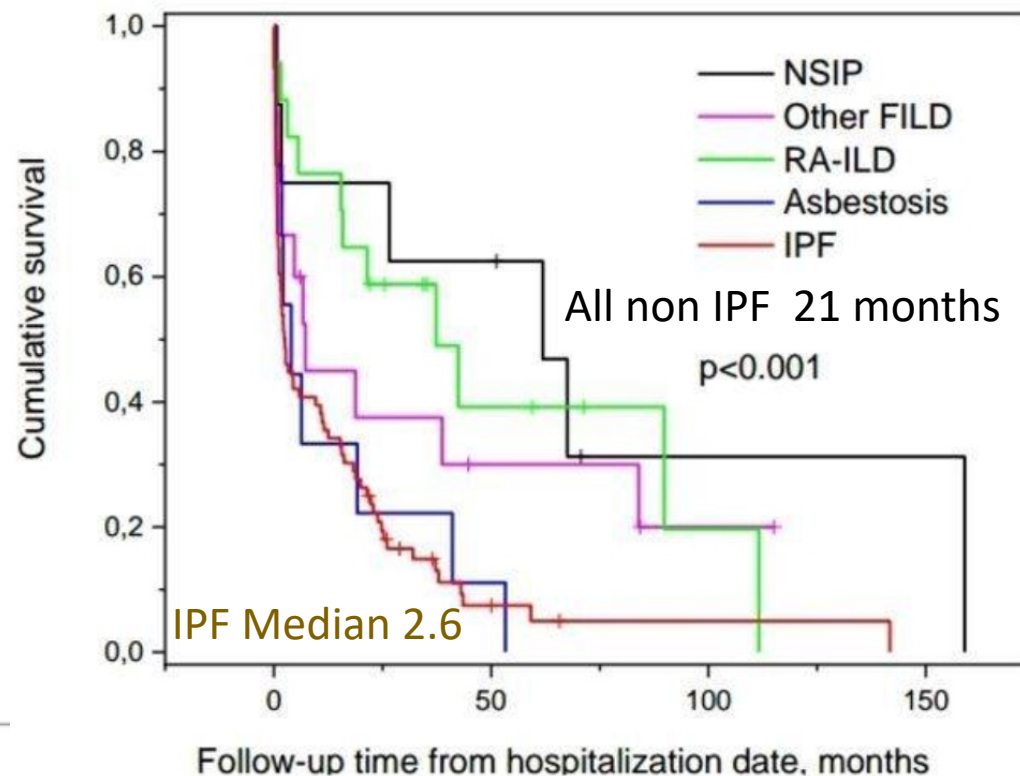
Better outcome after AE of non-IPF ILD

Toronto



89 patients admitted with AE-ILD 2015-2019

Finland



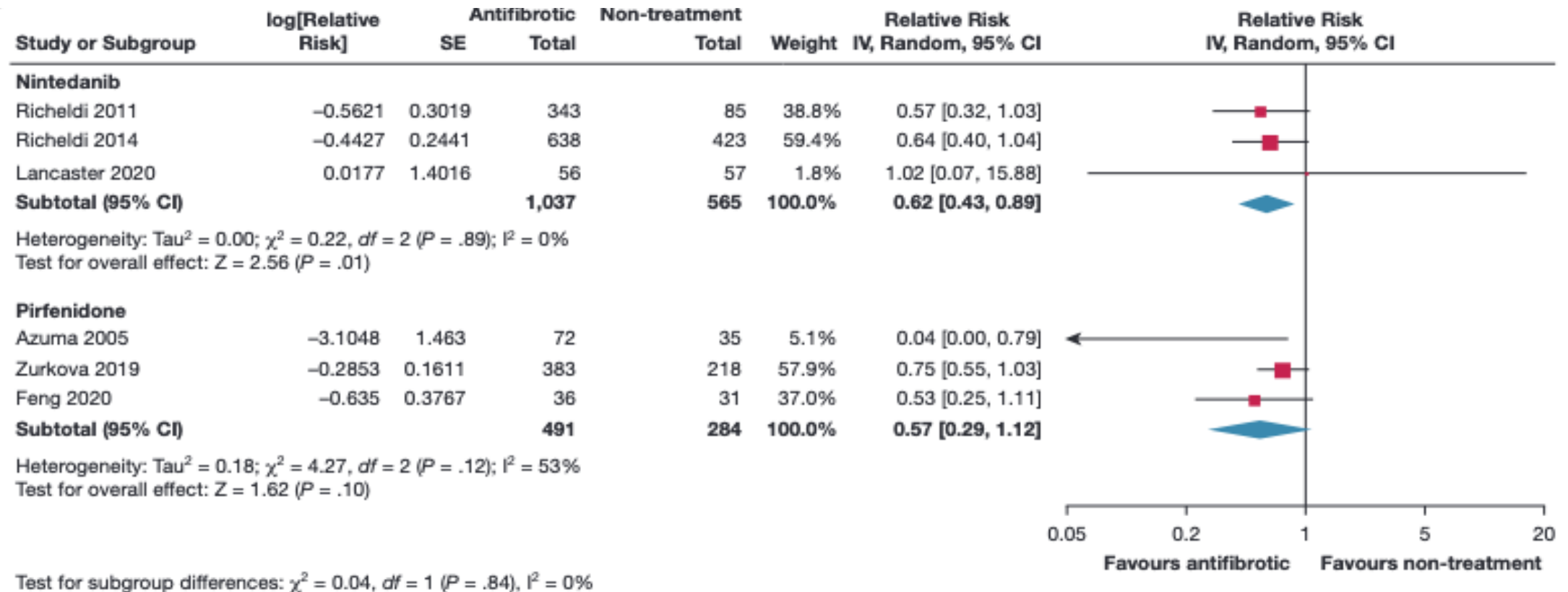
108 patients admitted with AE-ILD 2009-2017
Corticosteroids increased HR for death only in IPF

AE-ILD treatments



Anti-fibrotic therapy may reduce AE

Pooled relative risk for acute exacerbation in subgroup analysis by antifibrotic



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

Steroid responsiveness 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

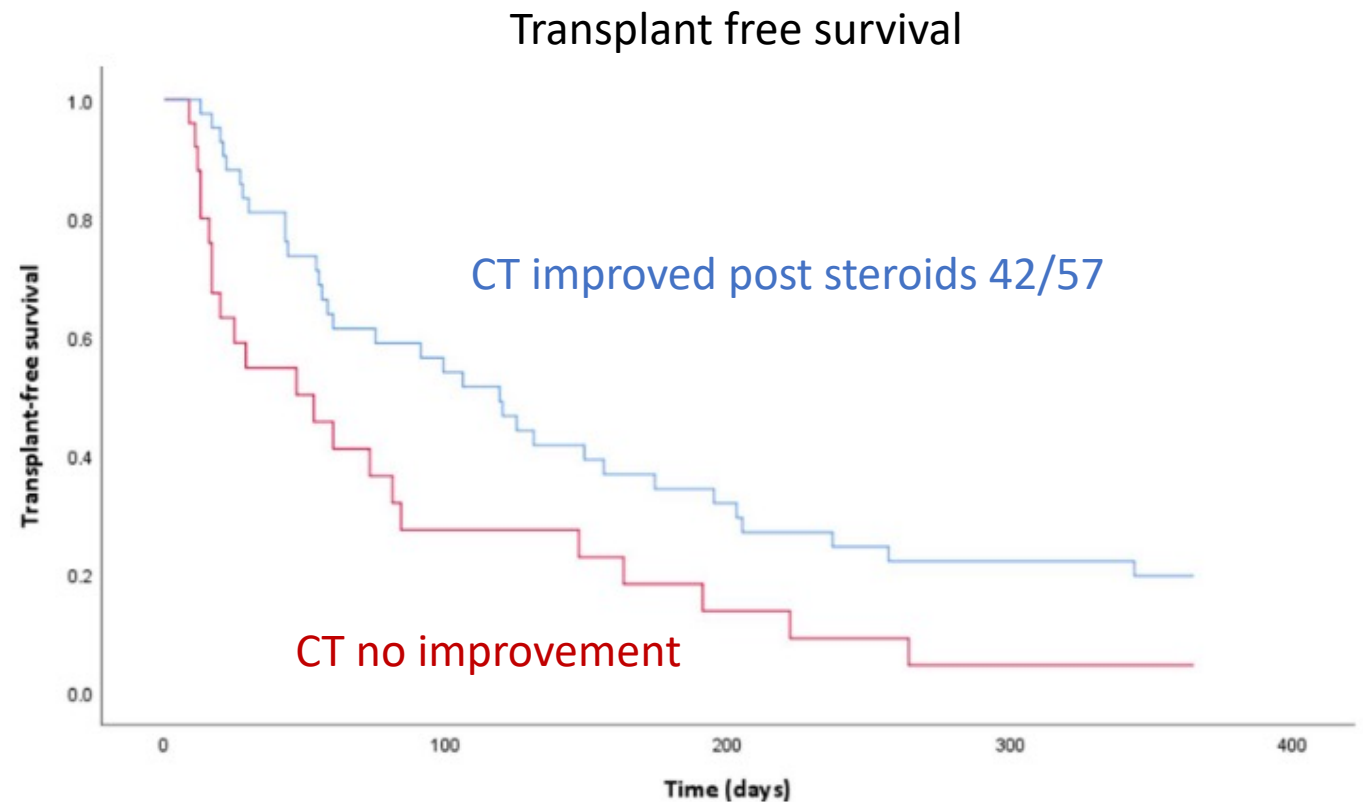
22 didn't get f/u scan

15 died or CMO

7 recovered

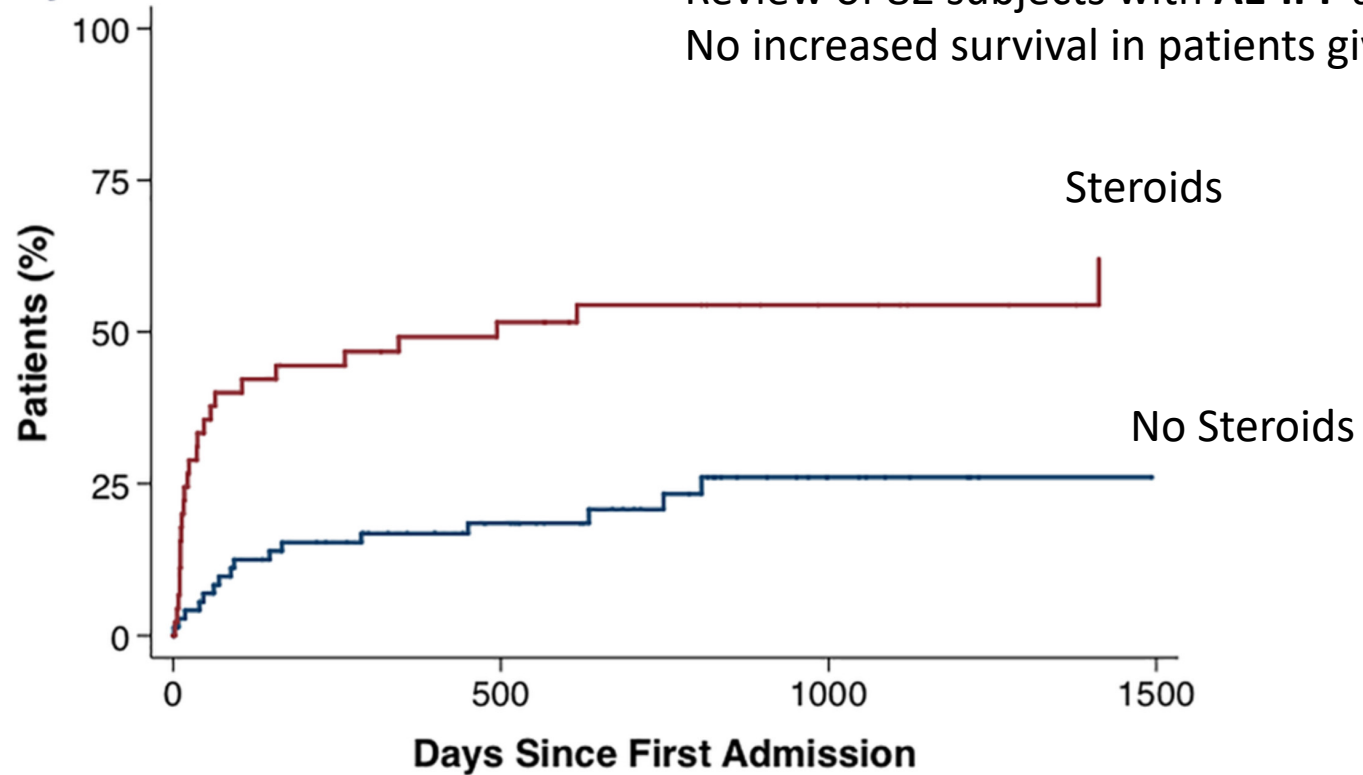
56 pts IPF

33 pts non-IPF



Steroids are not associated with survival in AE-IPF

Mortality



No. at Risk

Steroids	45	20	11	5
No Steroids	72	45	17	9

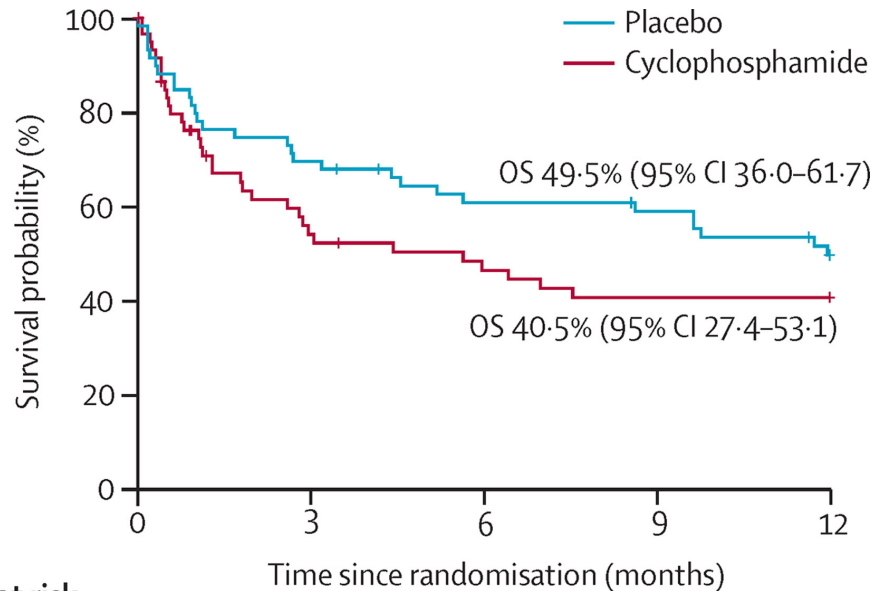
Thrombomodulin – no benefit in AE-IPF

Thrombomodulin Alpha for Acute Exacerbation of Idiopathic Pulmonary Fibrosis. A Randomized, Double-Blind Placebo-controlled Trial

Primary outcome: Day 90 survival
72.5% (29 of 40) in the ART-123 group
89.2% (33 of 37) in the placebo group,

Cyclophosphamide: no benefit in AE-IPF

EXAFIP trial 119 patients randomized across 31 hospitals in France



Number at risk (number censored)		0	3	6	9	12
Placebo	59 (0)	41 (0)	34 (2)	32 (1)	26 (1)	
Cyclophosphamide	60 (0)	29 (5)	24 (1)	21 (0)	21 (0)	

	Cyclophosphamide (n=60)	Placebo (n=59)	Difference (95% CI)	p value
Death at 3 months in the ITT population*	27/60 (45%)	18/59 (31%)	14.5 (-3.1 to 31.6)	0.10
Death at 3 months in the ITT population with available data	26/59 (44%)	18/59 (31%)	13.6 (-4.1 to 30.7)	0.13
Death at 3 months in the per-protocol population	17/42 (40%)	15/50 (30%)	10.5 (-9.6 to 30.1)	0.29

Data are n/N (%), unless otherwise specified. ITT=intention-to-treat. *The missing data for one patient have been replaced by death.

Table 2: Primary outcomes

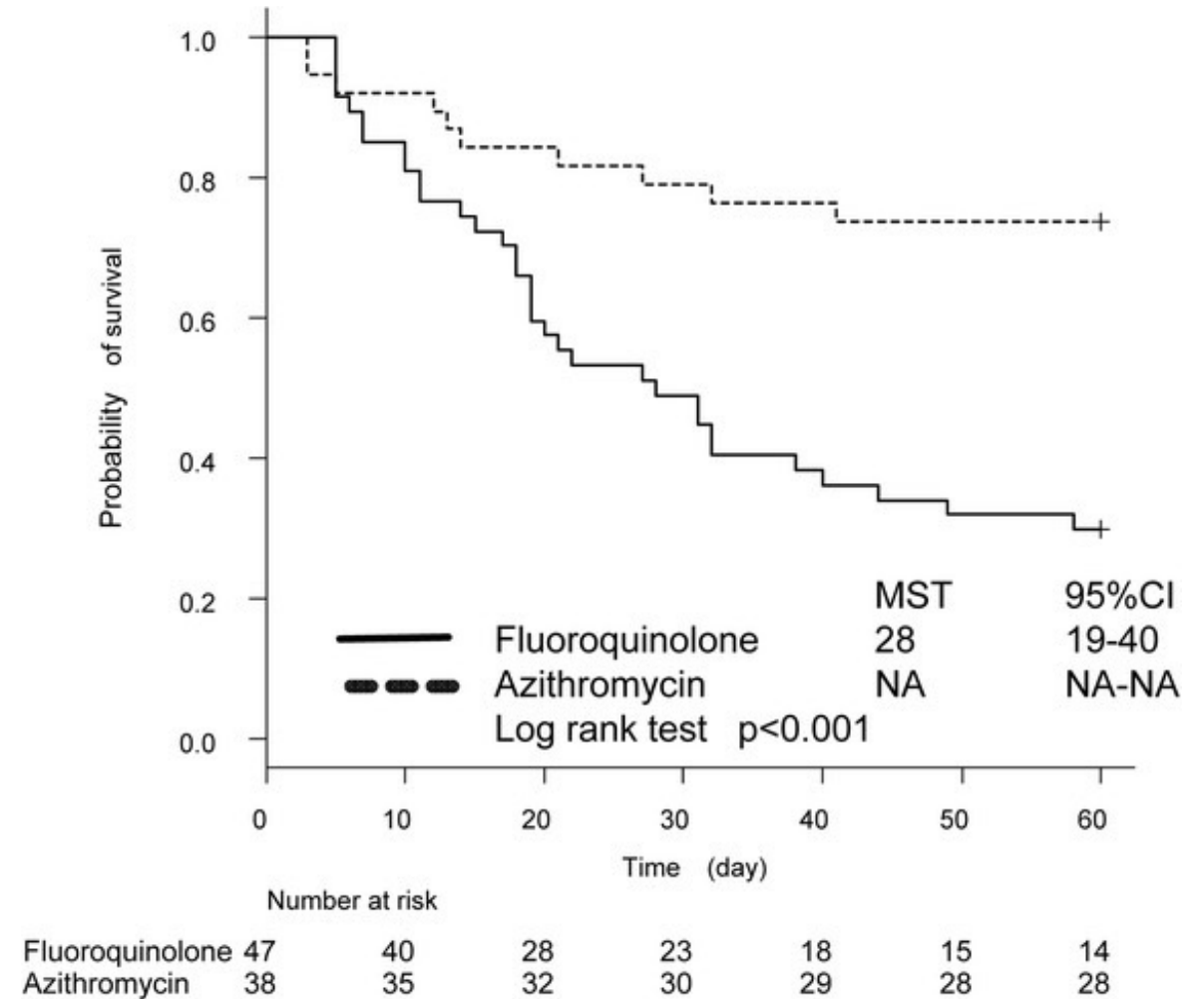
Azithromycin in AE-IPF

Single center retrospective study

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

Azithromycin IV 500mg x 5days

Substantially reduced mortality



IVIIG in AE-ILD

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

Treated with steroids + IVIG or steroids

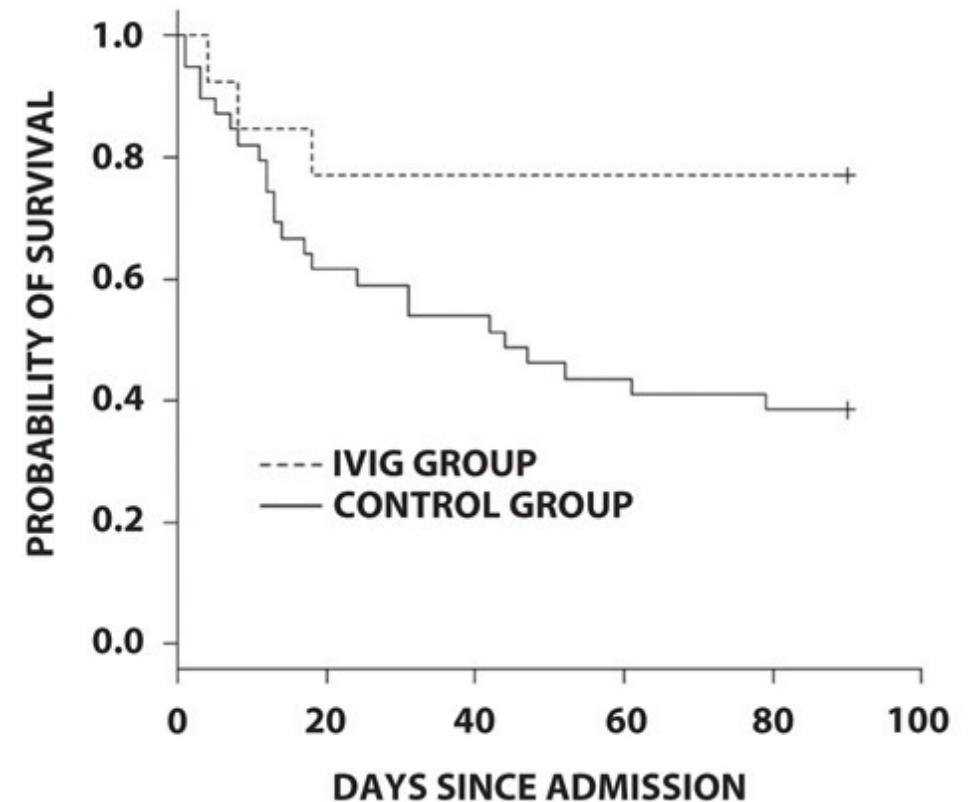
41 IPF, 11 other – CTD excluded

5 grams IVIG/day x 3-5 days

Better survival with IVIG

RCT ongoing; enrollment began 8/2022

jRCT1061220010



STRIVE-IPF Antibody reduction in AE-IPF

Exclusion: positive ANA, RF, CCP, anti SSA

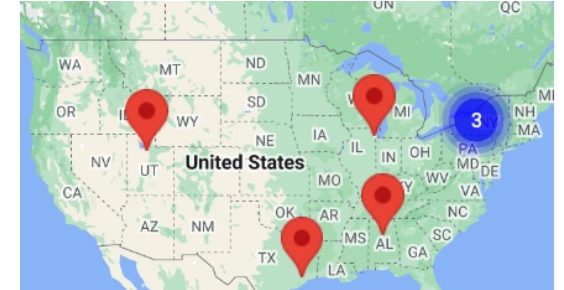
Treatment: Therapeutic plasma exchange, rituximab, IVIG, prednisone, antibiotics

Usual care: Prednisone, antibiotics

Prednisone = 60 x1, 20mg day 2-day 19;
(100 mg solumedrol on d6, d15)

Primary outcome: Six month survival

Secondary outcome: O2 needs, 6MWD



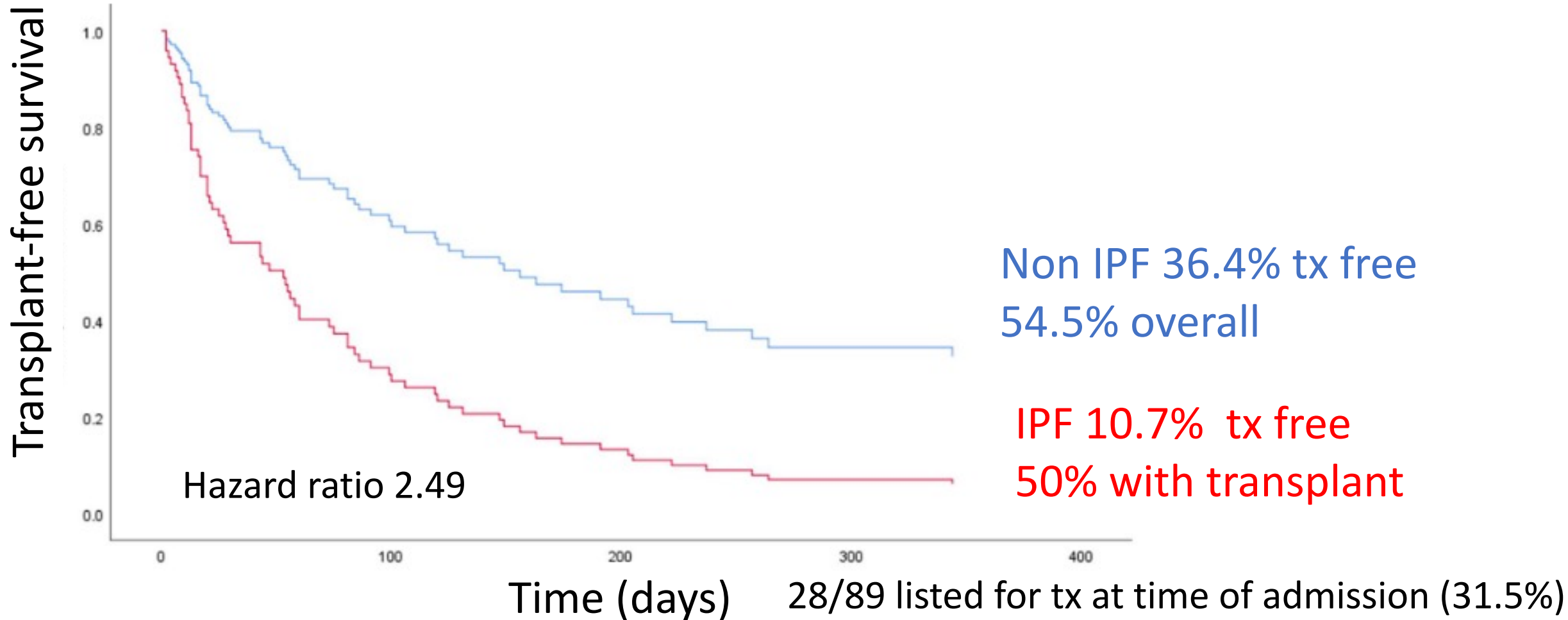
Recruiting centers:
U Alabama, Temple,
U Pitt, Baylor,
University of Utah,
Thomas Jefferson,
Loyola

NCT03286556



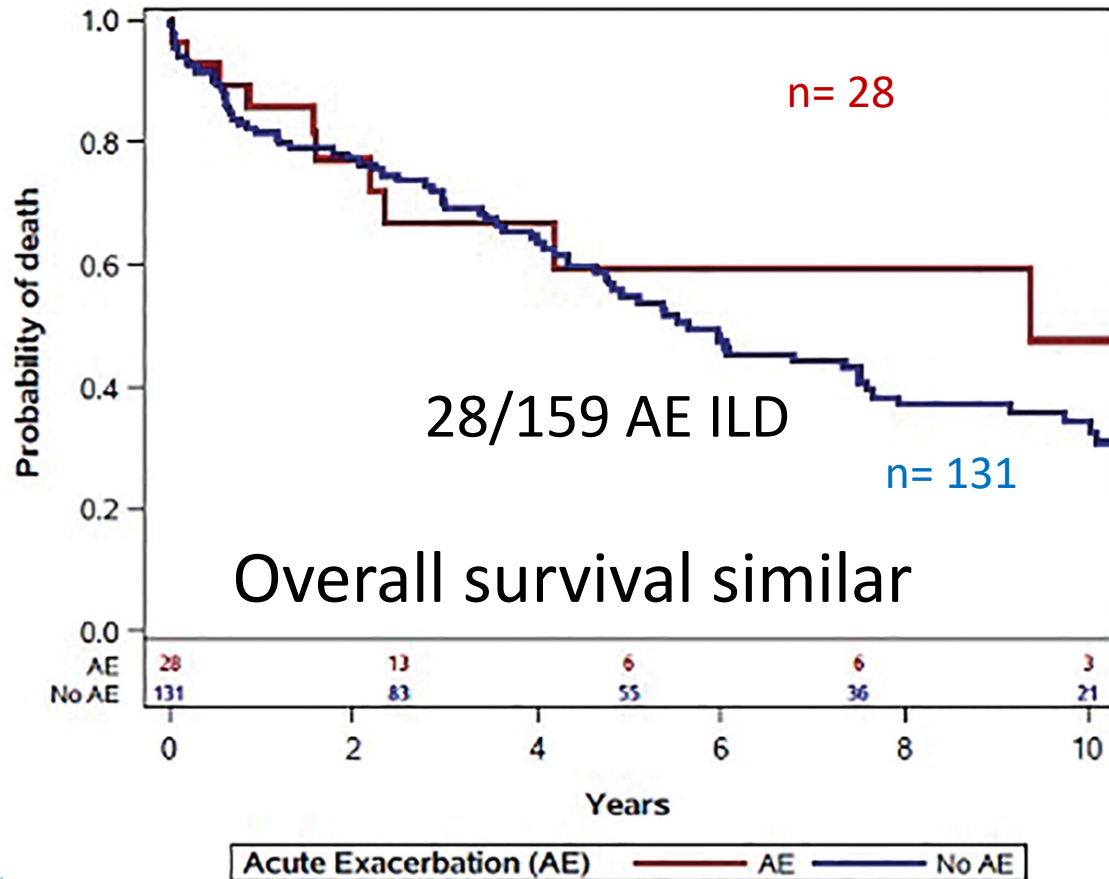
Transplant as treatment for AE-ILD

1-year transplant-free survival 20.2% but **51.7% overall survival**

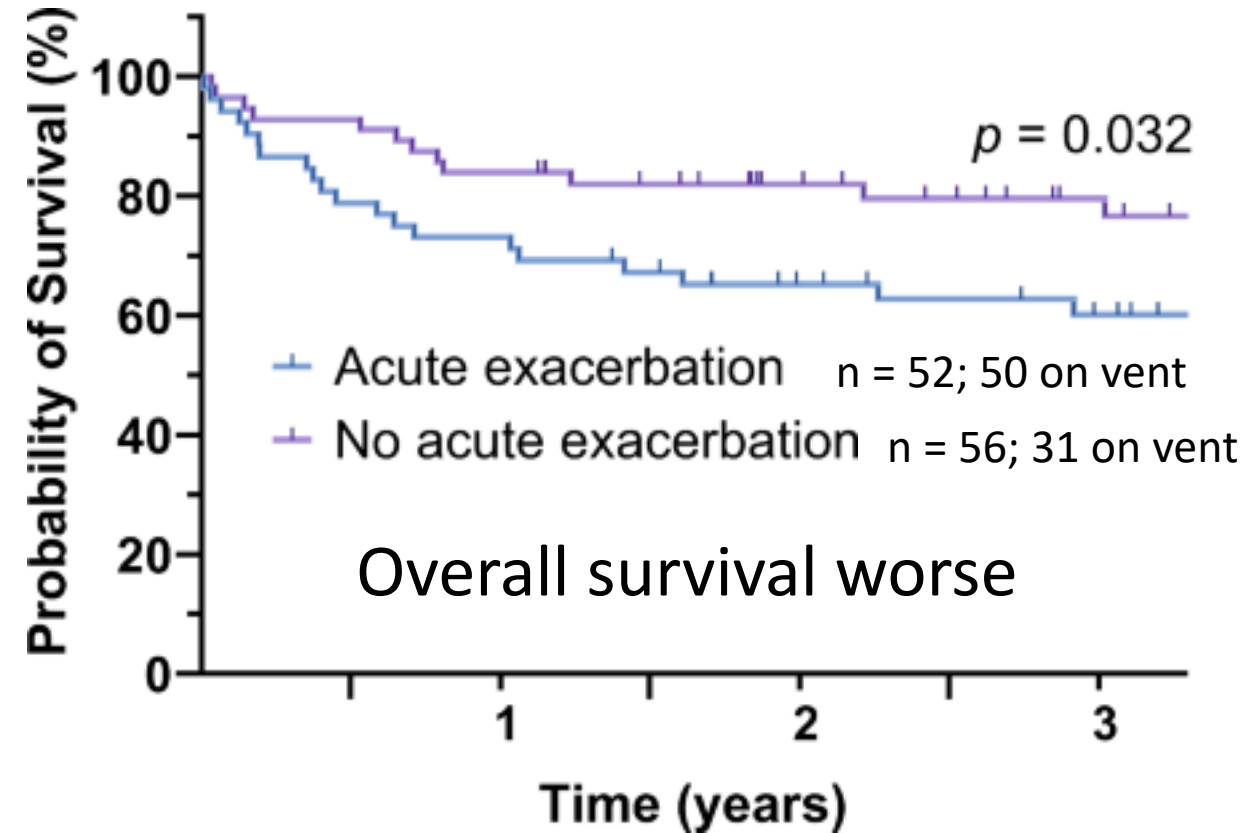


AE-ILD and survival post transplant

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



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



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

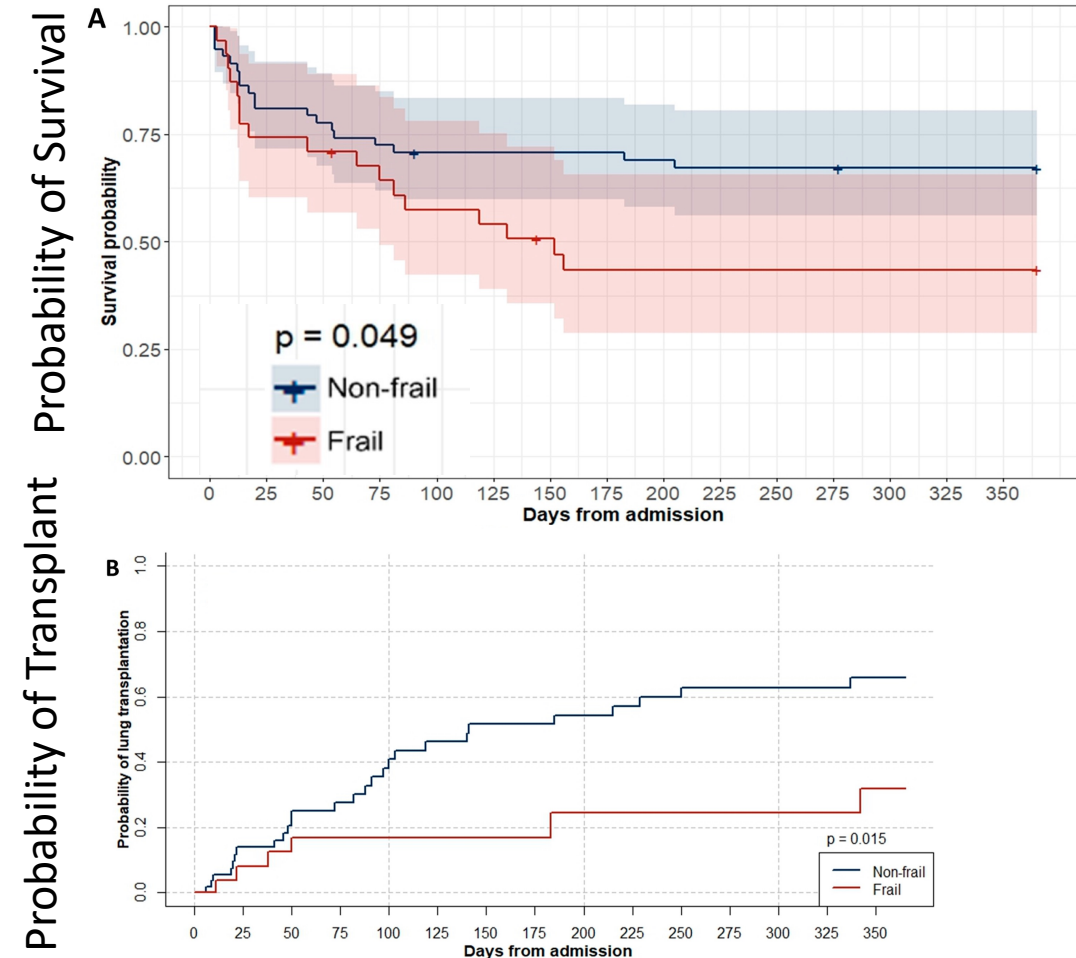
One year follow up

28% mortality

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

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

Survival post admission



Take home messages

- All fibrotic ILDs can have exacerbations
- Seems worse in IPF, more severe disease
- Likely better outcome if steroid responsive
- Cyclophosphamide and thrombomodulin no effect
- Ongoing trials for IVIG and combined antibody reduction
- Consider transplant, limited by frailty



Thank you

