Acute Exacerbations of ILD

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Disclosures

On the basis of our experience and available data, we do not have sufficient evidence to propose a treatment strategy in AE-IPF at this time.

Overview

Epidemiology

Presentation

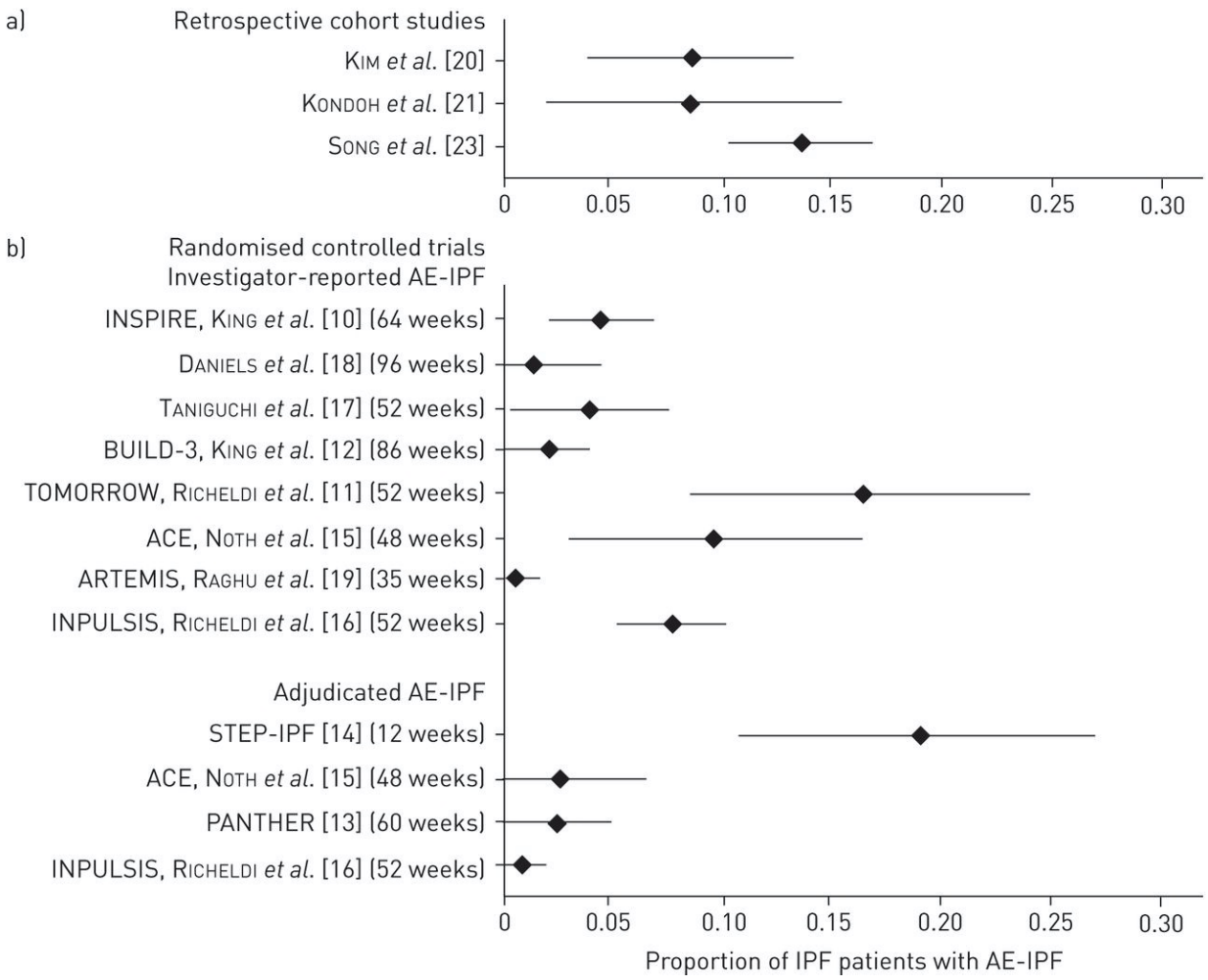
Definitions and testing

Prognosis

Treatment

Acute unexplained worsening in IPF

In IPF clinical trials proportion of patients with acute exacerbation (AE) ranges 5-20%



Ryerson CJ, Cottin V, Brown KK, Collard HR. Eur Respir J. 2015 Aug;46(2):512-20.
PMID: 26232481

Definitions

Defined in 2007

Revised by 2016 working group

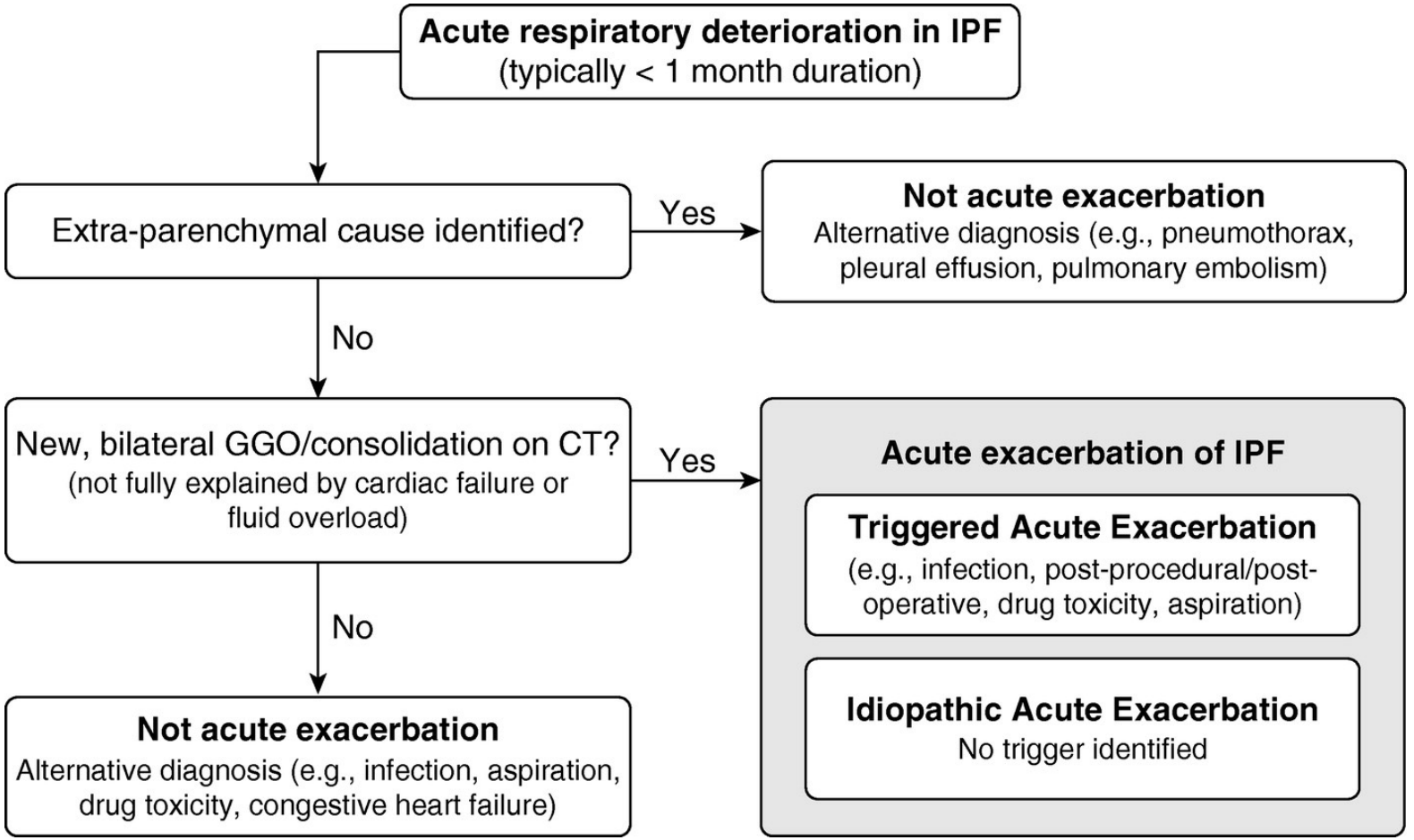
- Previous or concurrent diagnosis of IPF
- Acute worsening or development of dyspnea **within 1 month**
- CT with **new** bilateral ground-glass opacity and/or consolidation on a background pattern with usual interstitial pneumonia pattern
- Deterioration not fully explained by cardiac failure or fluid overload

- **Includes "triggered" exacerbations i.e. infection**

Kondoh et al Chest 1993 Jun;103(6):1808-12.
Collard HR, ,Moore BB, Flaherty KR, 2007; **176**: 636–643

Collard HR, Ryerson CJ, Corte TJ, et al. *Am J Respir Crit Care Med 2016; 194: 265–275*

Diagnosis of AE-IPF



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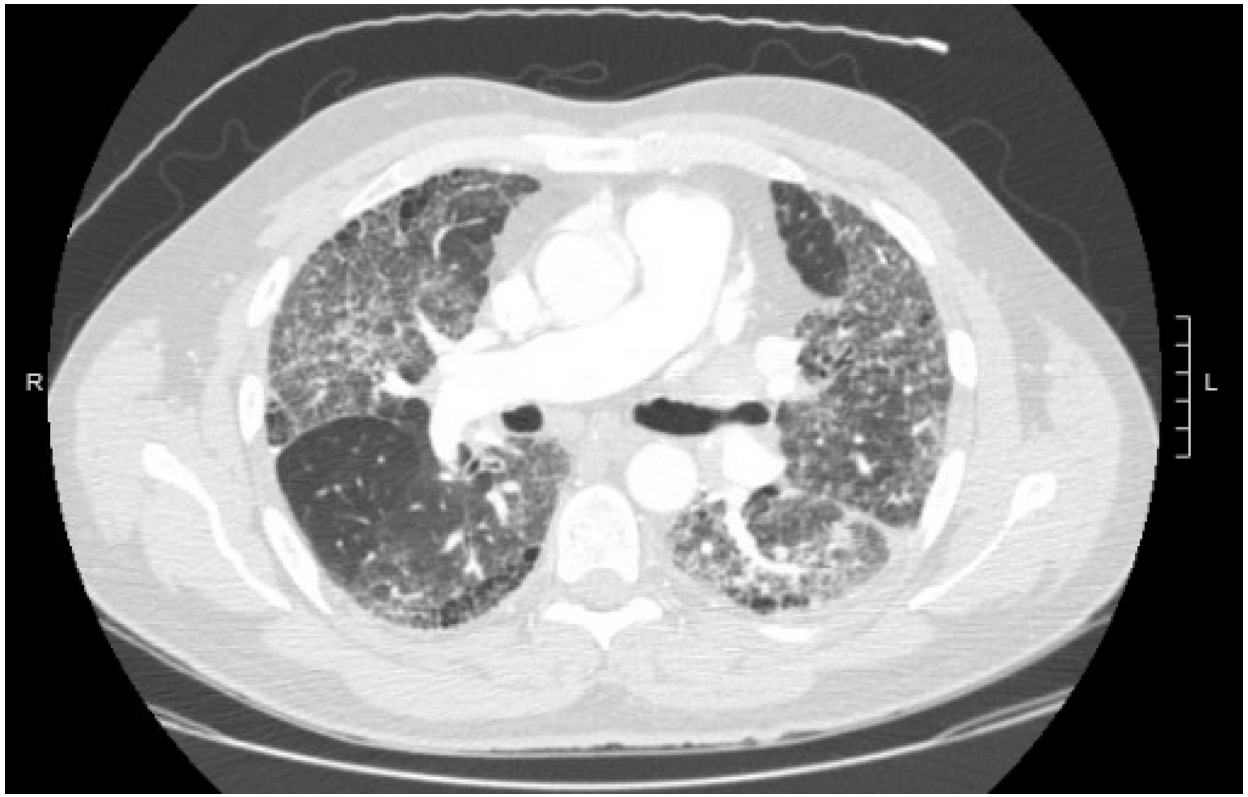
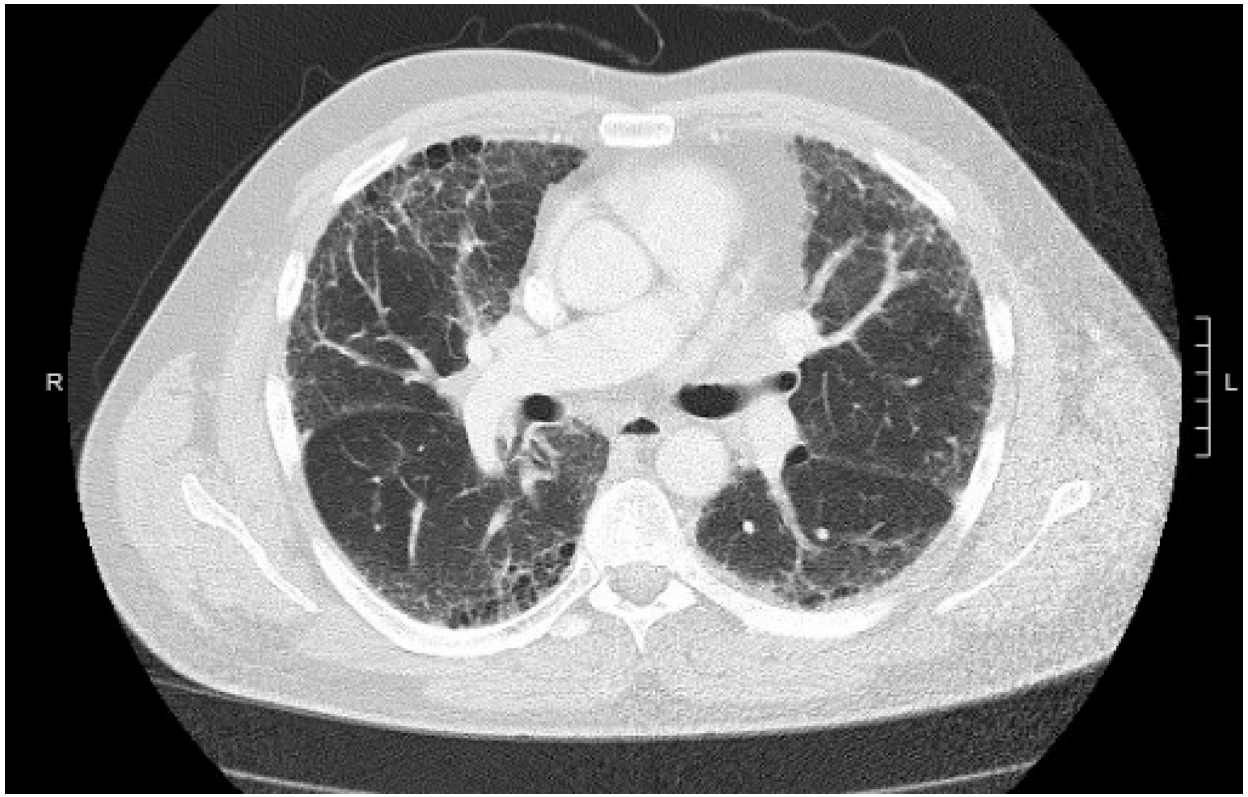
Acute Exacerbations of ILD



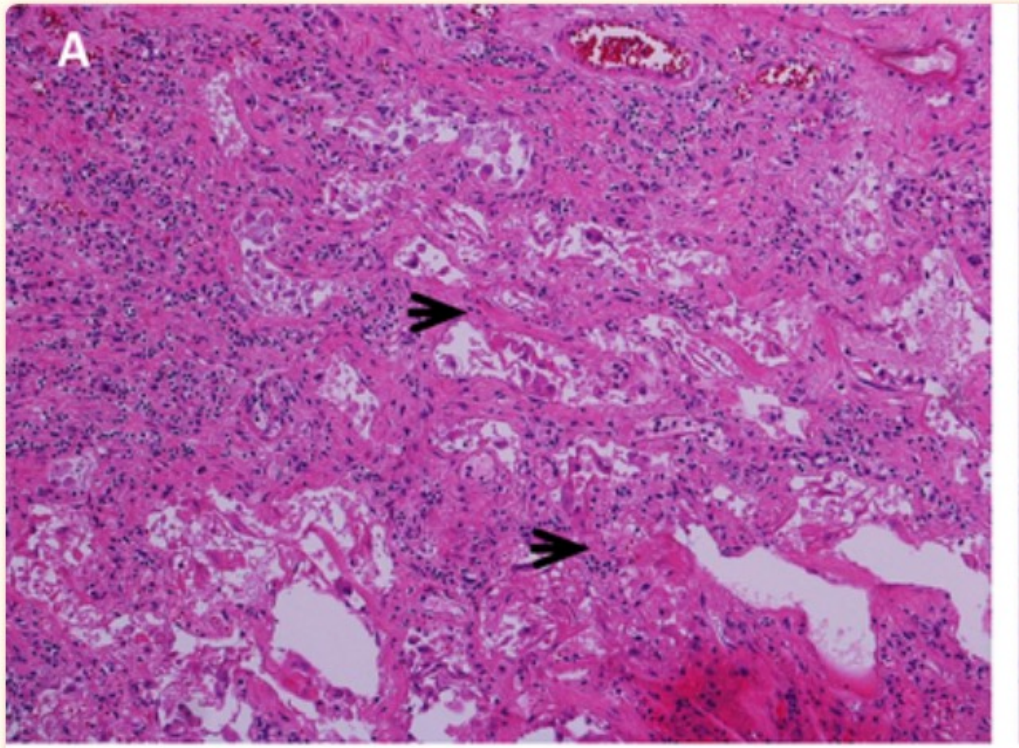
January – acutely worsened hypoxia



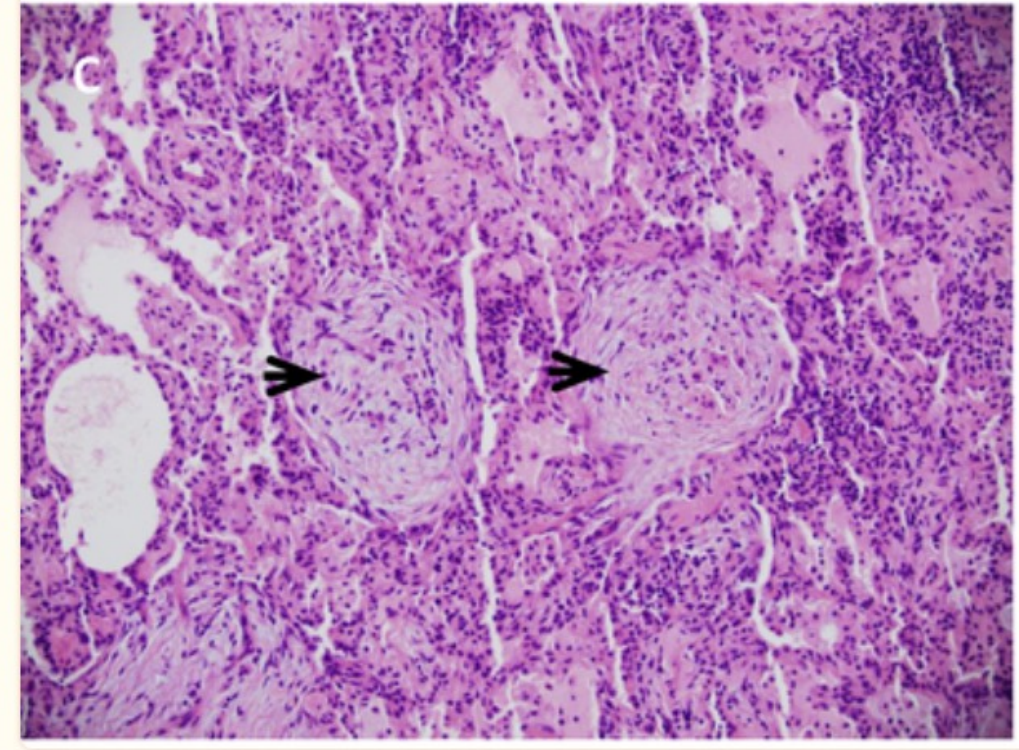
Prior November – stable exertional dyspnea

Acute Exacerbations

IPF with diffuse alveolar damage
Arrows showing hyaline membranes



Fibrotic NSIP with organizing pneumonia
Arrows on luminal fibroblastic plugs



Kershaw et al Respir Med. 2021 Jul; 183: 106400.

Acute Exacerbations of ILD

About half with attributable trigger

Cited mortality varies

- 2017 review of recent case series – in-hospital survival ~33%
- AE attribution as cause of death ranges 19 -40%

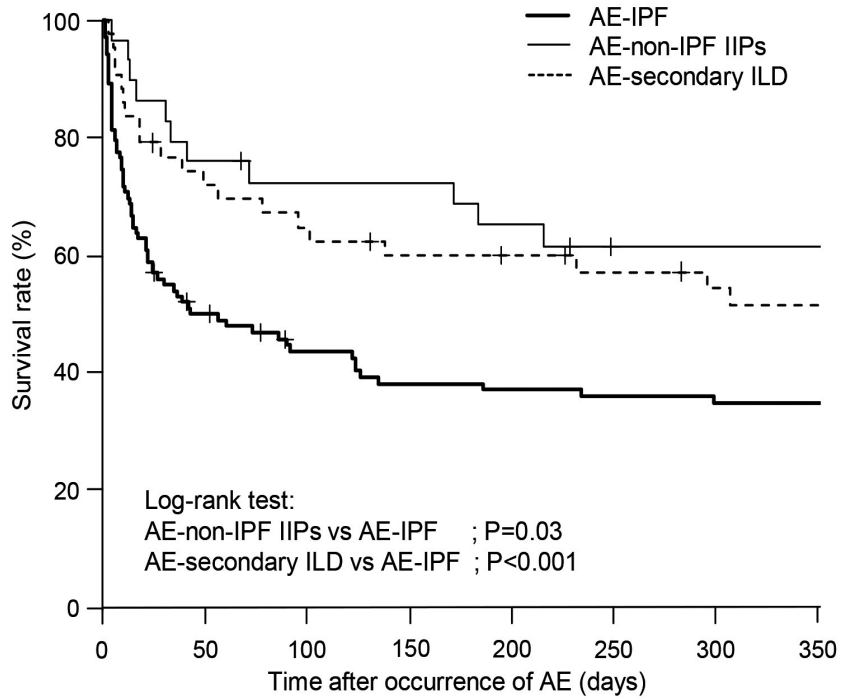
Well described in non-IPF ILD

- Appears less common than in IPF
- Increased if worse disease by PFTs
- Increased in CTD-ILD, HP with UIP pattern

Yasuhiro Kondoh, Vincent Cottin, Kevin K. Brown
European Respiratory Review 2017 26:
Kershaw et al. Respir Med. 2021 Jul; 183: 106400.

Worse survival in AE in IPF

174 patients with AE of ILD in Hamamastu 2002-2015

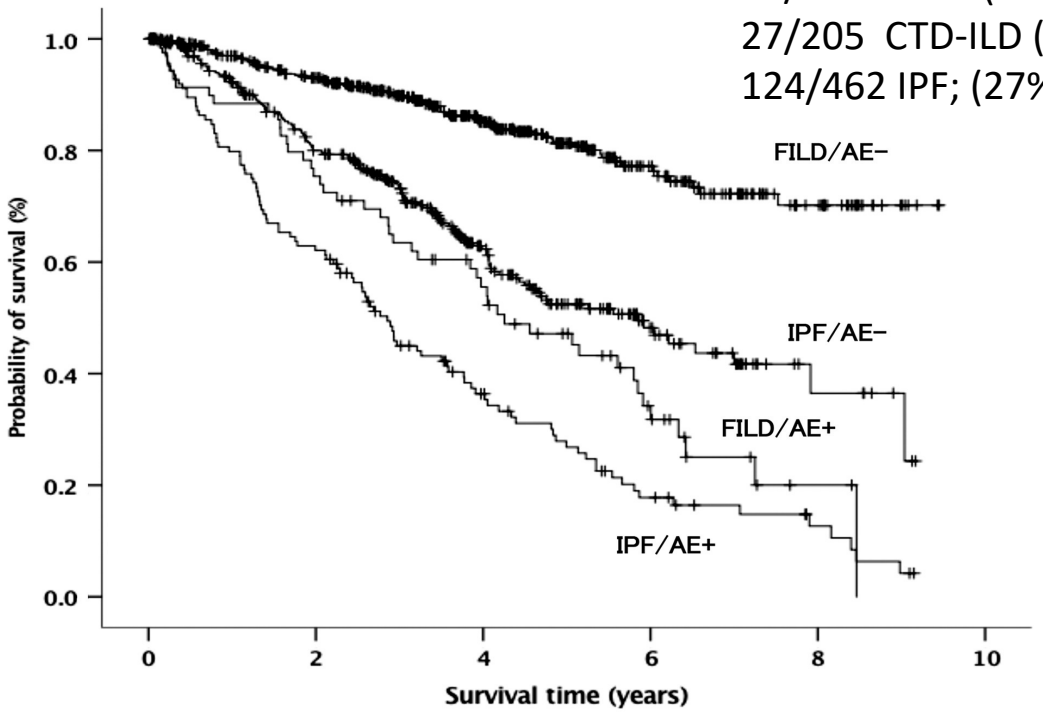


No. at risk

AE-IPF	102	49	40	35	34	33	32	32
AE-non-IPF IIPs	29	22	20	20	18	15	15	15
AE-secondary ILD	43	30	27	24	23	21	19	18

1070 patients; 193 with AE-ILD (2008-2015)

69/ 557 F-ILD (12%)
27/205 CTD-ILD (13%)
124/462 IPF; (27%)



Number at risk

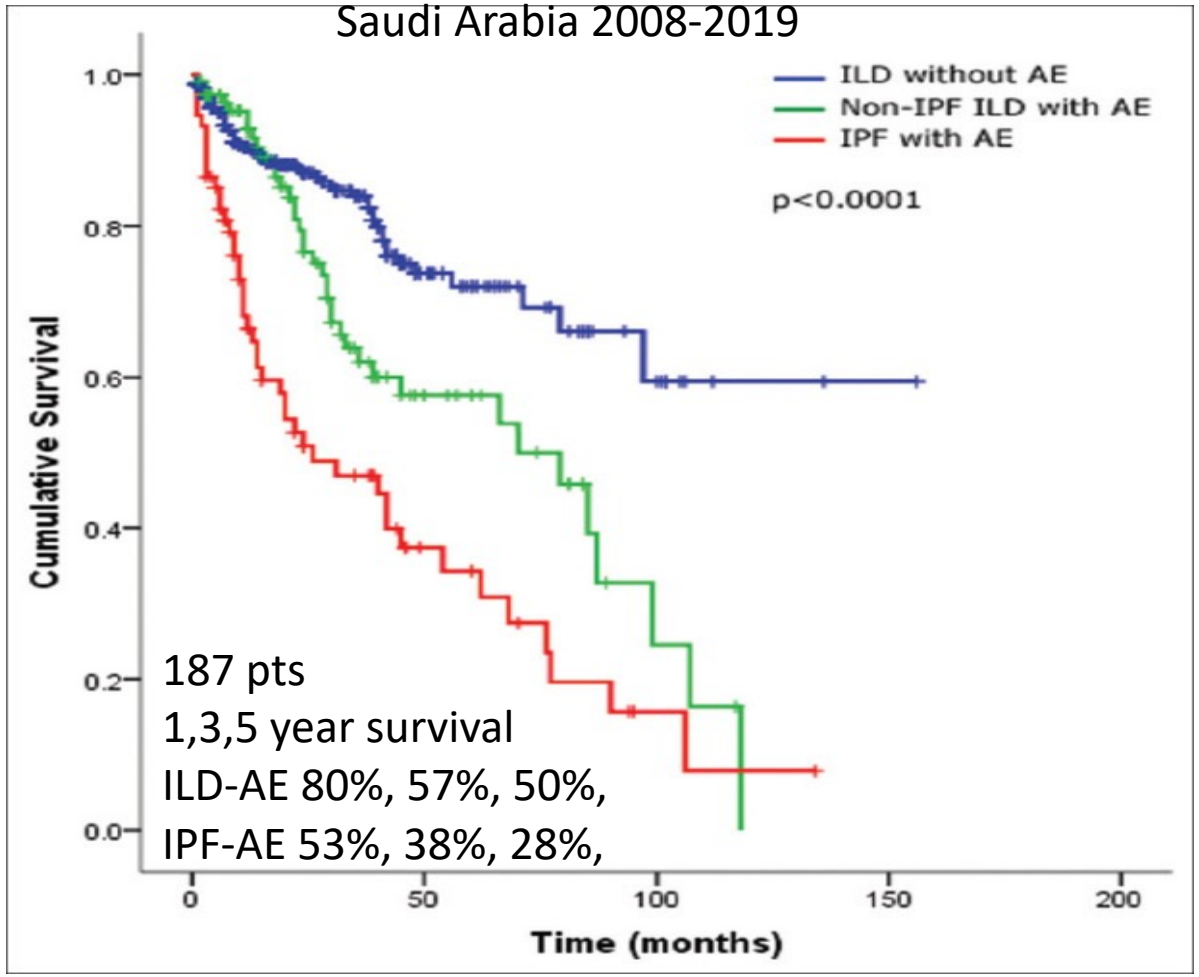
FILD/AE−	488	387	217	88	29
IPF/AE−	338	230	110	37	7
FILD/AE+	69	52	34	14	2
IPF/AE+	124	77	36	15	6

Miyashita et al. Clin Respir J 2021 Mar;15(3):336-344

Suzuki et al Respirology 2020 May;25(5):525-534 PMID: **31426125**

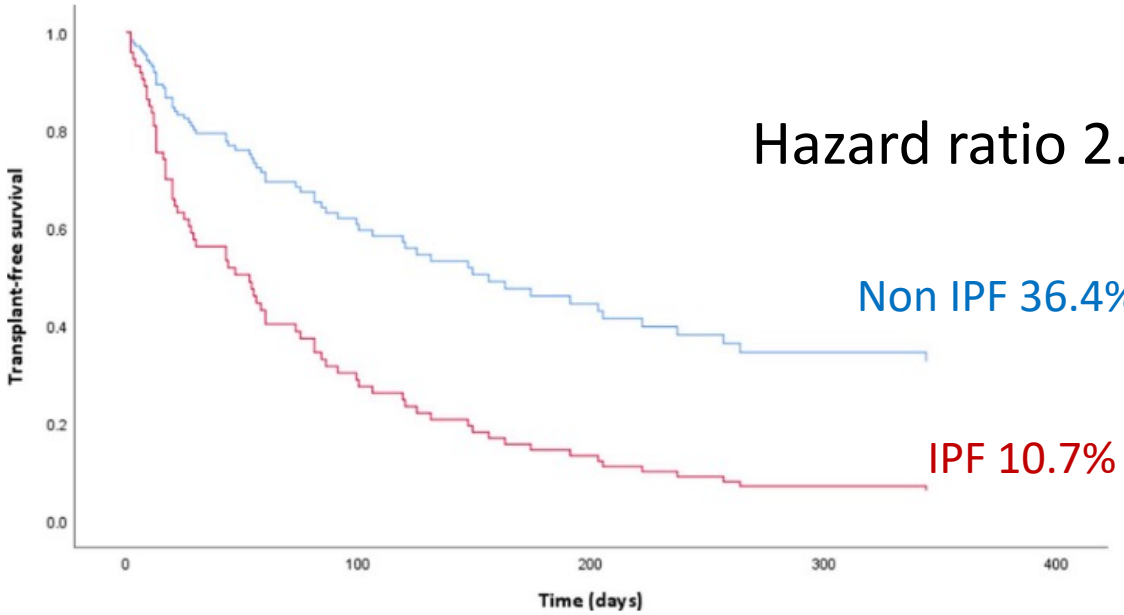
Worse survival in AE in IPF

Saudi Arabia 2008-2019



187 pts
1,3,5 year survival
ILD-AE 80%, 57%, 50%,
IPF-AE 53%, 38%, 28%,

Toronto 2015-2019



Hazard ratio 2.49

Non IPF 36.4%

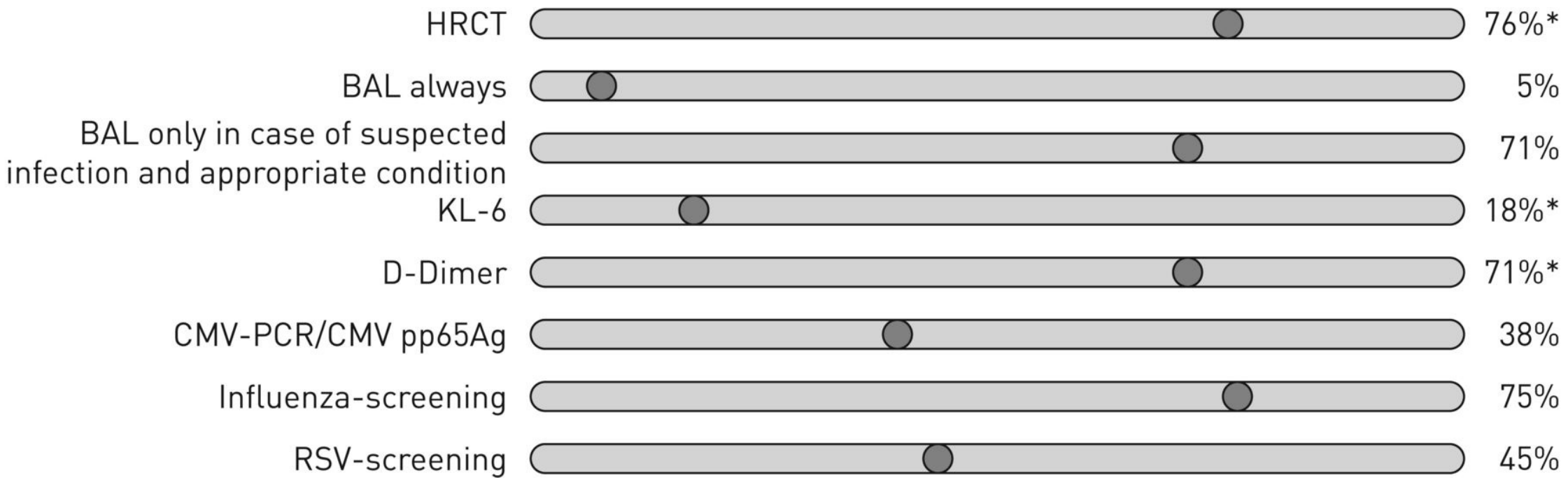
IPF 10.7%

89 patients admitted with AE-ILD in
1-year transplant-free survival 20.2%

Adams et al. Lung (2021) 199:379–38.
Alhamad Ann Thorac Med 2021 Apr-Jun;16(2):178-187.

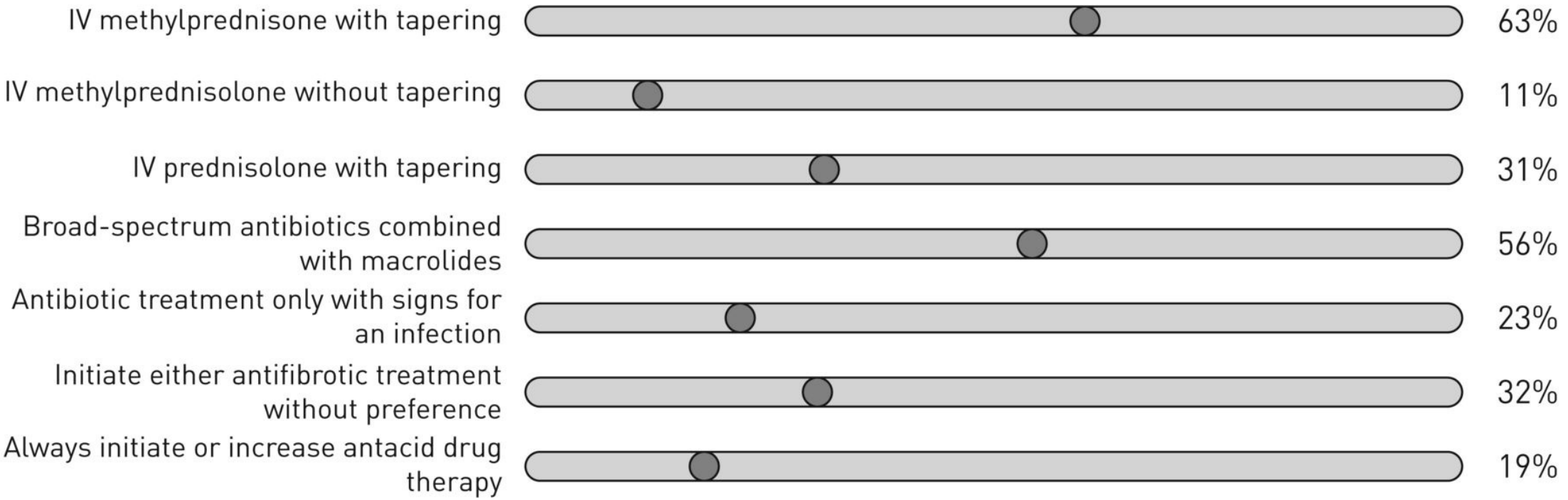
Practice patterns in AE-ILD: testing

International survey of 509 pulmonologists, 66 countries

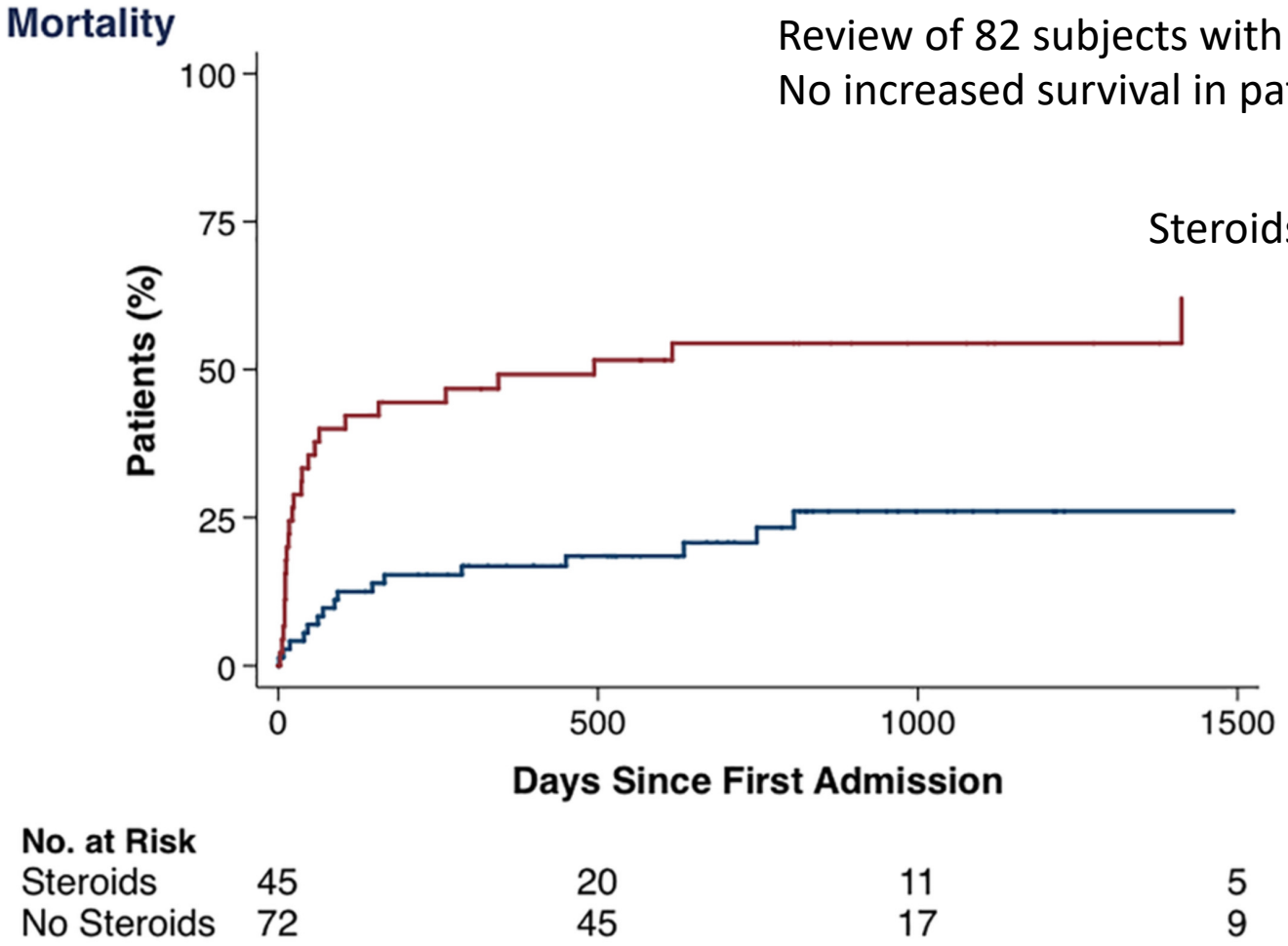


KL-6 testing overall 18%; 4% in North America 51% in Asia

Practice patterns in AE-ILD: treatment



Treatment controversies: steroids



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

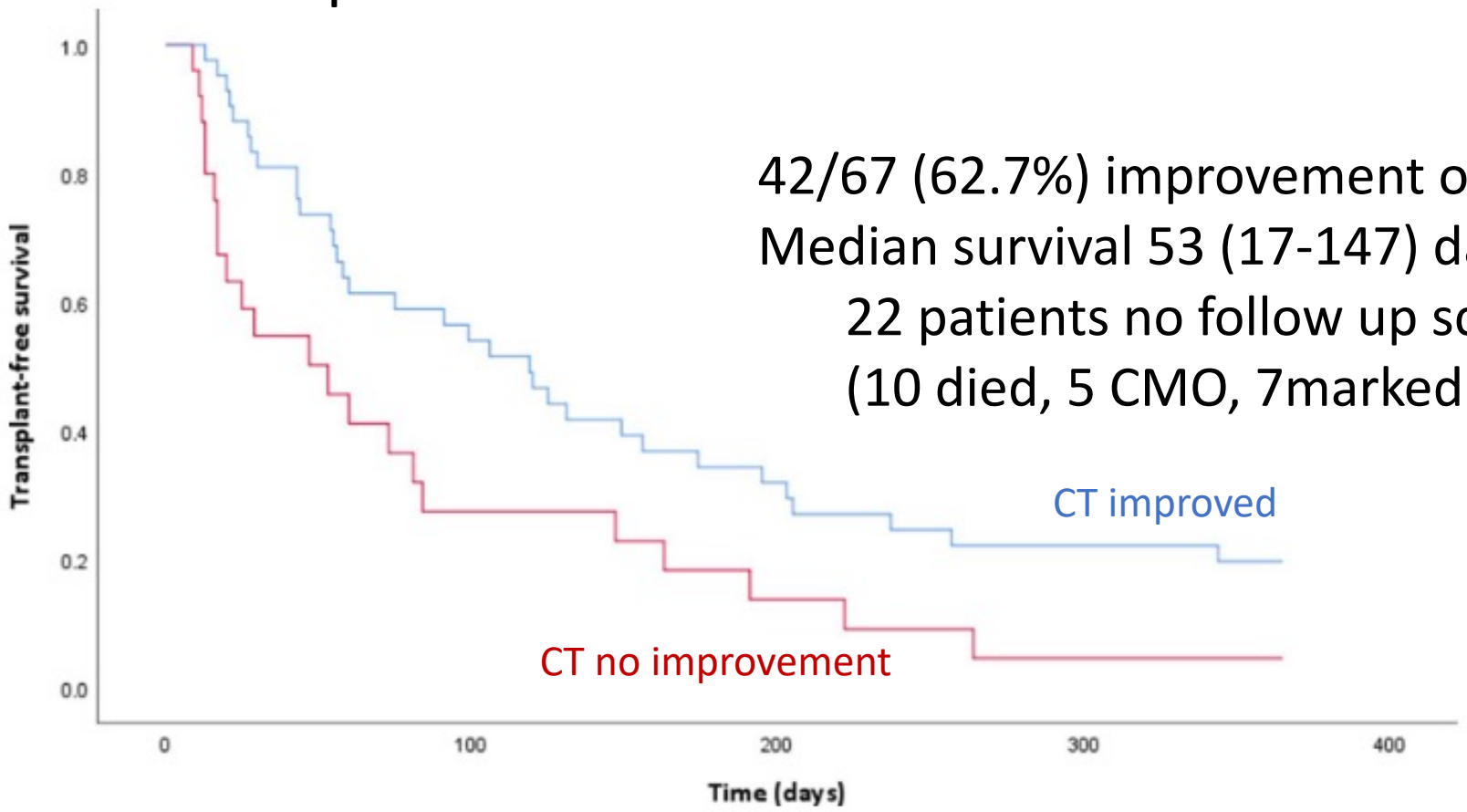
Steroids

No Steroids

Papiris et al Front Pharmacol 2022 Apr 14;13:836553
Farrand,et al. *Respirology* 25, 629–635.

Steroid responsiveness and outcome

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



42/67 (62.7%) improvement on 7 day CT scan

Median survival 53 (17-147) days vs 119 (44-237) days

22 patients no follow up scan

(10 died, 5 CMO, 7markedly improved

Adams, Lung (2021) 199:379–387

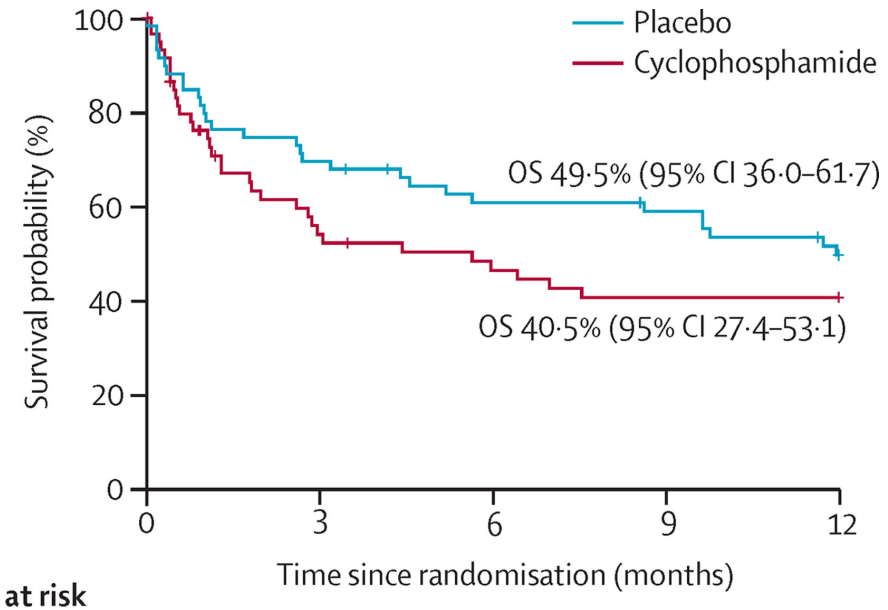
Treatment: Cyclophosphamide

Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomised, double-blind, placebo-controlled, phase 3 trial

Lancet Respir Med. 2022 Jan;10(1):26-34. Epub 2021 Sep 7.
PMID: 34506761

Cyclophosphamide: no improvement

119 patients randomized across 31 hospitals in France



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)

	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.

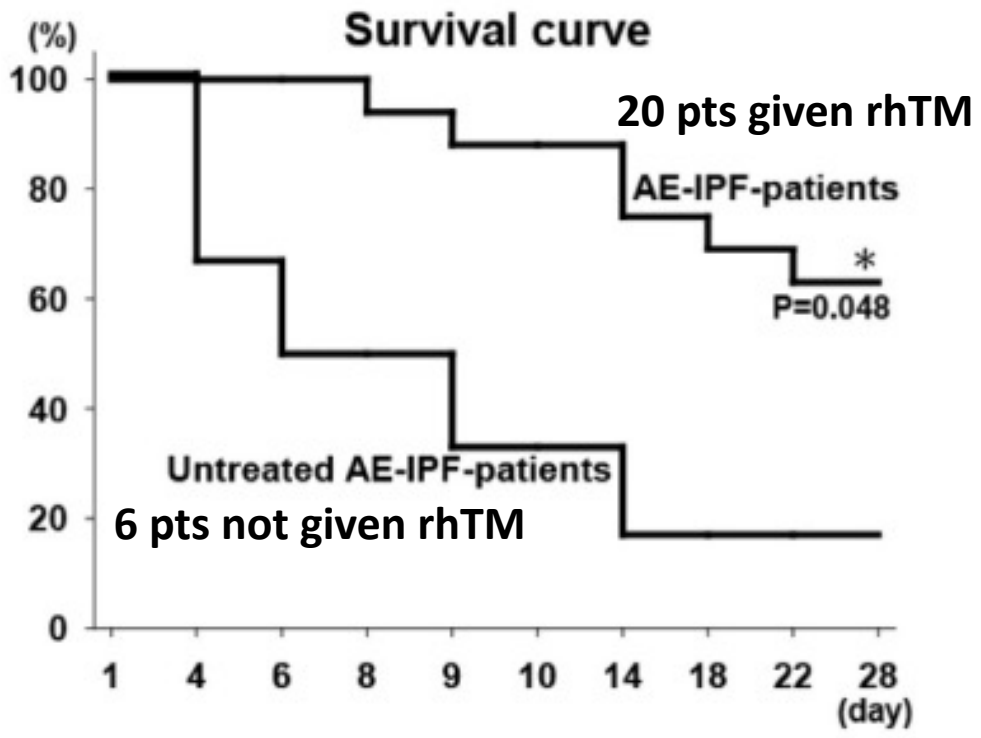
Table 2: **Primary outcomes**

Lancet Respir Med. 2022 Jan;10(1):26-34 Epub 2021 Sep 7.
PMID: 34506761

Other treatments: thrombomodulin

Thrombomodulin alpha – Anticoagulant approved in Japan for DIC

Binds to thrombin
Promotes protein C activation.
Inactivates activated factors V and VIII
Inhibits production of thrombin



Kondoh et al. Am J Respir Crit Care Med 2020 May 1;201(9):1110-1119.
Isshiki T, Sakamoto S, Homma S. Medicina (Kaunas). 2019 May 20;55(5):172.

Thrombomodulin no benefit in RCT

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

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

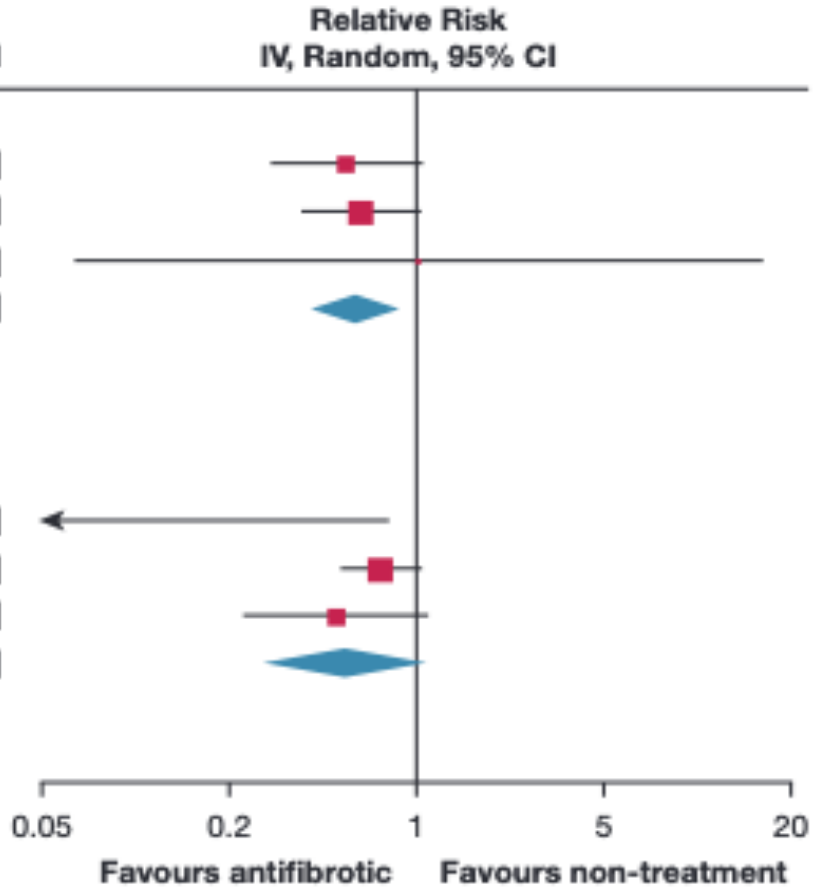
Kondoh et al. Am J Respir Crit Care Med 2020 May 1;201(9):1110-1119.
Isshiki T, Sakamoto S, Homma S. Medicina (Kaunas). 2019 May 20;55(5):172. K. Tsushima et al. / Pulmonary Pharmacology & Therapeutics 29 (2014) 233e240

Anti-fibrotic therapy may reduce AE

Pooled relative risk for acute exacerbation in subgroup analysis by antifibrotic

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: $Z = 1.62$ ($P = .10$)						

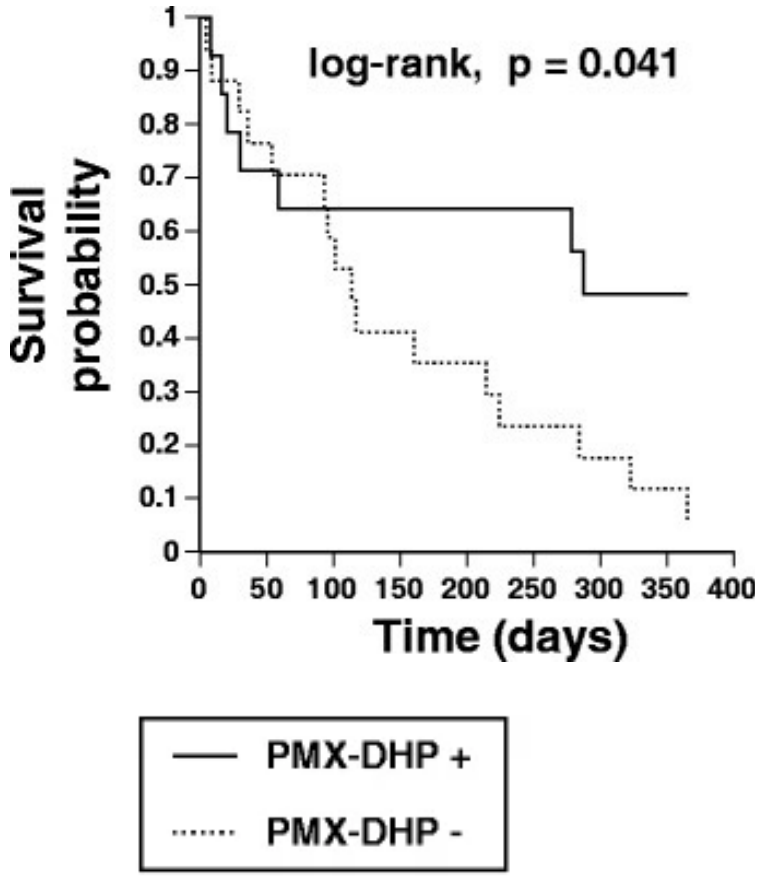
Test for subgroup differences: $\chi^2 = 0.04$, $df = 1$ ($P = .84$), $I^2 = 0\%$

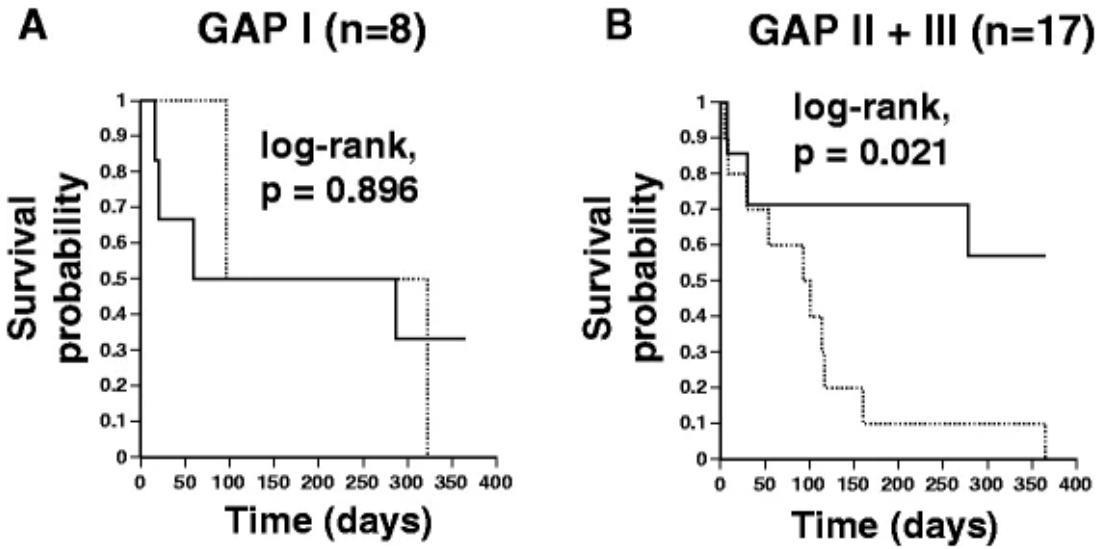


Petnak et al Chest 2021 Nov;160(5):1751-1763.
Urushiyama et al. ERJ Open Res. 2022 Oct; 8(4): 00209-2022.

Other treatments

Direct hemoperfusion with polymyxin B-immobilized fiber column (PMX-DHP)

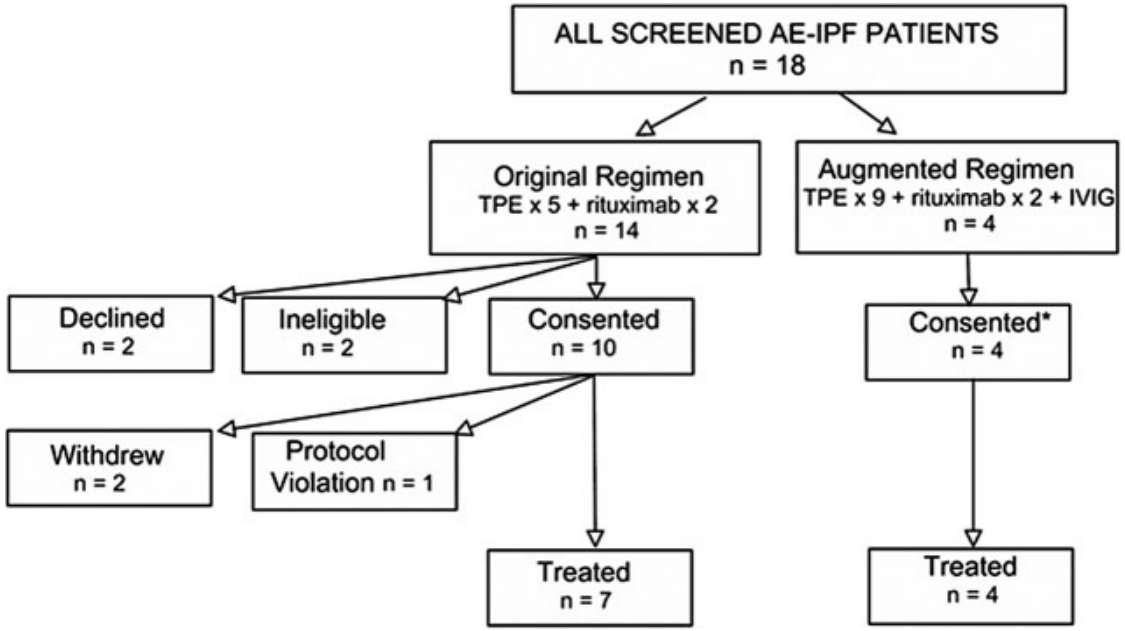




31 pts/41 episodes of AE-IPF; all given steroids
14 pts (20 episodes) treated with PMX-DHP.

Other treatments

Therapeutic plasma exchange, rituximab, IVIG



Pilot in 11 AE-IPF patients

No evidence of autoimmune disease

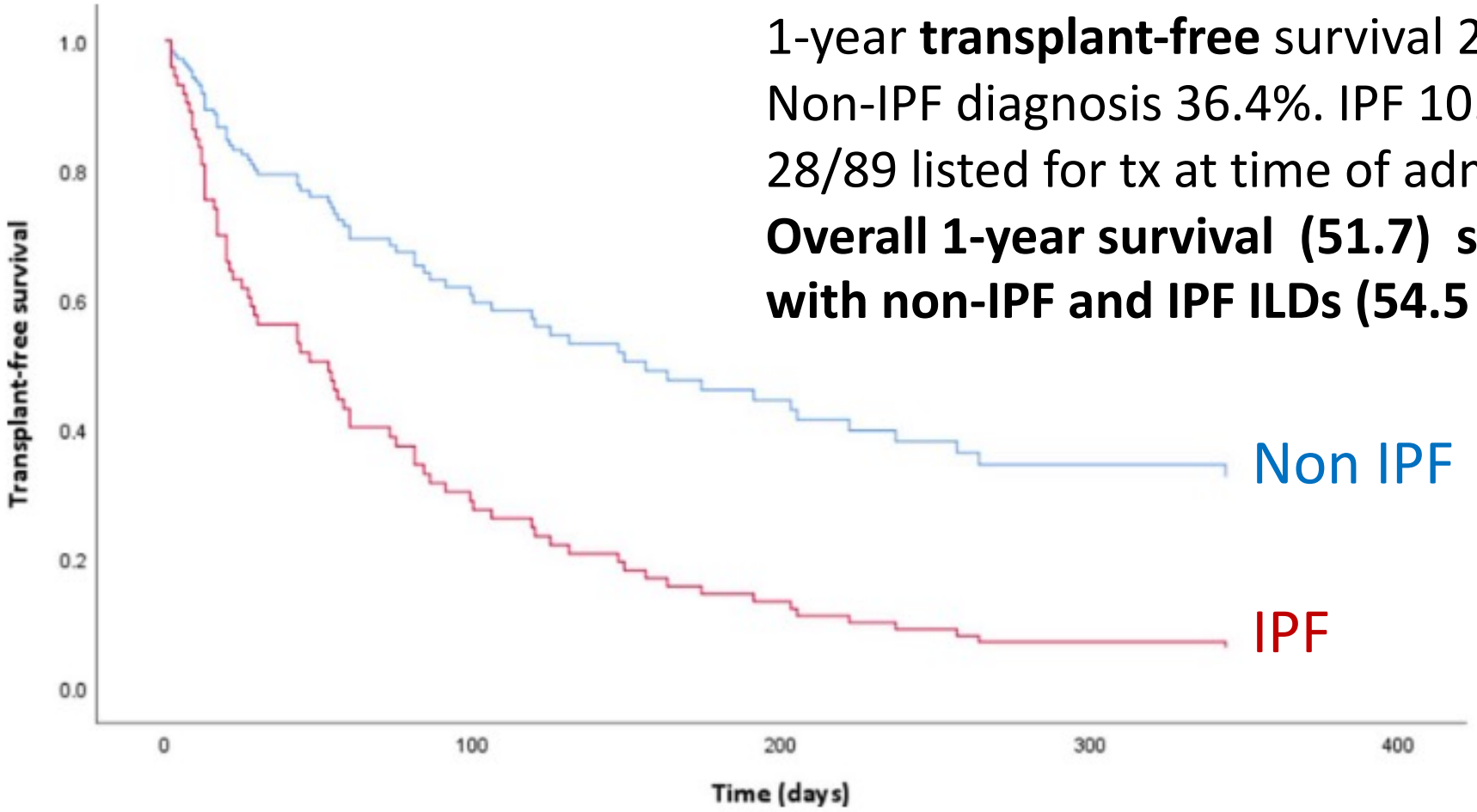
9 /11 improved gas exchange compared to 1/5 in historical conroals

One year survival 46.5% vs 0 in historical controls

No RCT data

Donahoe PLoS One. 2015; 10(6): e0127771.

Transplant helps survival in AE



89 AE-ILD in Toronto admitted 2015-2019
1-year **transplant-free** survival 20.2%
Non-IPF diagnosis 36.4%. IPF 10.7%
28/89 listed for tx at time of admission (31.5%)
Overall 1-year survival (51.7) similar in patients with non-IPF and IPF ILDs (54.5 vs 50.0%),

Adams et al. Lung (2021) 199:379–38.

Take home

All fibrotic ILDs can have exacerbations

Less common, better survival in non IPF

Unclear if steroids help

Cyclophosphamide and thrombomodulin did not work

Early repeat CT may help prognosticate