

# Acute Exacerbations of ILD

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# Disclosures

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**No financial disclosures.**

**Very minimal evidence-based guidance**

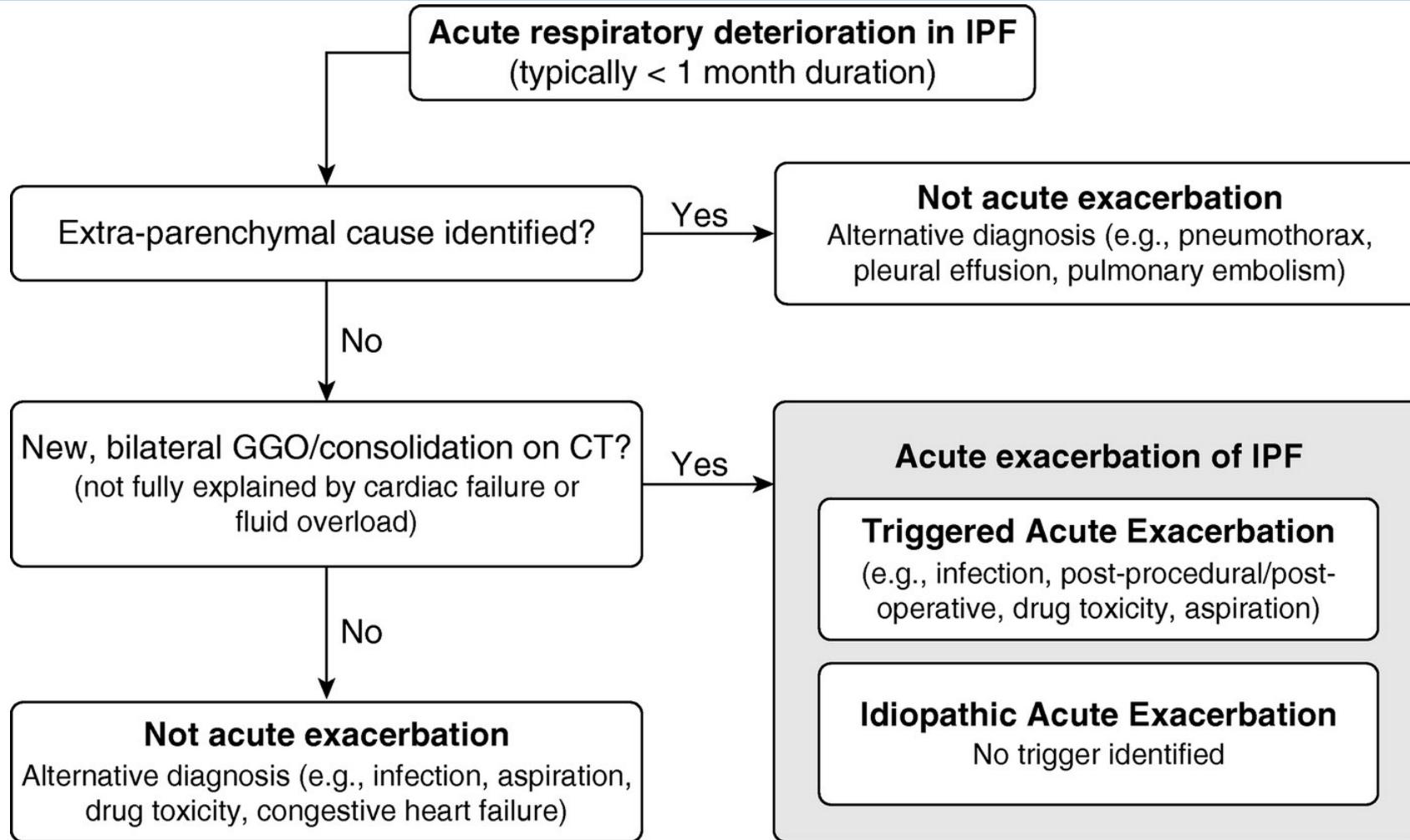


# Definition of Acute Exacerbation

## Defined in 2007, revised in 2016

- 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**
- Infection or otherwise “**triggered**” **exacerbations are included**

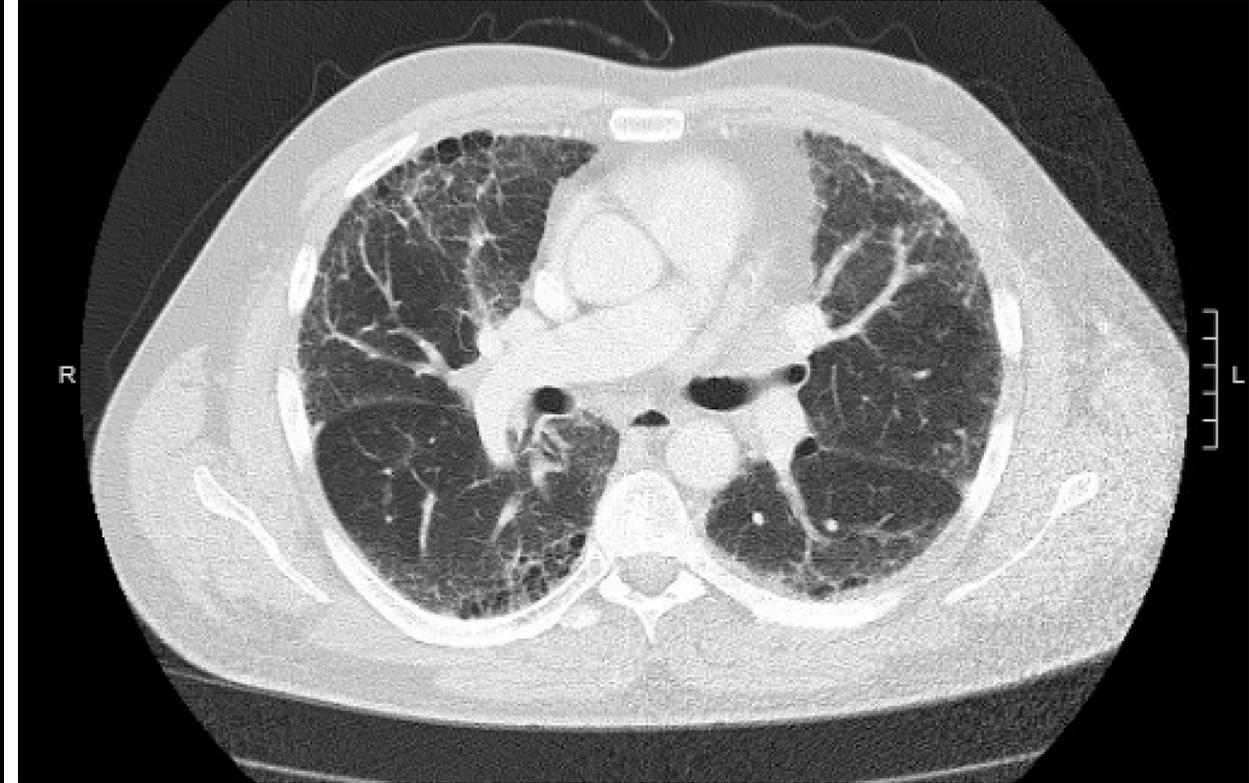
# Diagnosis of AE-IPF



# AED-ILD: Radiology



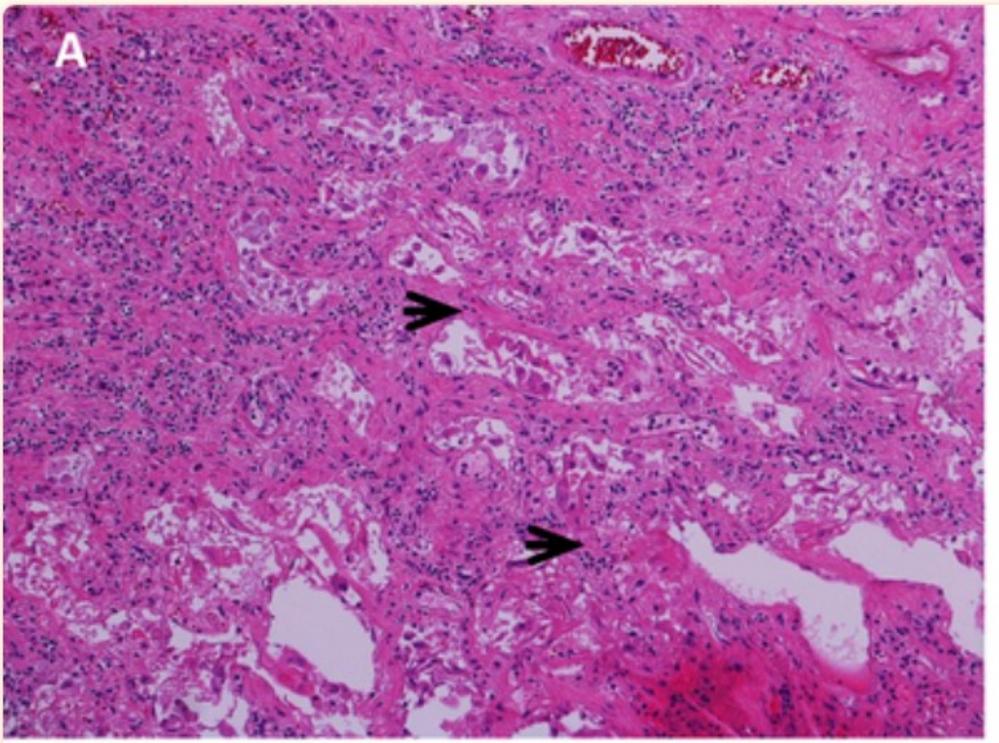
January – acutely worsened hypoxia



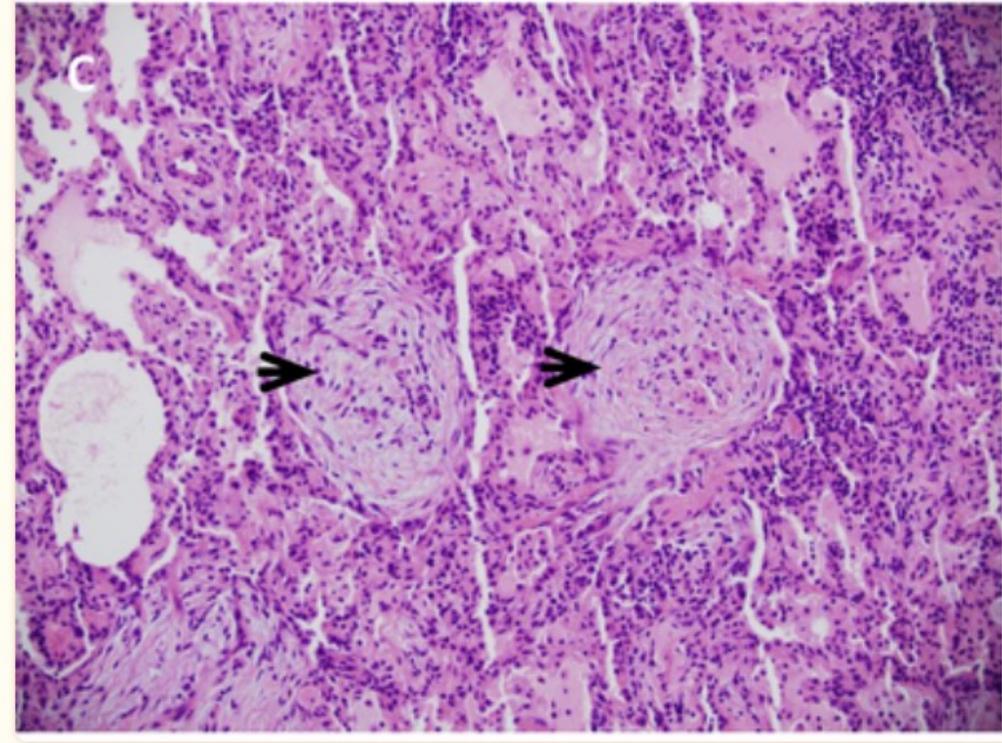
Prior November – stable exertional dyspnea

# AE-ILD: Pathology

IPF with diffuse alveolar damage  
Arrows showing hyaline membranes



Fibrotic NSIP with organizing pneumonia  
Arrows on luminal fibroblastic plugs



# Incidence of AE-ILD

**Overall estimate 2% and 16% over 24–60 weeks**

## **INPULSIS study in IPF**

AE in 5.9% of patients over 52 weeks

37 events/34 patients in nintedanib 5.3%; 5.3/100 p/years

42 events/35 patients in placebo 8.3%; 8.2/100 p/years

## **INBUILD study in PF-ILD**

332 nintedanib; 331 placebo

AE in 8.7% of patients over 19 months

30 day mortality 19%

HR 0.60 of AE for nintedanib; CI 0.35-1.02; p= 0.06

# Incidence of Acute Exacerbations

## One year incidence of AE

IPF 9.0% vs IIP 7.4%

## Overall incidence

AE-IPF in 66/306 (21.6%);

26/66 (40%) died within 3 months of AE

AE-Non IPF in 43/222 (19.4%)

30% died within 3 months

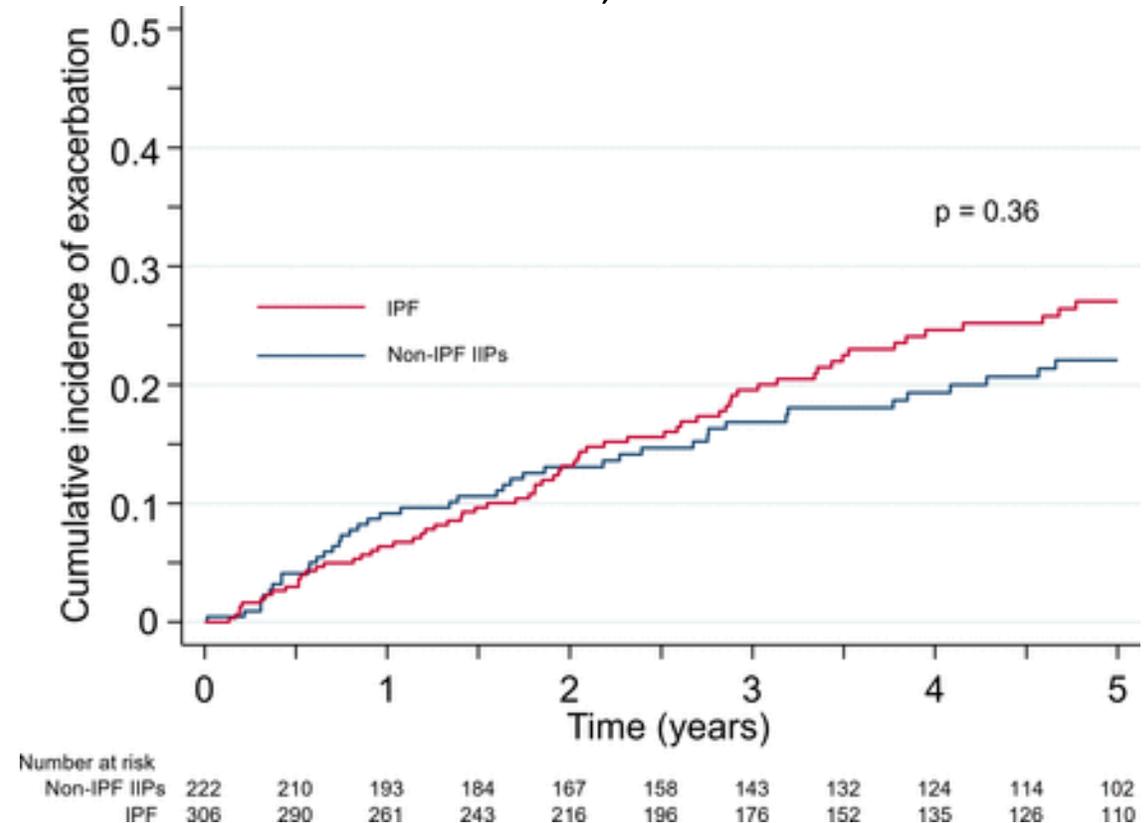
Similar Japanese cohort 2011-2019

27% AE in 305 with IPF

18% of 149 RA-ILD

Multicenter Japanese cohort 2013-2016

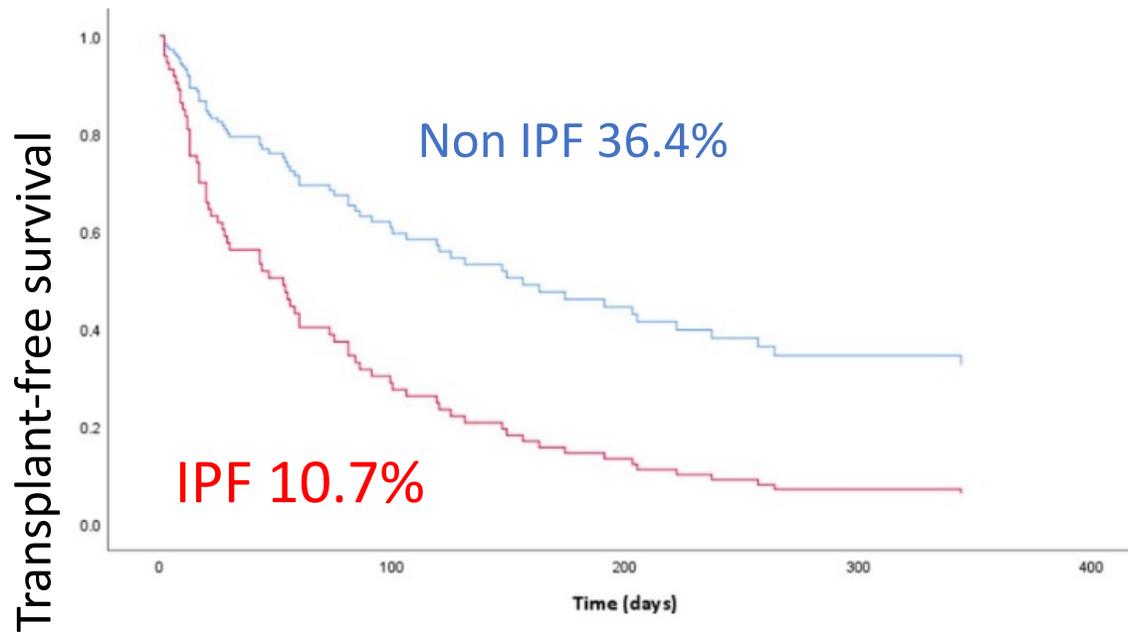
306 IPF; 222 Non IPF



# AE in non-IPF ILD may be less deadly

Toronto

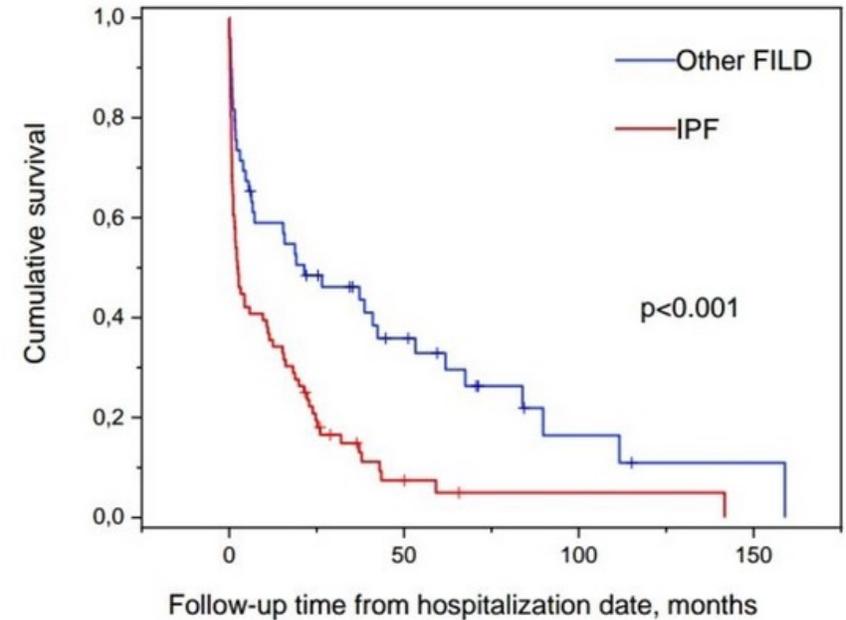
89 patients admitted with AE-ILD  
2015-2019



Hazard ratio 2.2 for death or transplant

Finland

128 patients admitted with AE-ILD  
2009-2017 79 IPF; 49 other f-ILD

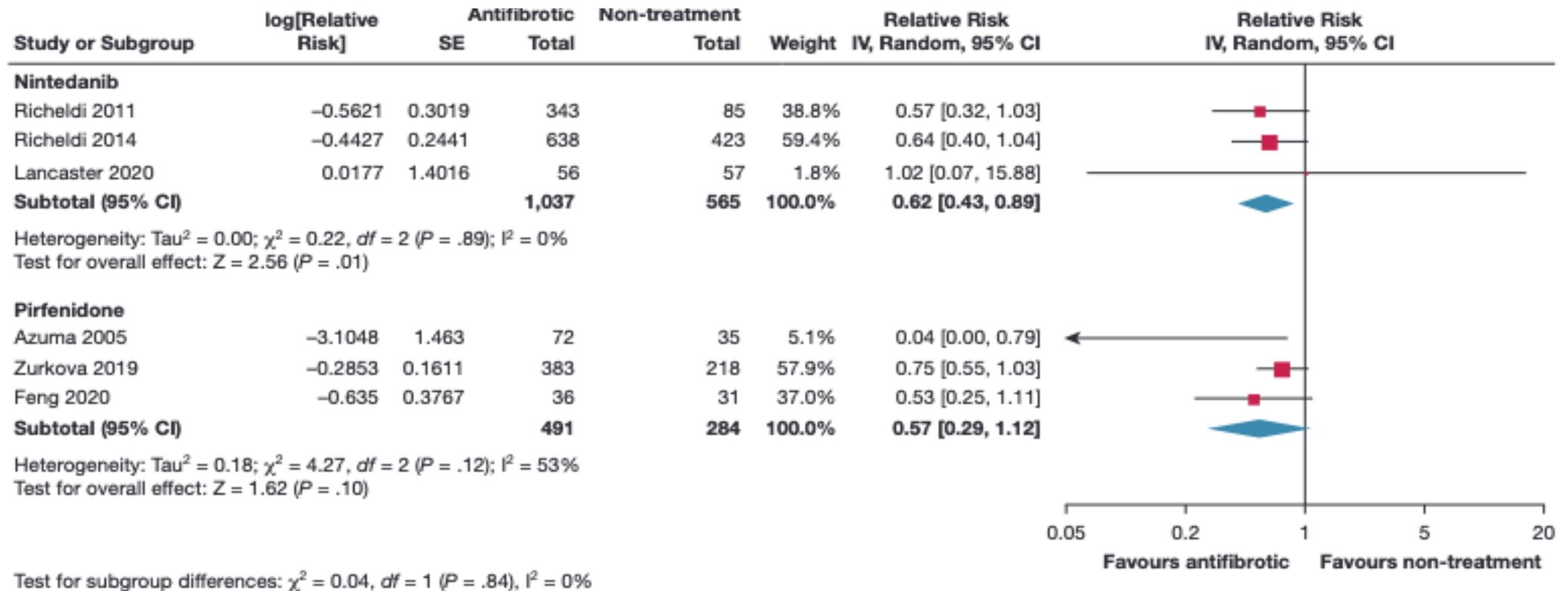


AE-IPF median survival 2.6 months  
AE-f ILD median survival 21 months

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# Anti-fibrotic therapy likely reduces AE

## Pooled relative risk for acute exacerbation in subgroup analysis by antifibrotic



Pooled RR for AE 0.63 (95%CI, 0.53-0.76);

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

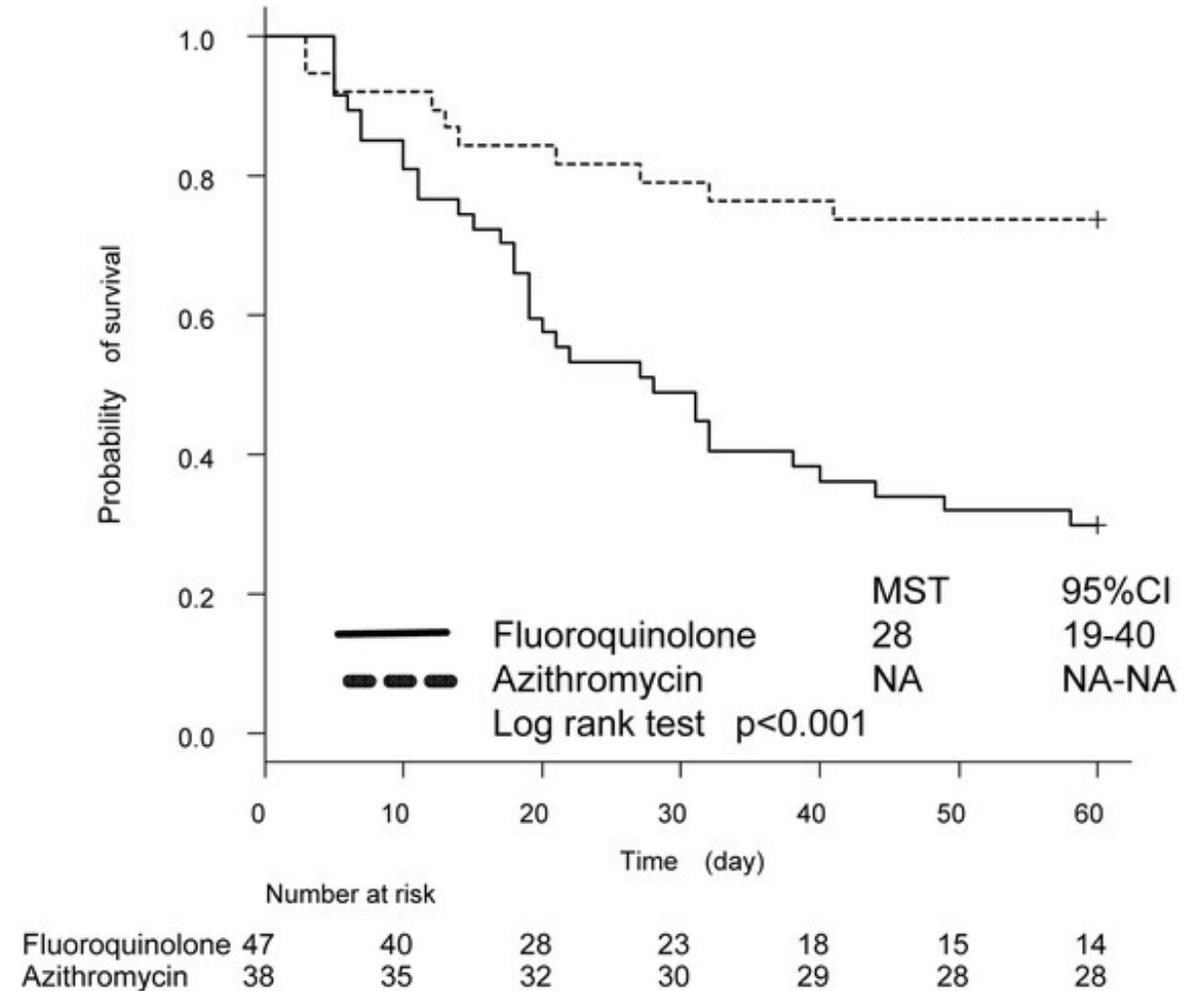
# Azithromycin in AE-IPF

Single center retrospective study

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

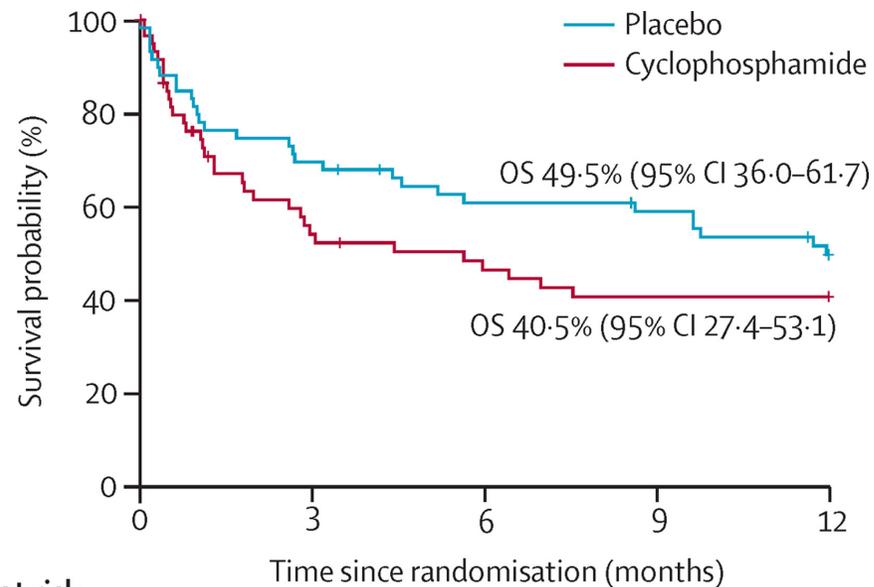
Azithromycin IV 500mg x 5days

Substantially reduced mortality



# Cyclophosphamide: no benefit in AE-IPF

**EXAFIP trial 119 patients** randomized across 31 hospitals in France  
Cyclophosphamide vs. placebo in addition to corticosteroids



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**

# 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,

# IVIIG in AE-ILD

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

Treated with steroids + IVIG or steroids

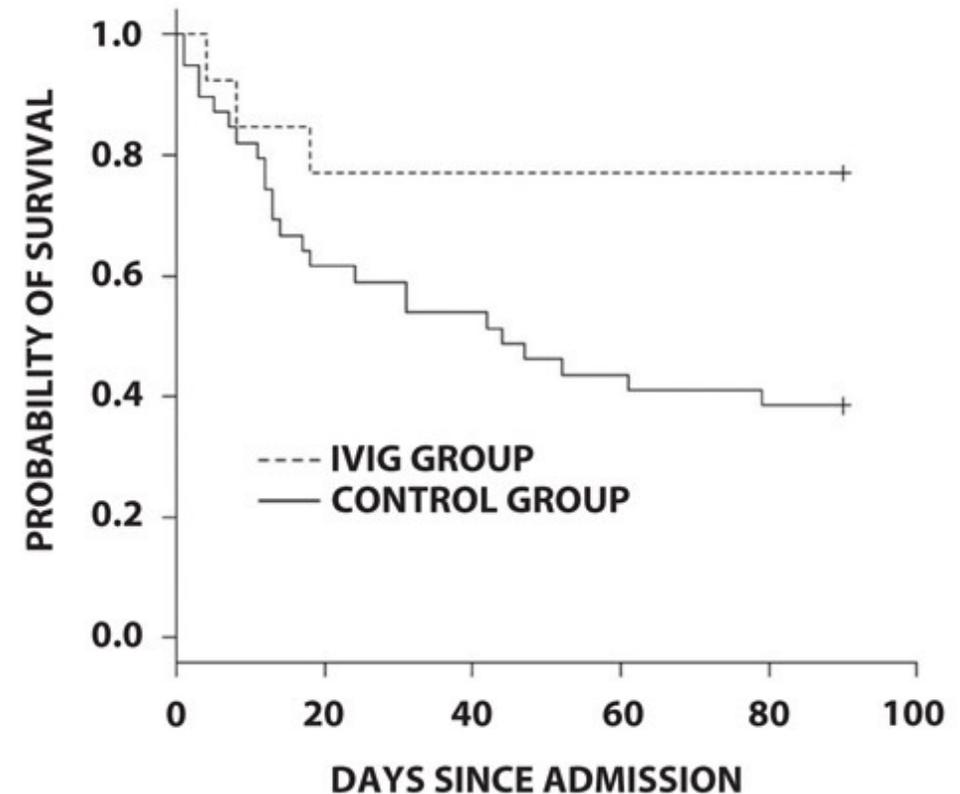
41 IPF, 11 other – CTD excluded

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

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

Usual care: Prednisone, antibiotics

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

Primary outcome: Six month survival

Secondary outcome: O2 needs, 6MWD

Exclusion: positive ANA, RF, CCP, anti SSA

Completed ⓘ

Autoantibody Reduction for Acute Exacerbations of Idiopathic Pulmonary Fibrosis (STRIVE-IPF)

ClinicalTrials.gov ID ⓘ NCT03286556

Sponsor ⓘ University of Alabama at Birmingham

Information provided by ⓘ Steven R. Duncan, MD, University of Alabama at Birmingham (Responsible Party)

Last Update Posted ⓘ 2024-08-28

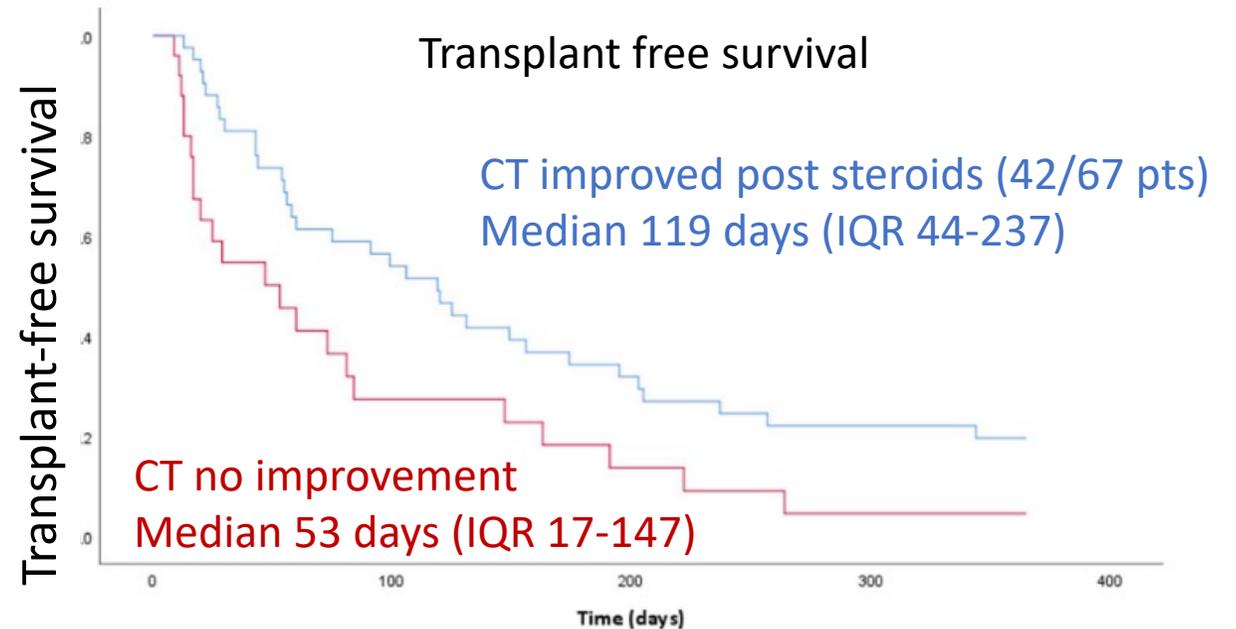
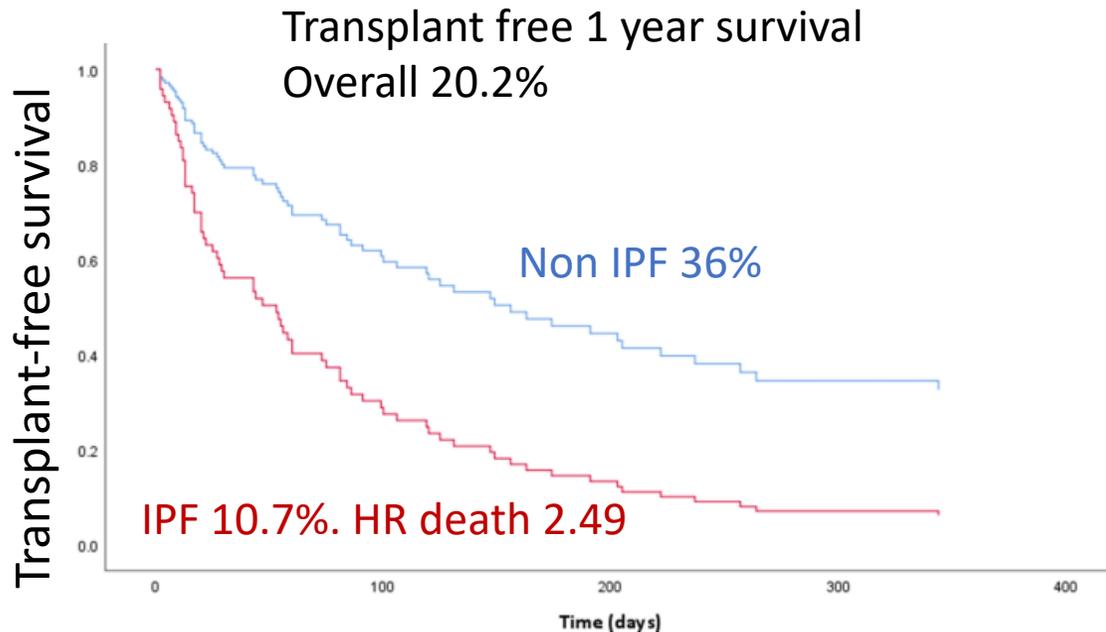
NCT03286556

# Steroid responsiveness in AE-ILD

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

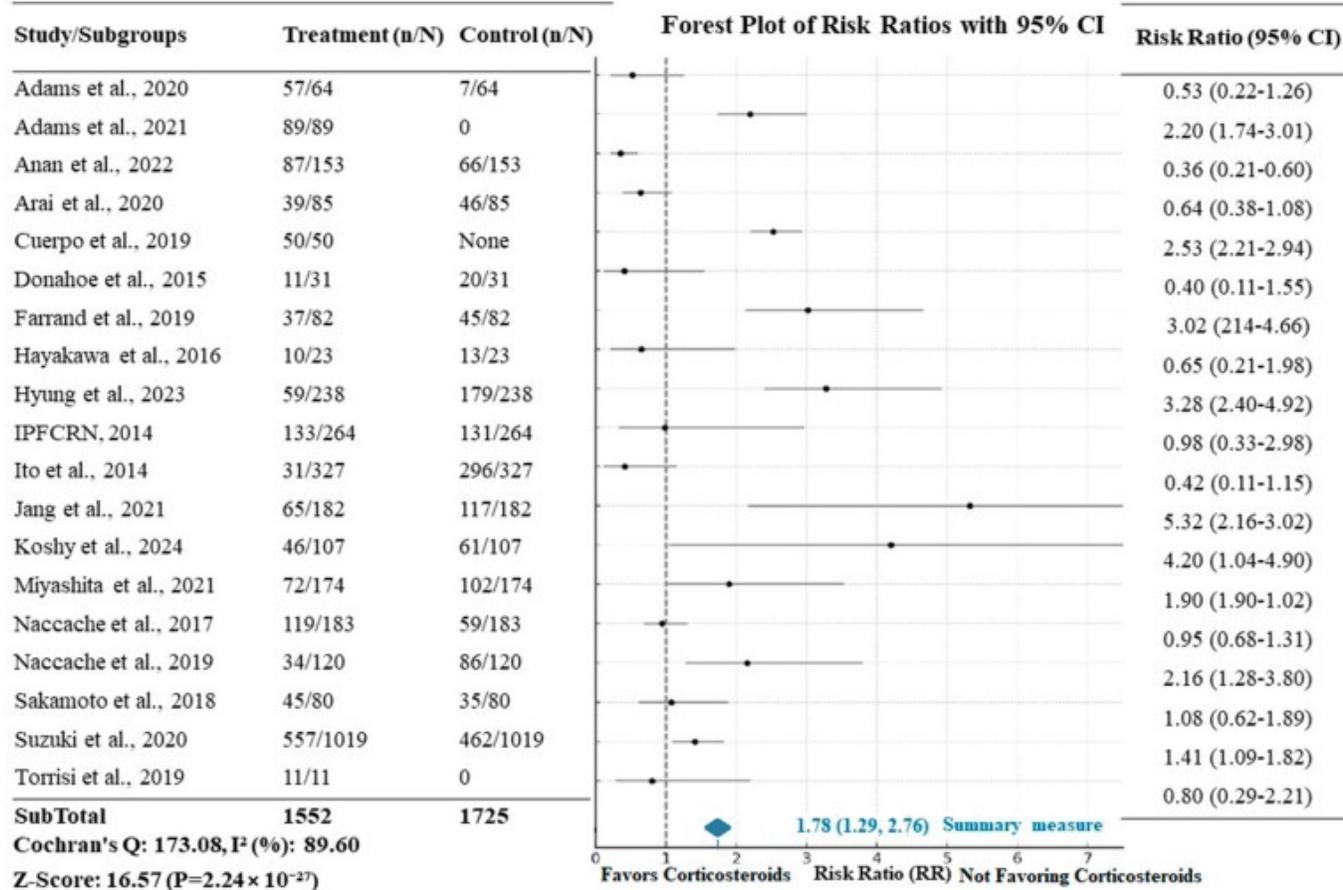
## Standardized protocol for AE-ILD

3 days 0.5-1g methylprednisolone; 4 days 1mg/kg prednisone



# Steroids may be harmful in AE-IPF

## Meta-analysis 2014-2024



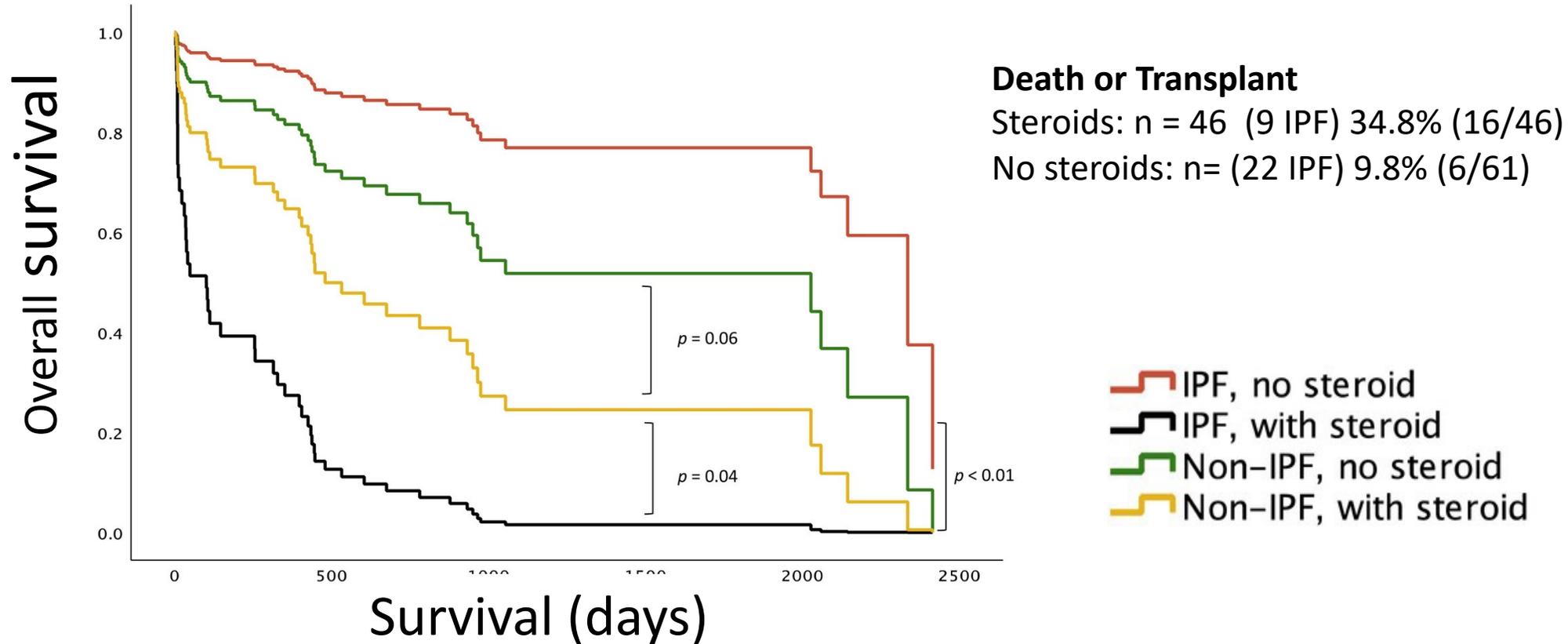
1552 patients receiving steroid vs 1725 control

**RR 1.78 for death in steroid group**

# Steroids might be associated with worse outcomes

Retrospective review 2 Australian centers 2010-2020

107 cases AE-ILD; 31 IPF, 76 non IPF



# Trials of corticosteroids in AE-IPF

Completed 

## Efficacy of Steroid Pulse Therapy in Acute Exacerbation of Idiopathic Pulmonary Fibrosis (AE-IPF) Admitted in ER

ClinicalTrials.gov ID  [NCT04996303](#)

Sponsor  Yonsei University

Information provided by  Yonsei University (Responsible Party)

Last Update Posted  2024-07-26

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Recruiting 

## Glucocorticoids Versus Placebo for the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis (EXAFIP2)

ClinicalTrials.gov ID  [NCT05674994](#)

Sponsor  Fondation Hôpital Saint-Joseph

Information provided by  Fondation Hôpital Saint-Joseph (Responsible Party)

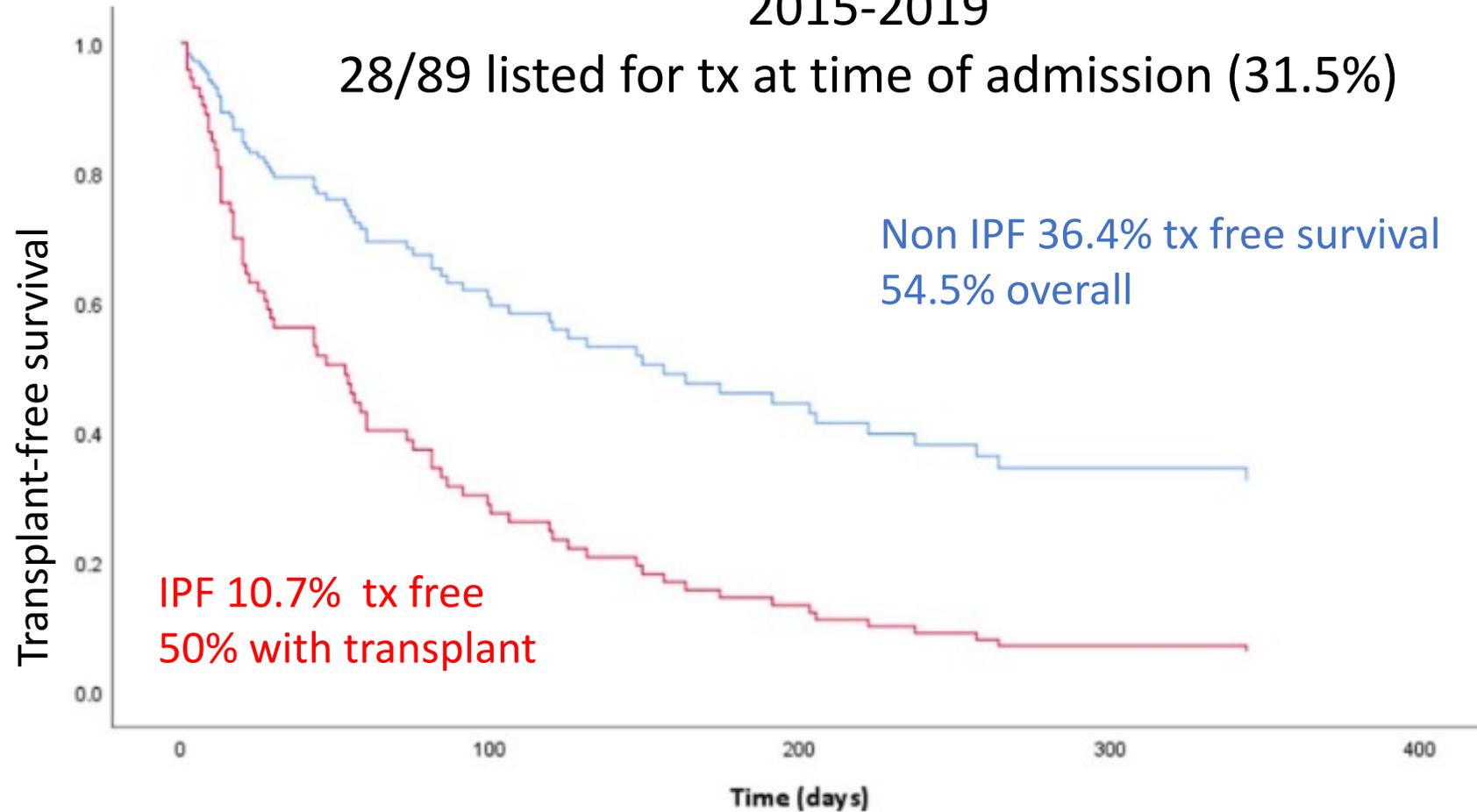
Last Update Posted  2023-12-15



# Transplant as treatment for AE-ILD

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

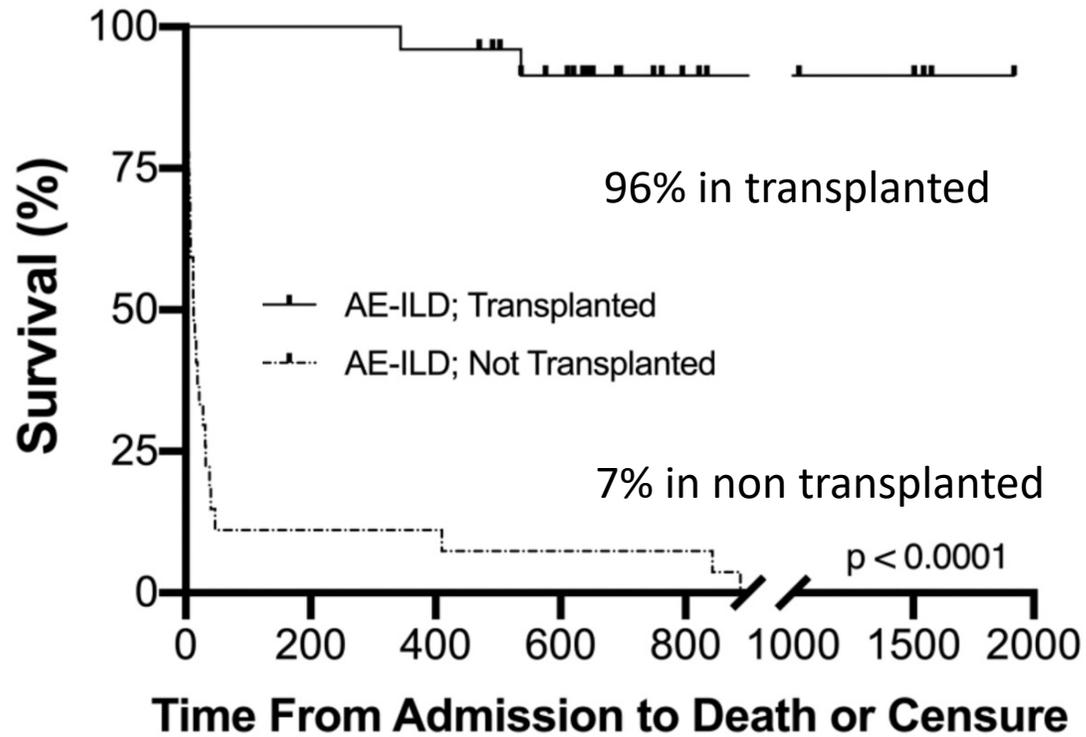
28/89 listed for tx at time of admission (31.5%)



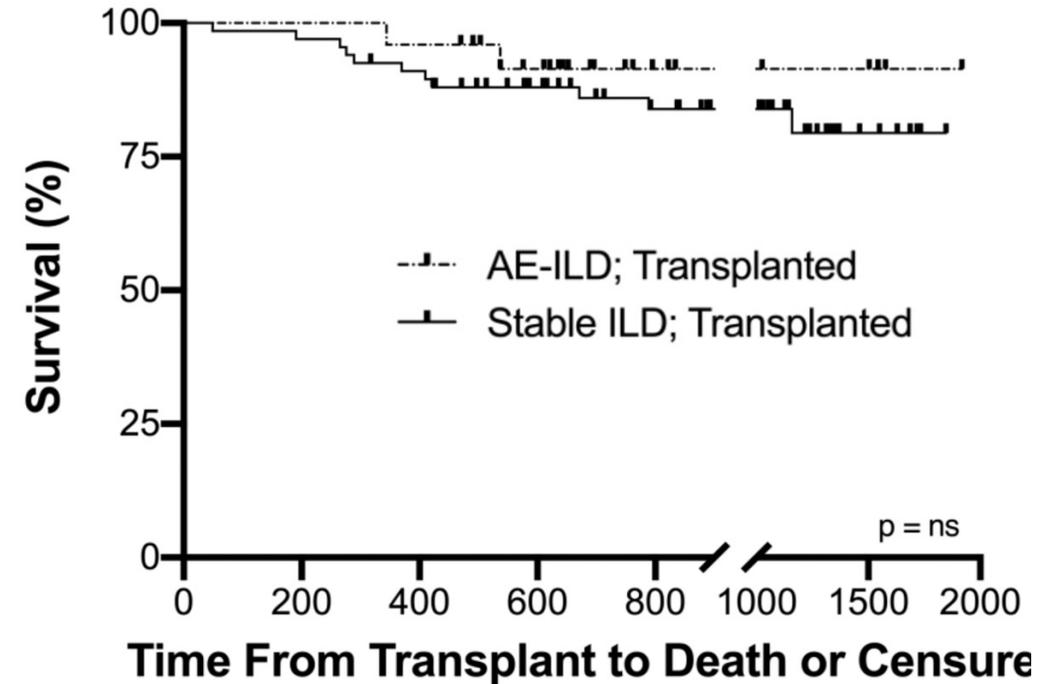
# Transplant as treatment for AE-ILD

53 patients admitted to U Florida 2015-2018  
18 emergently listed; 9 listed prior to AE

One year Survival Transplanted vs. Not

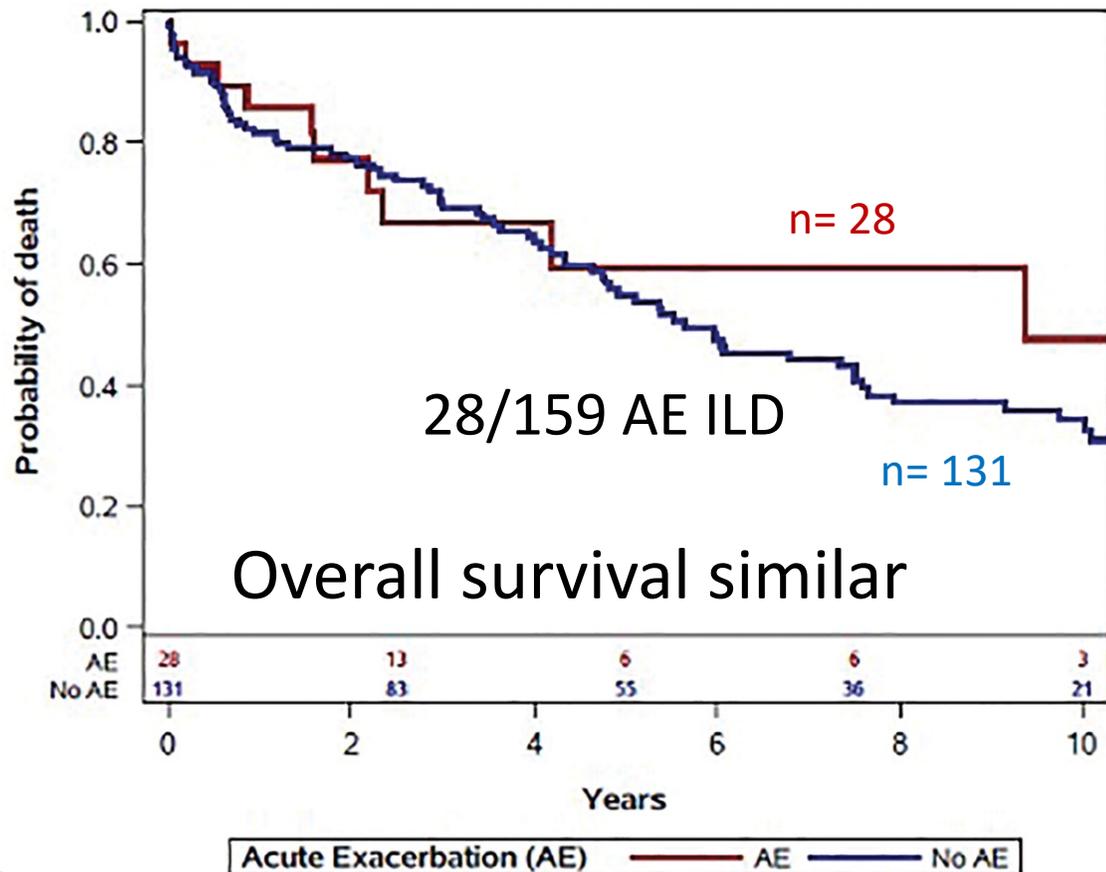


Survival AE-ILD vs stable ILD

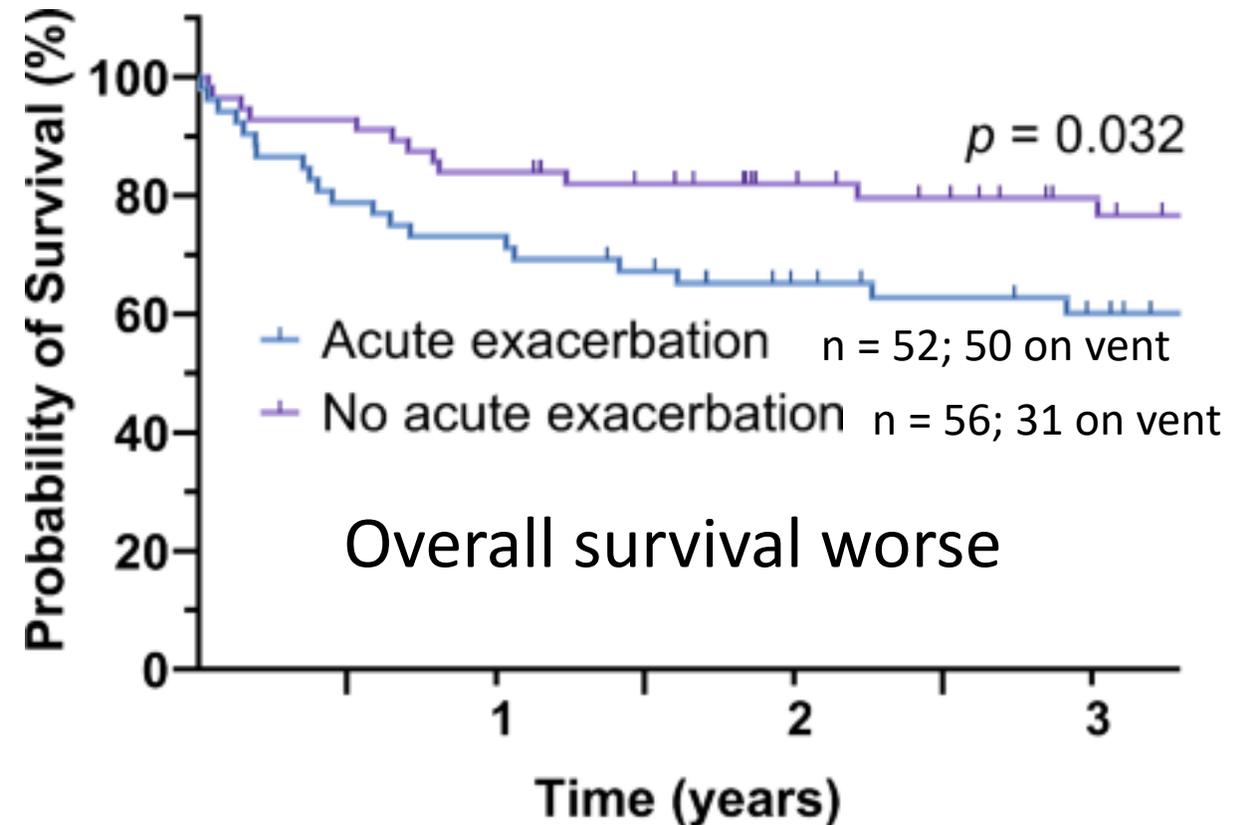


# AE-ILD vs stable ILD Post Transplant

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



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

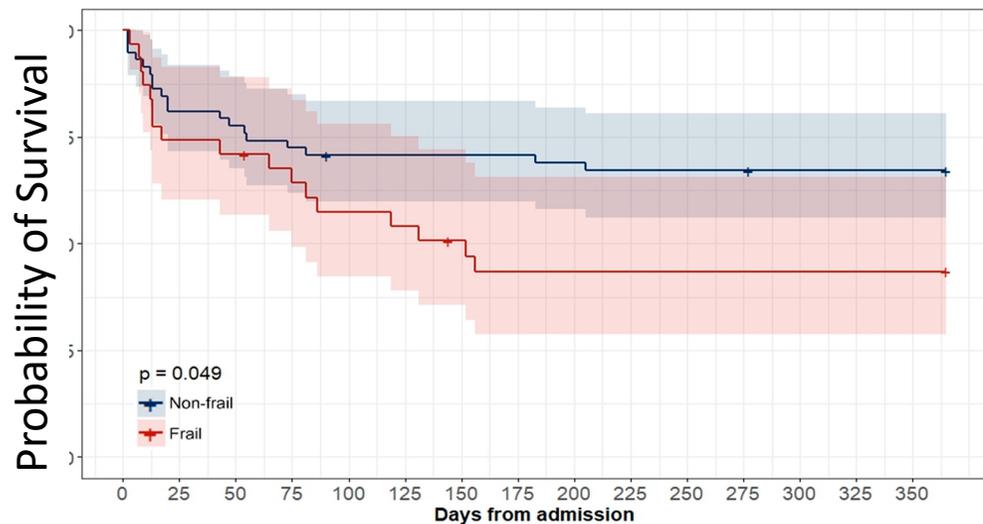


# Frailty, transplant, and survival after AE-ILD

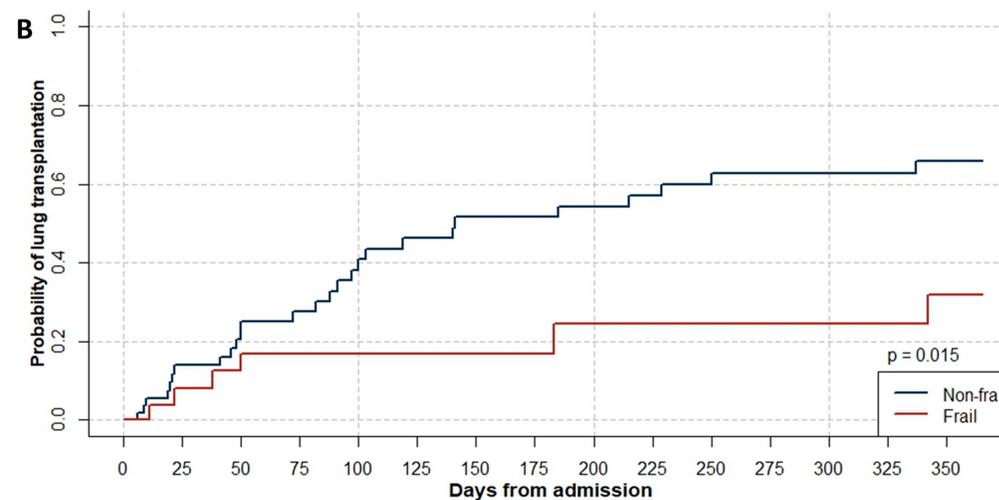
89 patients admitted to U Toronto with AE-ILD 1/2015-10/2019

Survival post admission

**35% of AE-ILD were frail; 22% mortality overall**



Probability of Transplant



# Take home messages

- All fibrotic ILDs can have exacerbations
- IPF, more advanced disease get sicker
- Probably not steroid responsive in IPF
- Likely better outcome if steroid responsive
- Cyclophosphamide and thrombomodulin not helpful
- Ongoing trials for steroids, IVIG, and combined antibody reduction
- Consider transplant watching by frailty



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