인제대학교
INJE UNIVERSITY

Does High-Dose Steroid Therapy Improve Prognosis in Acute Exacerbation of ILD? 2. Con

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Acute exacerbation of IPF

- Definition

An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality

- Diagnostic criteria

Previous or concurrent diagnosis of IPF

Acute worsening or development of dyspnea typically <1 mo duration

Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern

Deterioration not fully explained by cardiac failure or fluid overload

Collard HR et al. AJRCCM 2016;194(3):265-75

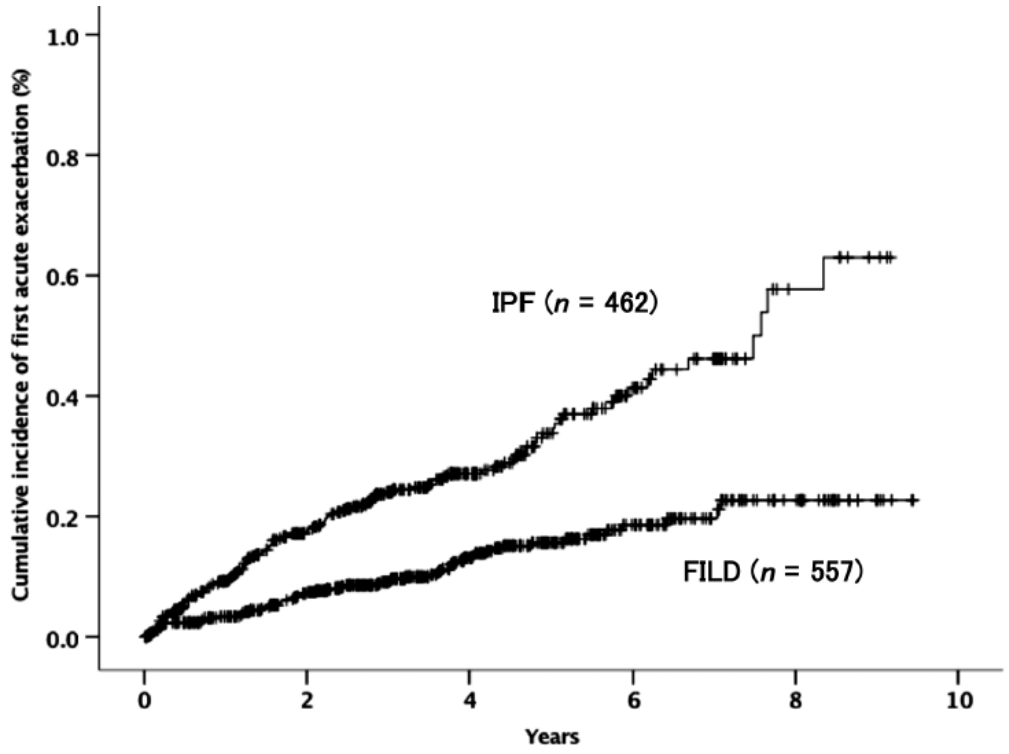
Table 2 | **Definitions and diagnostic criteria for acute exacerbation in IPF and in ILD in rheumatic disease**

Characteristic	Source of information		
	2007 definition of acute exacerbation in IPF[24]	**2016 definition of acute exacerbation in IPF**[27]	**2021 proposed definition of acute exacerbation in ILD in rheumatic disease**
Definition	An acute worsening of dyspnoea and lung function with an unidentifiable cause	An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality	An acute, clinically significant respiratory worsening characterized by new widespread alveolar abnormality in a patient with a known or concurrent diagnosis of rheumatic disease
Diagnostic criteria			
Disease	Previous or concurrent diagnosis of IPF	Previous or concurrent diagnosis of IPF	Rheumatic disease with previous or concurrent diagnosis of ILD
Symptoms	Unexplained worsening or development of dyspnoea <1 month duration	Acute worsening or development of dyspnoea typically <1 month duration	Acute worsening or development of dyspnoea typically <1 month duration
Imaging	HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with UIP	HRCT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern	HRCT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern of ILD
Infection	No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage	Not considered as an exclusion criterion for acute exacerbation	Not considered as an exclusion criterion for acute exacerbation
Triggers	Infections*, gastroesophageal reflux, microaspiration, surgery, bronchoscopy, air pollution	Infections*, gastroesophageal reflux, microaspiration, surgery, bronchoscopy, air pollution	Infections, opportunistic infections, DMARDs, gastroesophageal reflux, microaspiration, surgery, bronchoscopy, air pollution
Alternative causes	Exclusion of alternative causes, including the following: left heart failure, pulmonary embolism, identifiable causes of acute lung injury	Deterioration not fully explained by cardiac failure or fluid overload	Deterioration not fully explained by cardiac failure, fluid overload or DMARD use

*Opportunistic infections should always be considered. HRCT, high-resolution CT; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

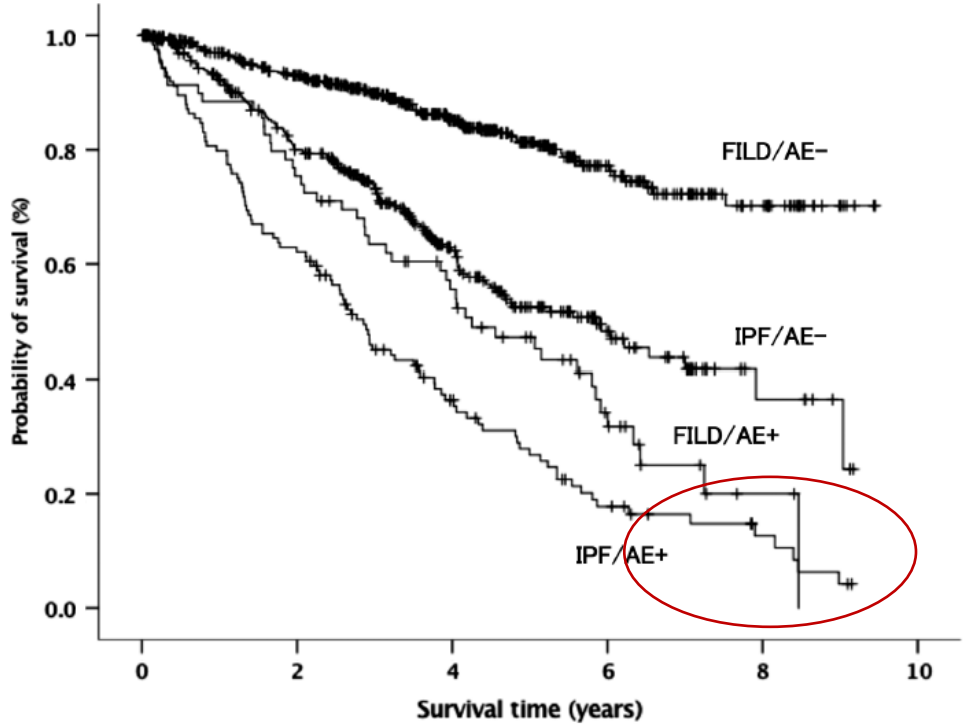
Acute exacerbation of IPF vs. fibrotic ILD

NSIP (n=22), fibrotic HP (n=29), CTD-ILD (n=205), unclassifiable ILD (n=209)



No. of patients (AE)										
IPF	0	40	71	92	99	109	117	120	123	124
FILD	0	18	36	44	56	62	66	67	69	69

The time to first AE was significantly longer in FILD than IPF

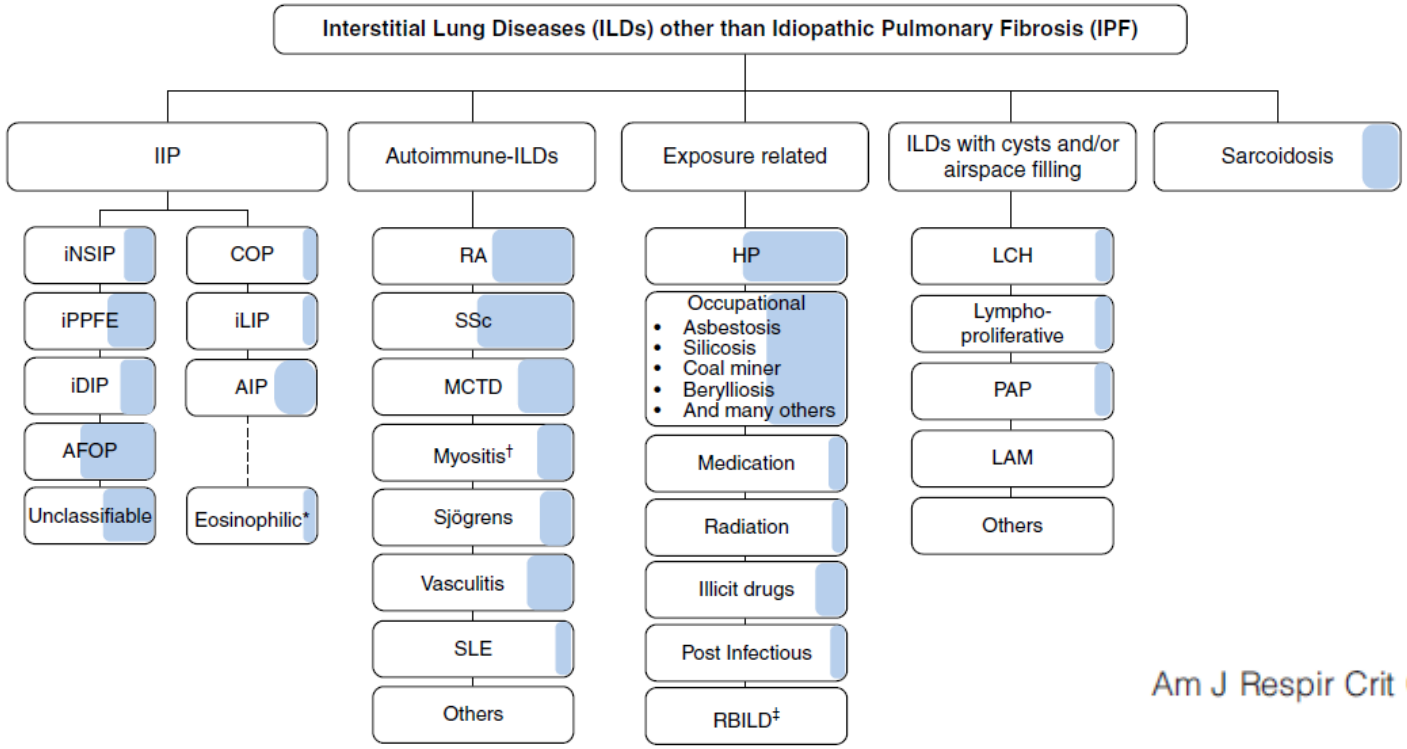


Number at risk					
FILD/AE−	488	387	217	88	29
IPF/AE−	338	230	110	37	7
FILD/AE+	69	52	34	14	2
IPF/AE+	124	77	36	15	6

Overall survival

Respirology (2020) **25**, 525–534

ILDs manifesting progressive pulmonary fibrosis



Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

Acute exacerbation of ILD

Exacerbation in patients with pre-existing IPF and other forms of fibrosing ILD

Respirology. 2024;29(9):747-50.

Acute exacerbation of idiopathic pulmonary fibrosis: international survey and call for harmonisation

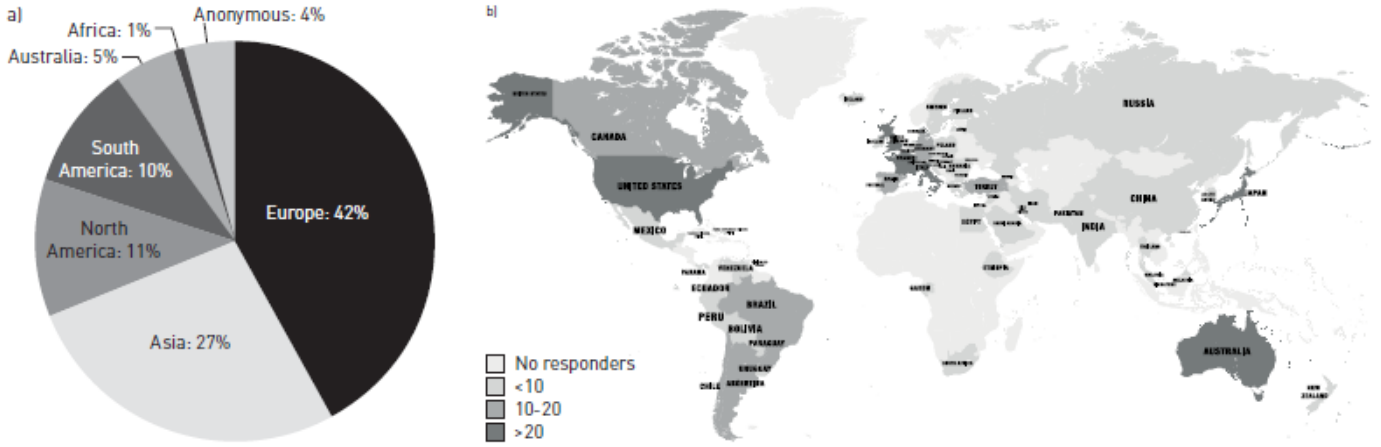


FIGURE 1 a) Participants (n=217 (42%) from Europe, n=136 (27%) from Asia, n=57 (11%) from North America, n=50 (10%) from South America, n=25 (5%) from Australia, n=5 (1%) from Africa and n=19 (4%) remained anonymous).

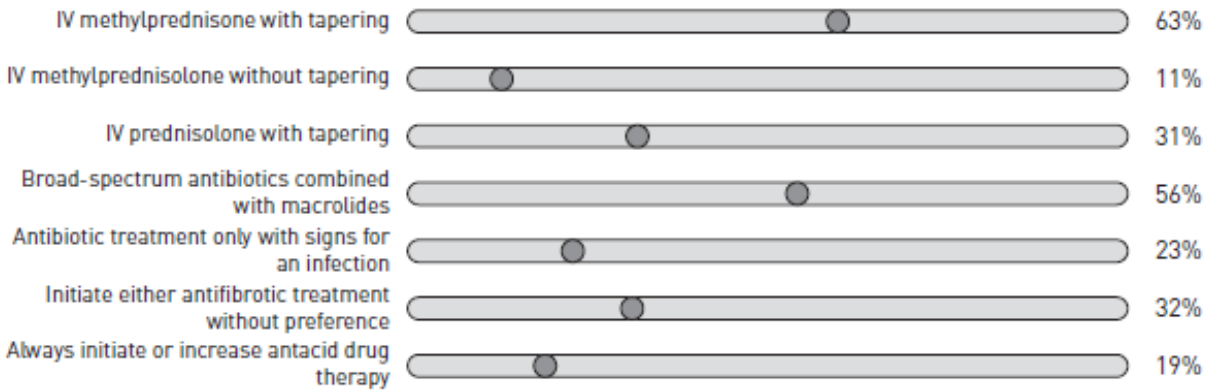


FIGURE 3 Main drug management approaches worldwide.

MPD 500-1000mg per day for 3 days followed by a slow tapering (63%)

Pulsed high dose steroids for 3 days only (11%)

Prednisolone with a dosage of 1 mg/kg per day followed by slow tapering (31%)

Eur Respir J 2020; 55: 1901760

Cons for high-dose steroid in AE-ILD

#1 Uncertainty of efficacy

#2 Heterogenicity of fibrotic ILDs

#3 Heterogenicity of causes (triggers)

#4 Heterogenicity of pathology

#5 Risk of side effects

Acute exacerbations of idiopathic pulmonary fibrosis: Does clinical stratification or steroid treatment matter?

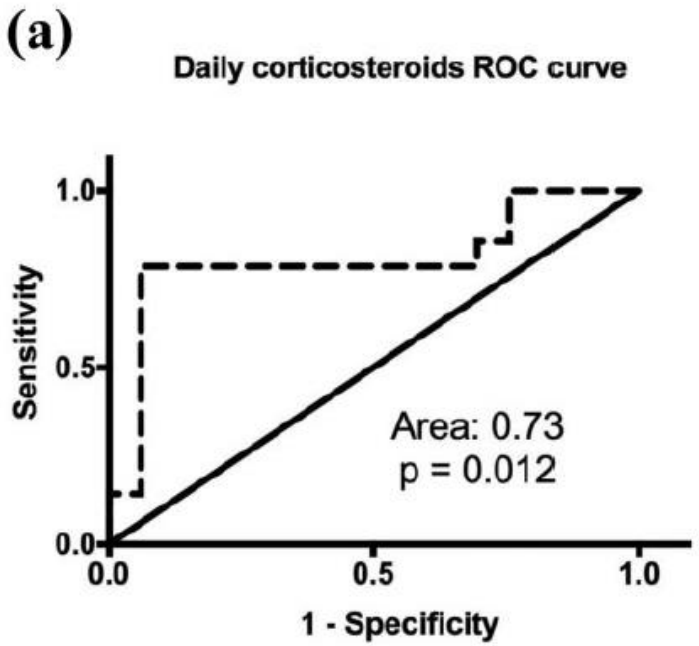
Sandra Cuerpo[1], Jorge Moisés[1], Fernanda Hernández-González[1], Mariana Benegas[2], Jose Ramirez[3], Marcelo Sánchez[2], Àlvar Agustí[1,4] and Jacobo Sellares[1,4]

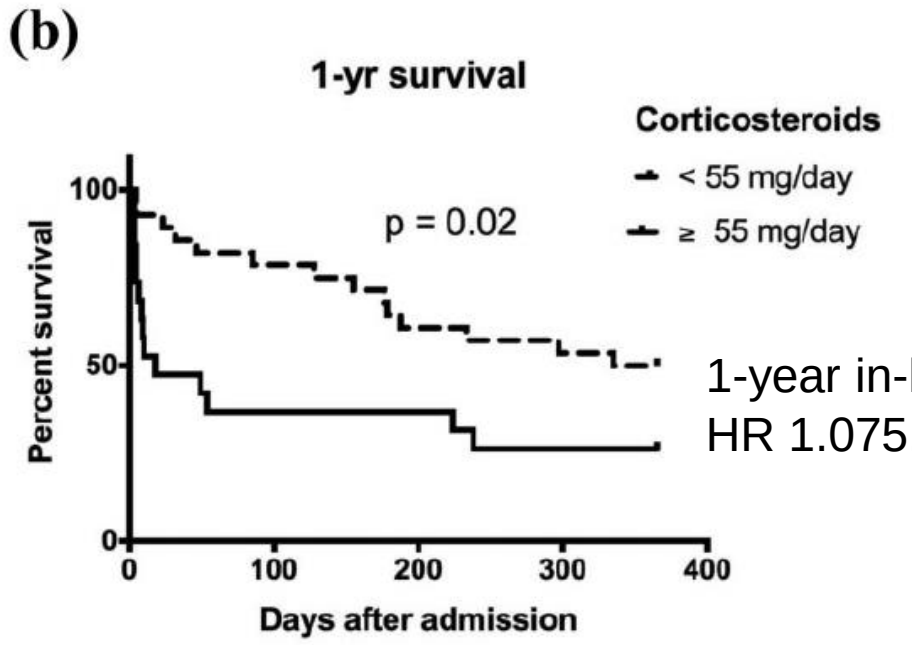
Chronic Respiratory Disease 2019
Volume 16: 1–8

50 patients

Table 4. Association between corticosteroids dose and in-hospital mortality.

	Dead	Alive	*p* Value
Average daily dose (mg/day), median (25th–75th percentile)	60 (52.5–60)	40 (25–55)	0.010
Length of treatment (days), mean ± SD	5.78 ± 4.33	7.30 ± 4.90	0.32
Total corticosteroid dose (mg), median (25th–75th percentile)	280 (110–450)	240 (9.5–410)	0.584





1-year in-hospital mortality
HR 1.075, 95% CI 1.044-1.107, p<0.001

Corticosteroid use is not associated with improved outcomes in acute exacerbation of IPF

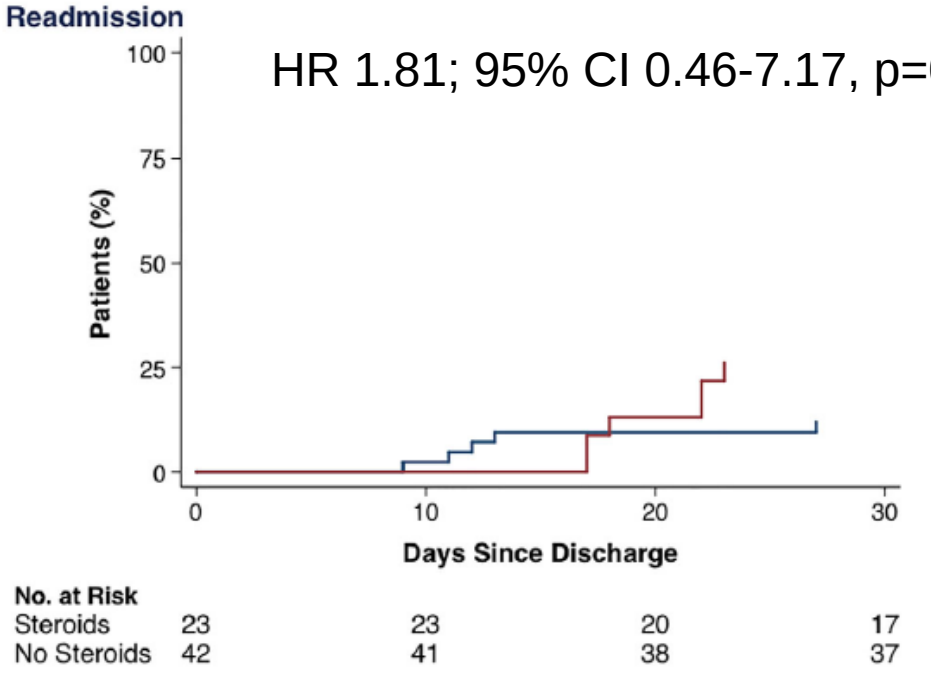
ERICA FARRAND,[1] ERIC VITTINGHOFF,[2] BRETT LEY,[1] ATUL J. BUTTE[3] AND HAROLD R. COLLARD[1]

Respirology (2020) **25**, 629–635

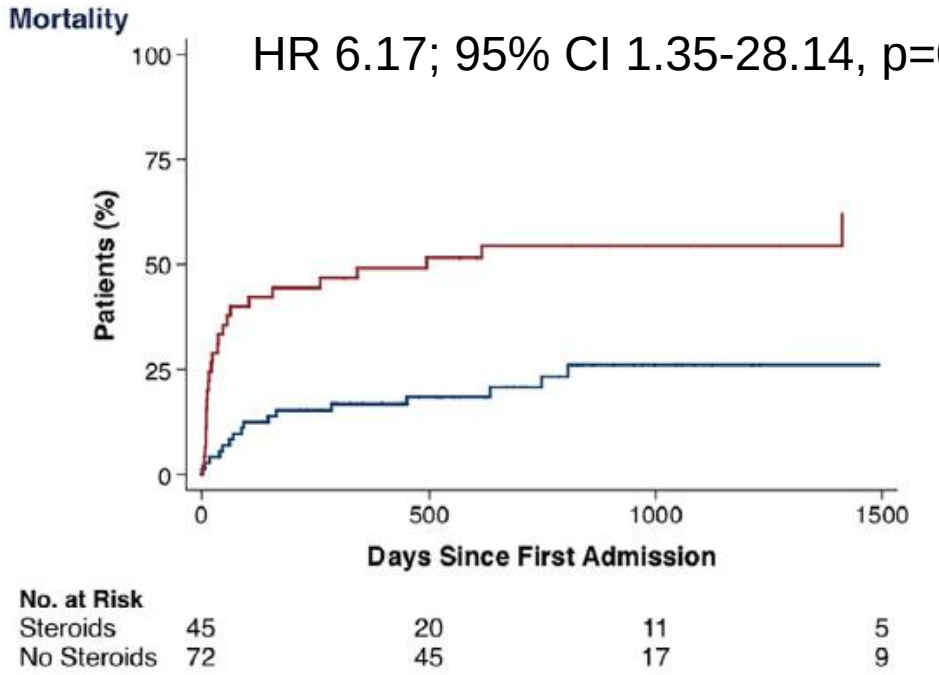
Corticosteroids (n=37)

at least MPD pulse ≥500mg/day or high-dose prednisolone (≥0.5mg/kg) for 2 days or more

No corticosteroids (n=45)



HR 1.81; 95% CI 0.46-7.17, p=0.40



HR 6.17; 95% CI 1.35-28.14, p=0.019

Adjusted for corticosteroid use, mechanical ventilation, ICU admission and Charlson comorbidity index

Steroid therapy in acute exacerbation of fibrotic interstitial lung disease

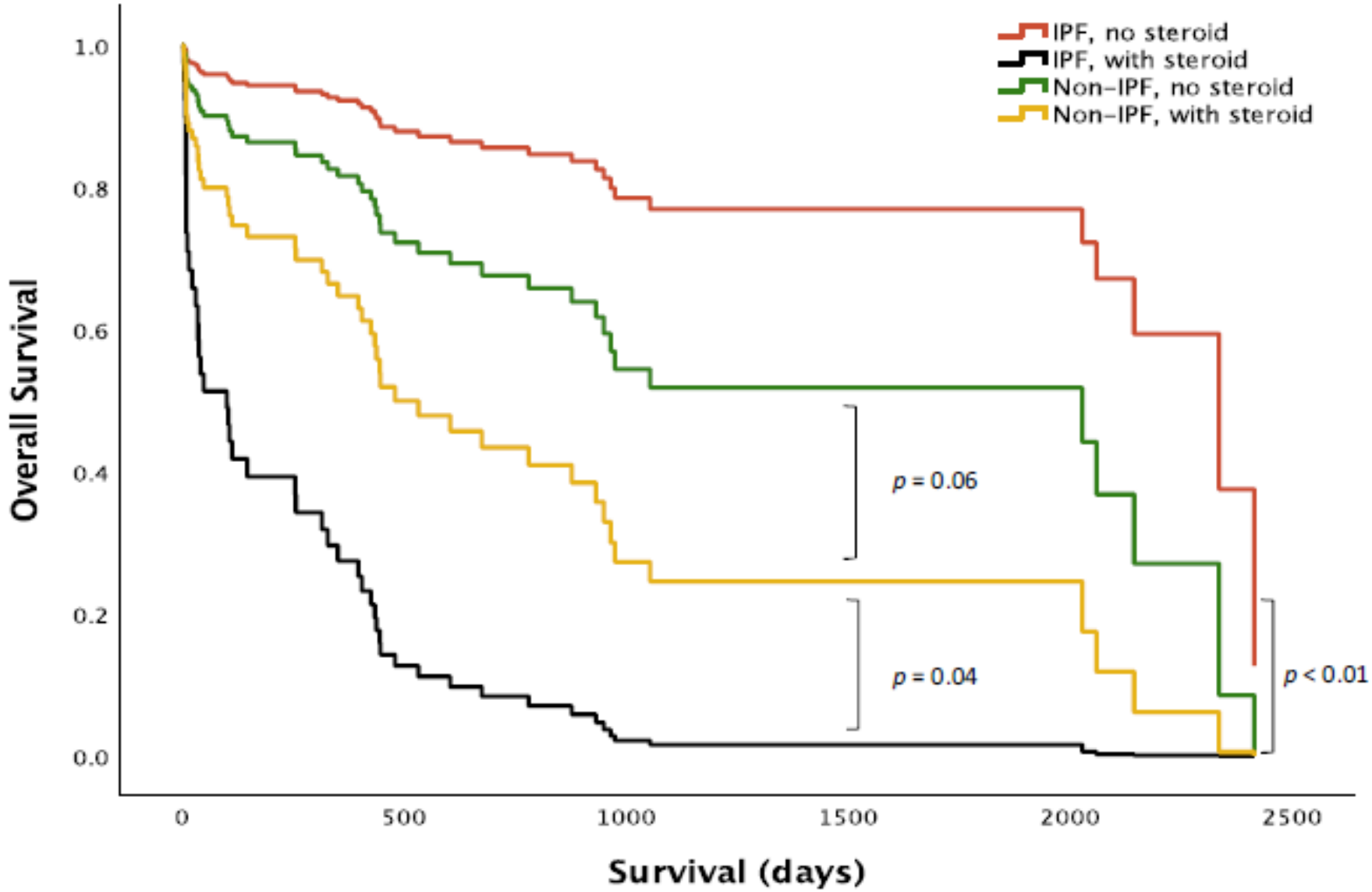
Kavya Koshy[1,2] | Hayley Barnes[1] | Erica Farrand[3] | Ian Glaspole[1,4]

Retrospective cohort study

Prednisolone (≥0.5mg/kg) for 3 days or more

Outcome	Corticosteroids ($n = 46$)	No corticosteroids ($n = 61$)	
In-hospital death or lung transplantation within admission	16 (35%)	6 (10%)	OR 4.11; 95% CI 1.00–16.83; $p = 0.049$[b]
IPF deaths (% of IPF)	10 (32%)	4 (13%)	$p = 0.04$
HP	3 (14%)	0 (0%)	$p = 0.21$
CTD-ILD	3 (12%)	0 (0%)	$p = 0.08$
Unclassifiable	5 (36%)	1 (7%)	$p = 0.09$
Other	1 (7%)	1 (7%)	$p = 0.43$
Median survival (days)[a]	221 (3–2144)	520.5 (5–3292)	HR 3.25; 95% CI1.56–6.77; $p < 0.01$[b]
Transplantation within 1 year	4 (12%)	8 (15%)	OR 0.32; 95% CI 0.36–2.89; $p = 0.31$
Requiring rehabilitation	3 (9%)	14 (26%)	OR 0.27; 95% CI 0.04–2.16; $p = 0.22$
New or increased domiciliary oxygen on discharge	13 (39%)	23 (42%)	OR 0.86; 95% CI 0.24–3.01; $p = 0.81$
Readmission within 30 days	8 (17%)	13 (21%)	OR 1.94; 95% CI 0.41–9.13; $p = 0.40$

Respirology. 2024;29:795–802.

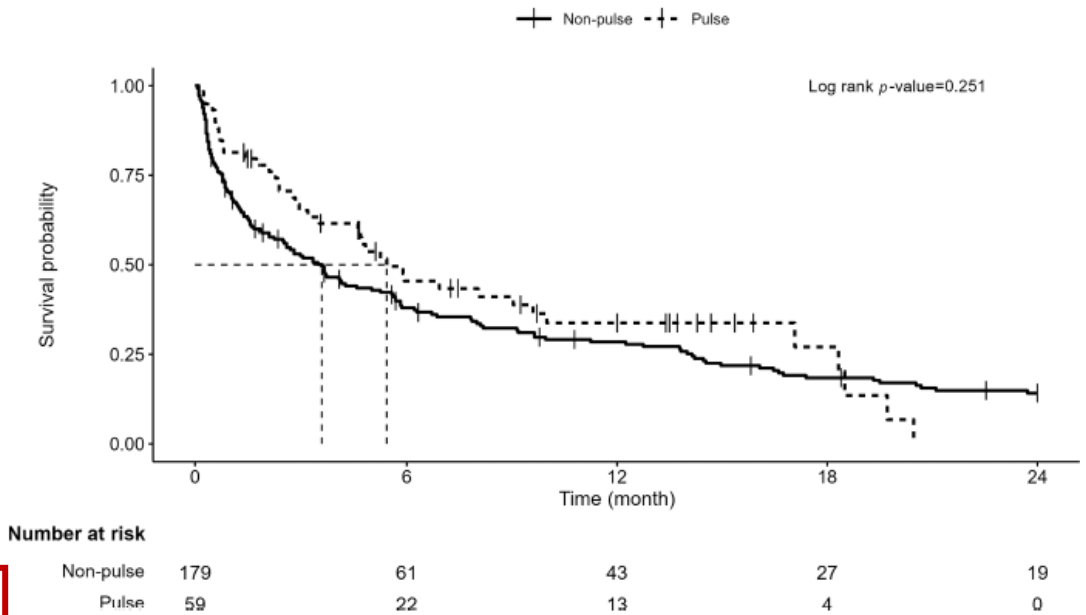


Respirology. 2024;29:795–802.

Pulse versus non-pulse corticosteroid therapy in patients with acute exacerbation of idiopathic pulmonary fibrosis

Kwonhyung Hyung[1] | Jong Hyuk Lee[2] | Joong-Yub Kim[1] | Sun Mi Choi[1] | Jimyung Park[1]

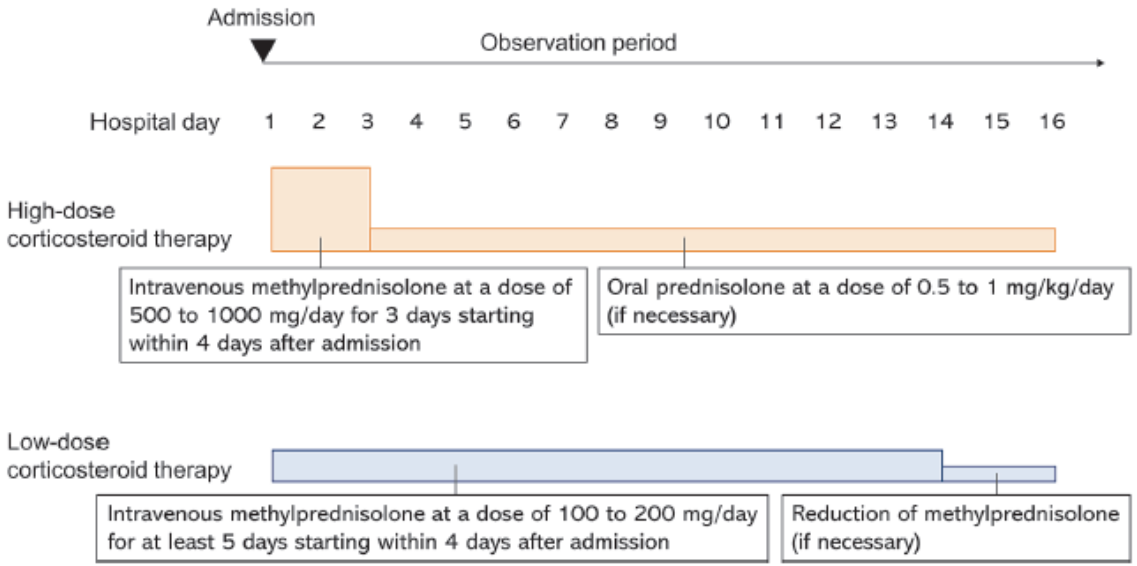
	Pulse regimen ($n = 59$)	Non-pulse regimen ($n = 179$)	p-value
Respiratory support			0.073
Low-flow oxygen	46 (78.0)	115 (64.2)	
High-flow oxygen or mechanical ventilation	13 (22.0)	64 (35.8)	
Steroid therapy			
Interval from admission to initiation of steroid therapy, day	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.522
Average daily steroid dose			
Day 1–3 dose, mg	500 (129–500)	50 (40–60)	<0.001
Dose per weight, mg/kg	6.4 (2.1–8.6)	0.9 (0.7–1.0)	<0.001
Day 4–7 dose, mg[b]	51 (30–173)	40 (30–55)	0.004
Dose per weight, mg/kg	0.8 (0.5–3.4)	0.7 (0.5–0.9)	0.014
Day 8–14 dose, mg[b]	27 (20–44)	25 (13–39)	0.026
Dose per weight, mg/kg	0.5 (0.3–0.8)	0.4 (0.2–0.6)	0.032
Death from any cause			
In-hospital mortality	11 (18.6)	65 (36.3)	0.018
3-month mortality	21 (35.6)	85 (47.5)	0.149
12-month mortality	35 (59.3)	125 (69.8)	0.183



Respirology. 2024;29:235–242.

Efficacy of initial high- versus low-dose intravenous corticosteroid therapy in patients with acute exacerbation of idiopathic interstitial pneumonia: A nationwide observational study

Nobuyasu Awano[1], Taisuke Jo[2,3], Takehiro Izumo[1], Minoru Inomata[1], Kojiro Morita[4,5], Hiroki Matsui[4], Kiyohide Fushimi[6], Hirokazu Urushiyama[3], Takahide Nagase[3], Hideo Yasunaga[4]



High mortality

Table 3 Outcomes in the high- and low-dose corticosteroid groups before and after stabilized IPTW

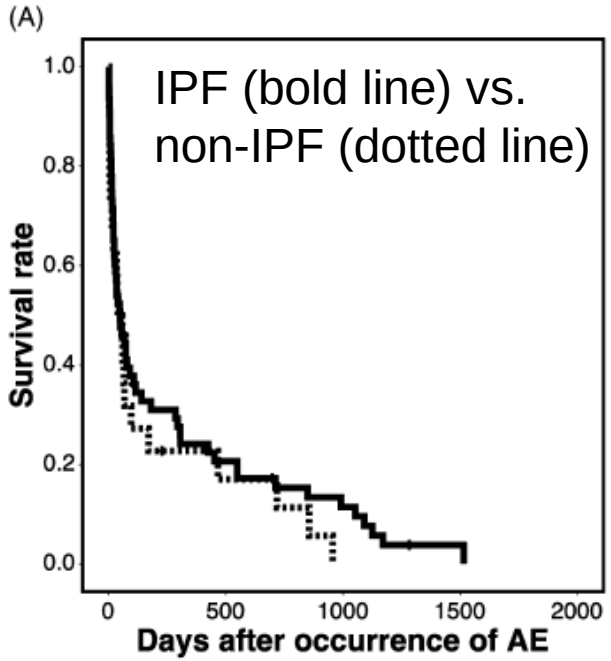
	Patients before IPTW estimation		Patients after IPTW estimation	
	High-dose corticosteroid group	Low-dose corticosteroid group	High-dose corticosteroid group	Low-dose corticosteroid group
All patients, (n)	16998	319	16998	311
In-hospital mortality, n (%)	8593 (50.6)	150 (47.0)	8593 (50.6)	147 (47.3)
28-day mortality, n (%)	5468 (35.2)	87 (27.3)	5463 (32.1)	92 (29.6)
Infection during hospitalization, n (%)	1018 (6.0)	25 (7.8)	1018 (6.0)	31 (10.0)
Length of hospital stay (days), median (IQR)	26 (16–42)	25 (11–45)	26 (16–42)	25 (16–42)
Duration of steroid use (days), median (IQR)*	23 (13–40)	21 (12–40)	23 (13–40)	20 (12–39)
Discharge to home, n (%)	6169 (36.3)	121 (37.9)	6168 (36.3)	117 (37.6)
Survivors, (n)	8405	169	8405	166
Infection during hospitalization, n (%)	325 (3.9)	10 (5.9)	325 (3.9)	11 (6.6)
Length of hospital stay (days), median (IQR)	30 (19–46)	25 (15–45)	30 (19–46)	27 (16–47)
Duration of steroid use (days), median (IQR)*	28 (16–43)	21 (9–43)	28 (16–43)	21 (10–44)

IPTW, inverse probability of treatment weighting; IQR, interquartile range
* Steroids include methylprednisolone and prednisolone.

Annals of Clinical Epidemiology 2023;5(2):37–47

High-dose prednisolone after intravenous methylprednisolone improves prognosis of acute exacerbation in idiopathic interstitial pneumonias

Toru ARAI,[1,2] Kazunobu TACHIBANA,[2] Chikatoshi SUGIMOTO,[1] Yasushi INOUE,[2] Sayoko TOKURA,[2,3] Tomohisa OKUMA,[4] Masanori AKIRA,[3] Masanori KITAICHI,[5] Seiji HAYASHI[2] AND Yoshikazu INOUE[1]



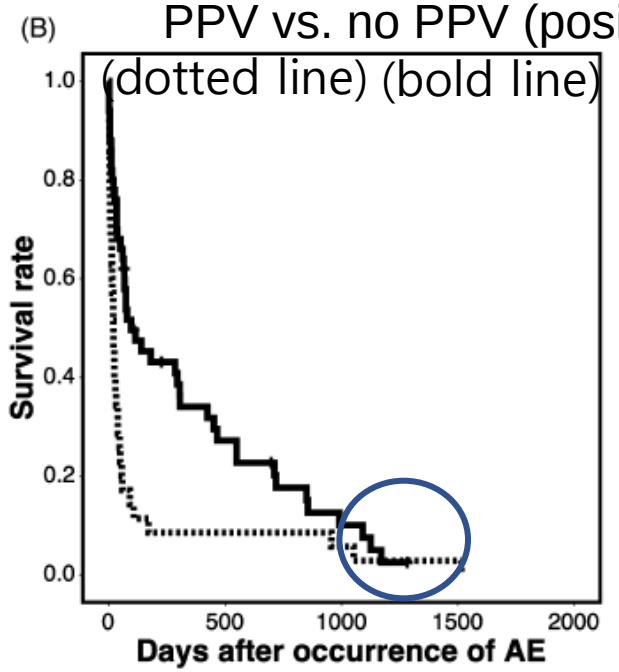


Table 4 Poor prognostic significance of treatment for all, no-PPV and PPV AE-IIPs cases; multivariate Cox proportional hazard regression analysis

Parameters	HR	95% CI	*P*-value
All cases			
PMX-DHP (yes)	1.065	0.613–1.849	0.824
Initial PSL (high)†	0.775	0.454–1.323	0.350
Immunosuppressant (yes)	0.728	0.456–1.163	0.184
No PPV cases			
PMX-DHP (yes)	0.563	0.209–1.516	0.256
Initial PSL (high)†	0.429	0.204–0.903	0.026
Immunosuppressant (yes)	0.689	0.349–1.360	0.283
PPV cases			
PMX-DHP (yes)	1.087	0.543–2.174	0.814
Initial PSL dose (high)†	1.623	0.619–4.255	0.324
Immunosuppressant (yes)	0.937	0.468–1.879	0.855

No PPV case

1g pulse of methylprednisolone IV for 3 days followed by prednisolone
High dose: ≥ 0.6 mg/kg (n=67) vs. Low dose: < 0.6mg /kg (n=18)

Respirology (2017) **22**, 1363–1370

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

Keisuke Anan[1,2,3], Yuki Kataoka[1,3,4,5], Kazuya Ichikado[2], Kodai Kawamura[2], Takeshi Johkoh[6], Kiminori Fujimoto[7], Kazunori Tobino[8], Ryo Tachikawa[9], Hiroyuki Ito[10], Takahito Nakamura[11], Tomoo Kishaba[12], Minoru Inomata[13], Tsukasa Kamitani[14], Hajime Yamazaki[5], Yusuke Ogawa[1] and Yosuke Yamamoto[1*]

Corticosteroid pulse at 1g/day for 3 days

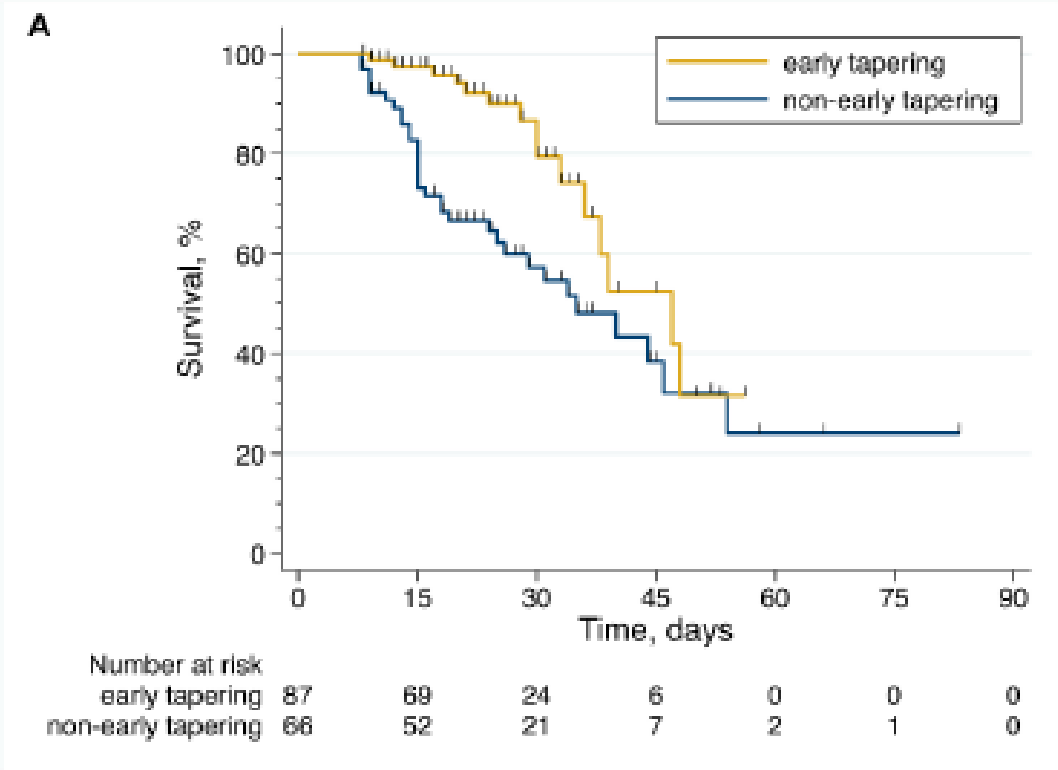
Early tapering: reduction in corticosteroid maintenance dose of >10% within two weeks of admission

High dose: ≥ 1mg/kg/day, moderate: 0.5-1.0mg/kg/day, low: <0.5mg/kg/day

	Multi-center cohort data			Administrative cohort data		
Variable	**Overall (n = 153)**	**Early tapering group (n = 87)**	**Non-early tapering group (n = 66)**	**Overall (n = 229)**	**Early tapering group (n = 87)**	**Non-early tapering group (n = 142)**
Steroid pulse therapy	119 (78%)	70 (80%)	49 (74%)	117 (51%)	54 (62%)	63 (44%)
Dose of steroid (low/moderate/high)	26 (17%)/ 66 (43%)/ 61 (40%)	9 (10%)/38 (44%)/ 40 (46%)	17 (26%)/28 (42%)/ 21 (32%)	73 (32%)/ 68 (30%) / 88 (38%)	10 (11%) / 27 (31%)/ 50 (57%)	63 (44%)/ 41 (29%)/ 38 (27%)

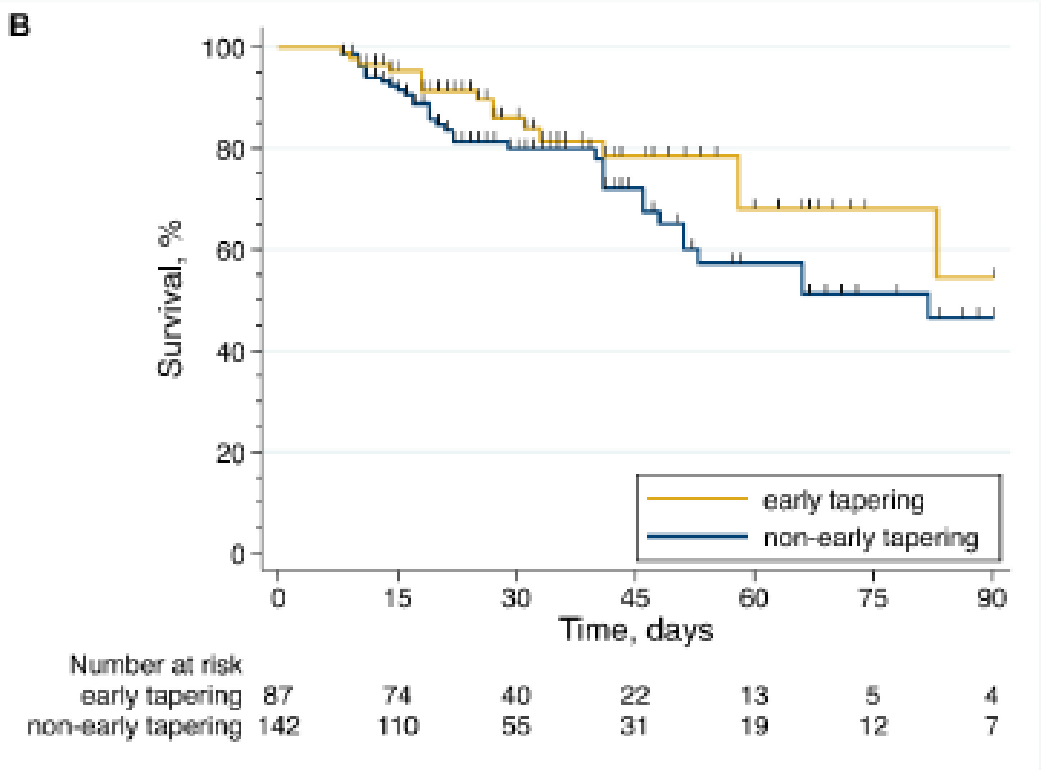
Mortality (early tapering vs. non-early tapering)

Adjusted HR 0.41 (0.19-0.87)



Multicenter cohort

Adjusted HR 0.59 (0.31-1.13)



Administrative cohort

Cons for high-dose steroid in AE-ILD

#1 Uncertainty of efficacy

#2 Heterogenicity of fibrotic ILDs

#3 Heterogenicity of causes (triggers)

#4 Heterogenicity of pathology

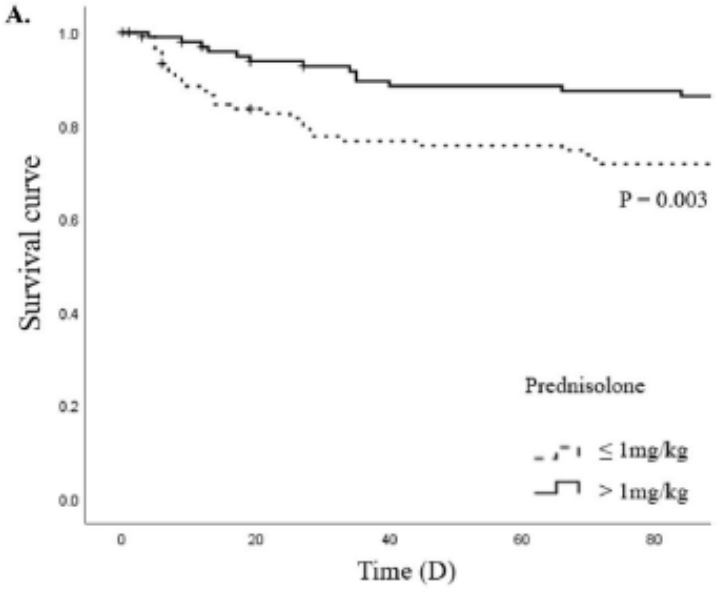
#5 Risk of side effects

Corticosteroid responsiveness in patients with acute exacerbation of interstitial lung disease admitted to the emergency department

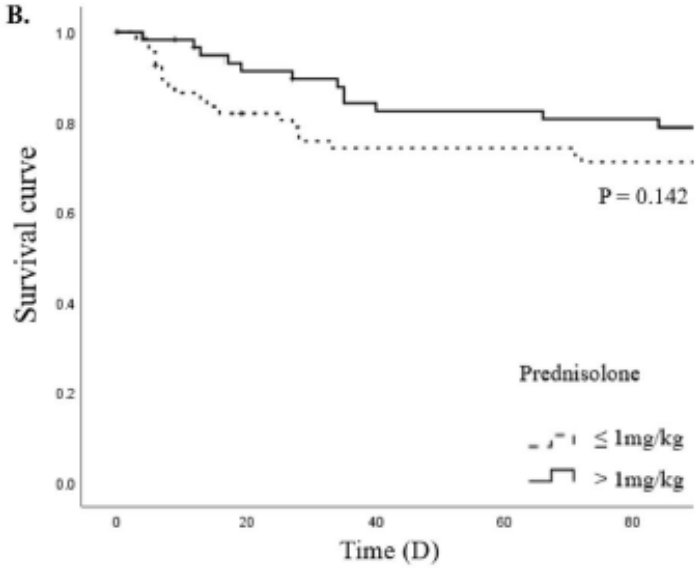
Hye Jin Jang, Seung Hyun Yong, Ah Young Leem, Su Hwan Lee, Song Yee Kim, Sang Hoon Lee, Eun Young Kim, Kyung Soo Chung, Ji Ye Jung, Young Ae Kang, Young Sam Kim, Joon Chang & Moo Suk Park

CTD-ILD
NSIP
COP
Sarcoidosis
HP
Other condition

Total patients

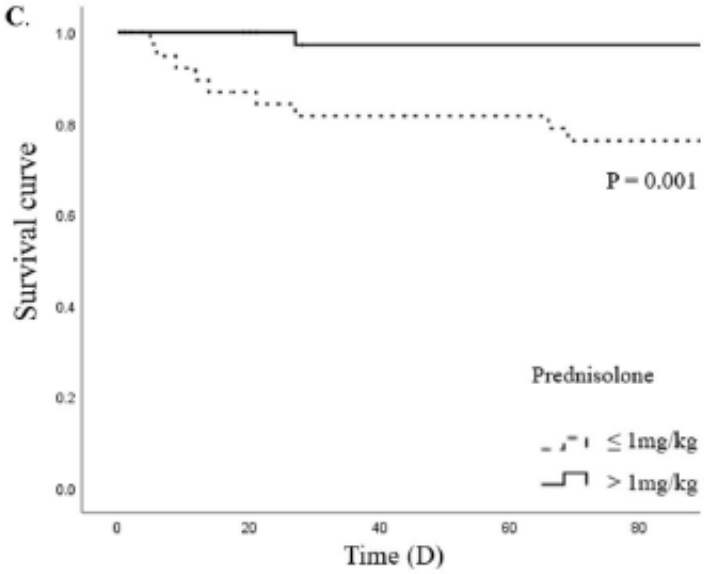


IPF (n=117)



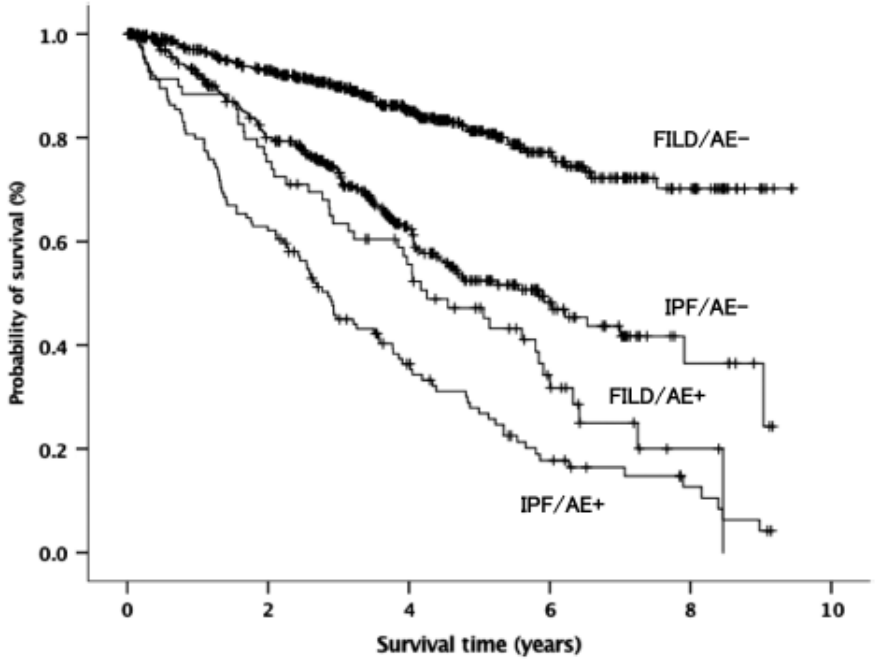
Mortality 25.6%

Non-IPF (n=65)



Mortality 15.4%

Mortality differences between IPF and non-IPF



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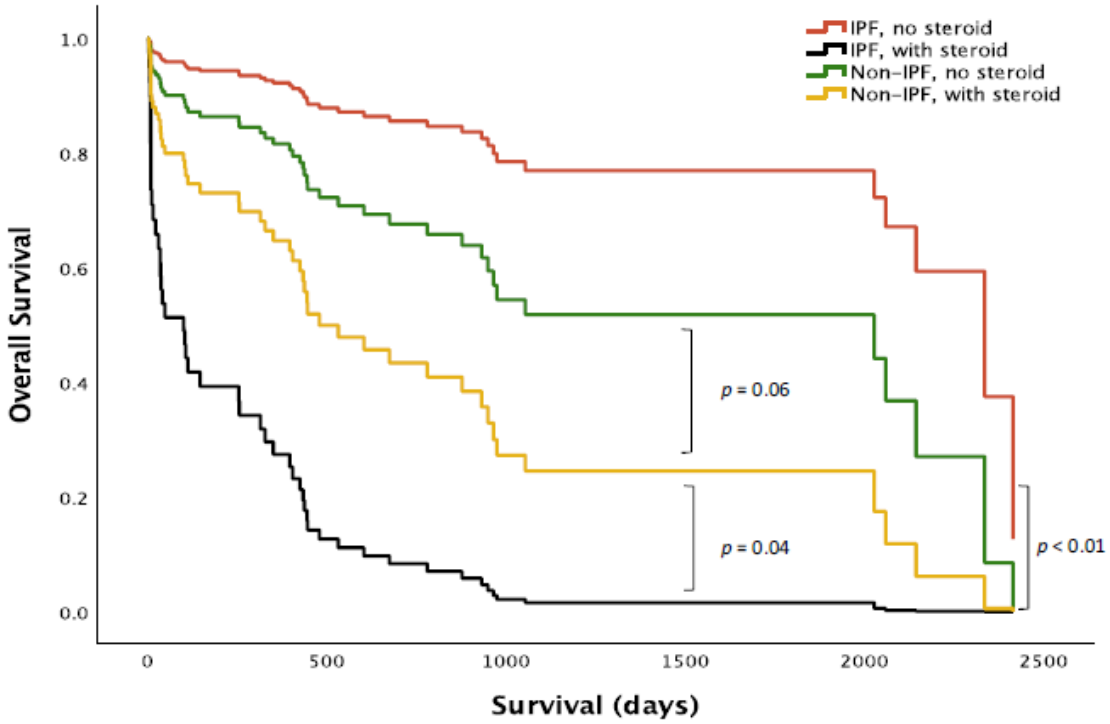
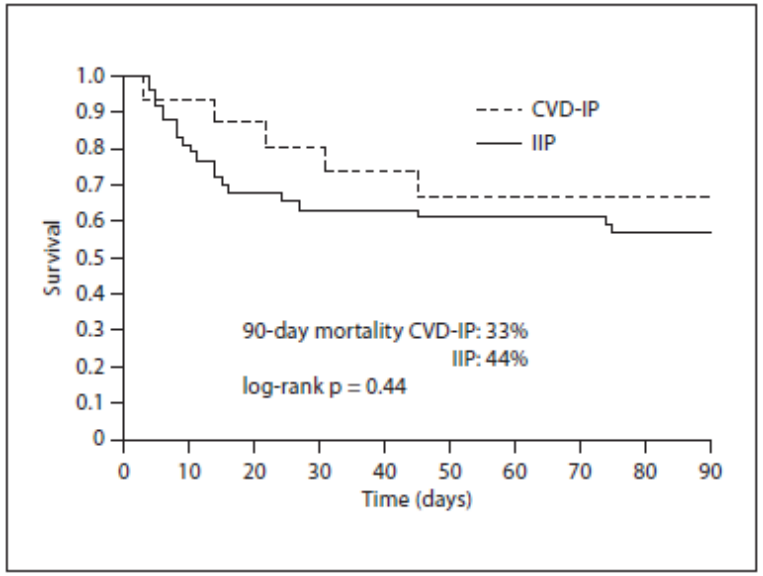
Respirology (2020) **25**, 525–534

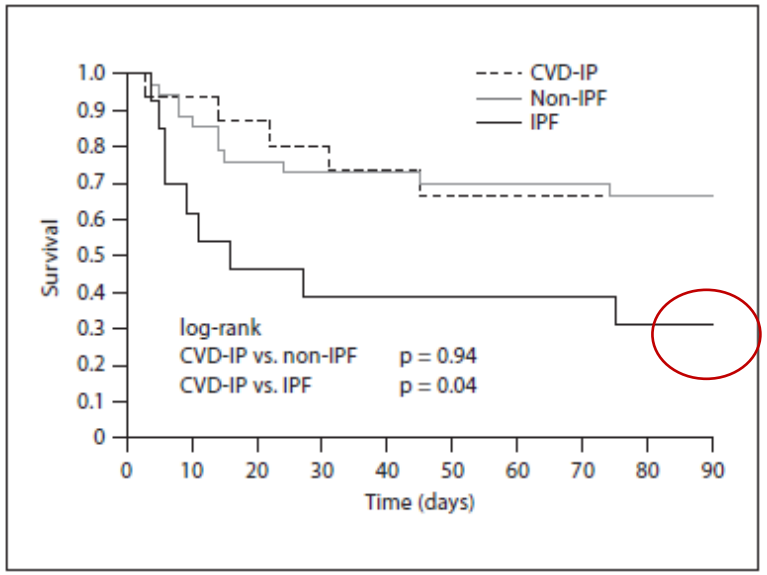


Respirology. 2024;29:795–802.

Clinical Features and Outcome of Acute Exacerbation of Interstitial Pneumonia: Collagen Vascular Diseases-Related versus Idiopathic

Ryo Tachikawa[a] Keisuke Tomii[a] Hiroyuki Ueda[b] Kazuma Nagata[a]
Shigeki Nanjo[a] Ayako Sakurai[a] Kyoko Otsuka[a] Reiko Kaji[a] Michio Hayashi[a]
Nobuyuki Katakami[a] Yukihiro Imai[c]





CTD-ILDs n=15
IIPs n=47 (IPF 13)

	CVD-IP	IIP	p value
AE, cases	15	47	
High-dose corticosteroids	15 (100)	47 (100)	NS
Intravenous cyclophosphamide	9 (60)	25 (53)	NS
Antibiotics	13 (87)	43 (91)	NS
PMX-DHP	1 (7)	3 (6)	NS
Ventilator	8 (53)	29 (62)	NS
Invasive/NIV/both	1/7/0	6/21/2	
Intensive care unit	8 (53)	36 (77)	NS

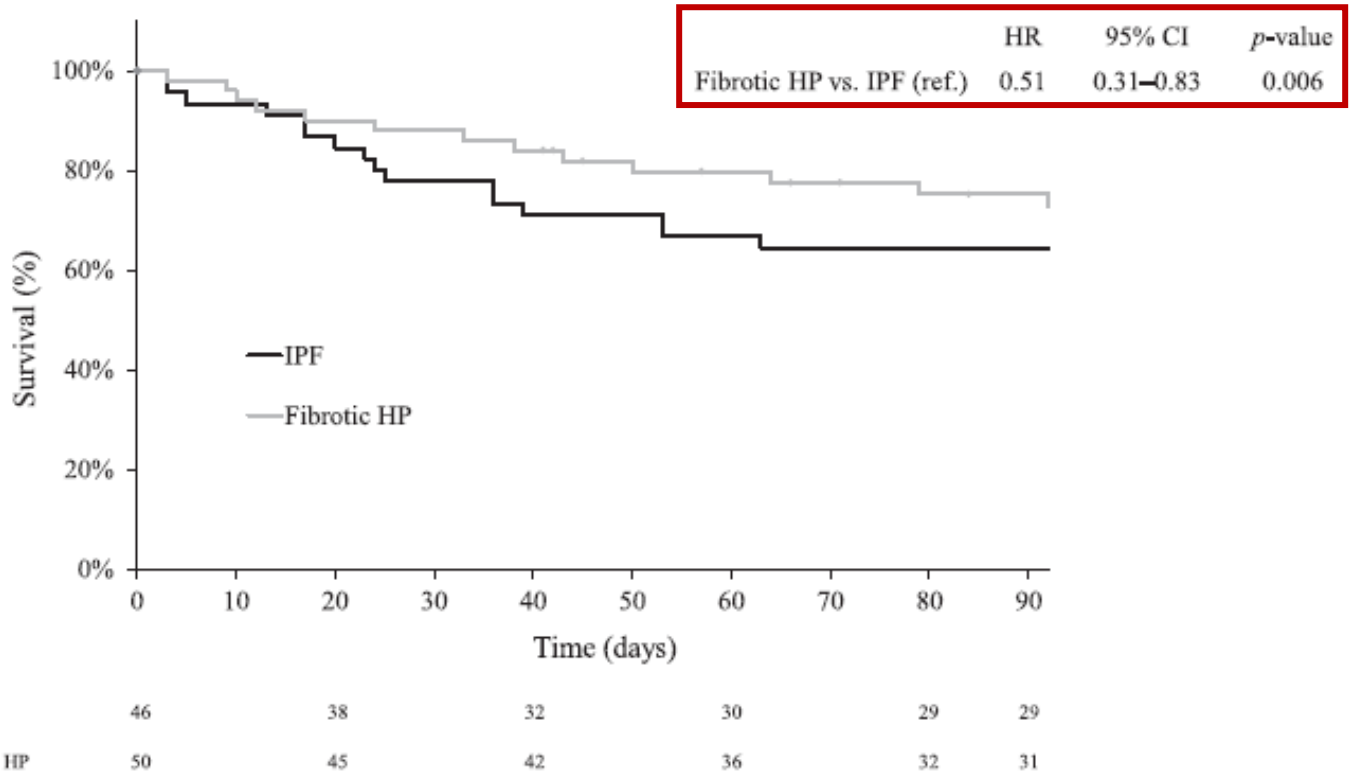
Respiration 2012;83:20–27

Acute exacerbation in patients with Fibrotic HP vs. IPF

Risk factors for AE in patients with fibrotic HP

Parameters	HR	95% CI	*p* values
Univariate Cox regression analysis			
Age (years)	1.01	(0.97–1.05)	0.60
Sex, female versus male (ref.)	0.97	(0.55–1.70)	0.97
BMI (kg/m^2)	1.02	(0.94–1.11)	0.66
Smoker versus never smoker (ref.)	1.17	(0.65–2.13)	0.60
Sampling method, TBLC versus SLB (ref.)	1.06	(0.53–2.12)	0.87
FVC %pred	0.97	(0.96–0.99)	0.001
DLco %pred	0.98	(0.97–0.995)	0.009
BAL in lymphocytes (%)	0.995	(0.98–1.01)	0.38
IgG testing, positive versus negative (ref.)	1.10	(0.45–2.65)	0.84
Treatment at diagnosis, yes versus no (ref.)	2.41	(0.58–10.0)	0.23
Multivariate Cox regression analysis			
FVC %pred	0.98	(0.96–0.997)	0.023
DLco %pred	0.99	(0.97–1.002)	0.09

Survival curves from onset of AEs



Respiration 2023;102:803–812

Cons for high-dose steroid in AE-ILD

#1 Uncertainty of efficacy

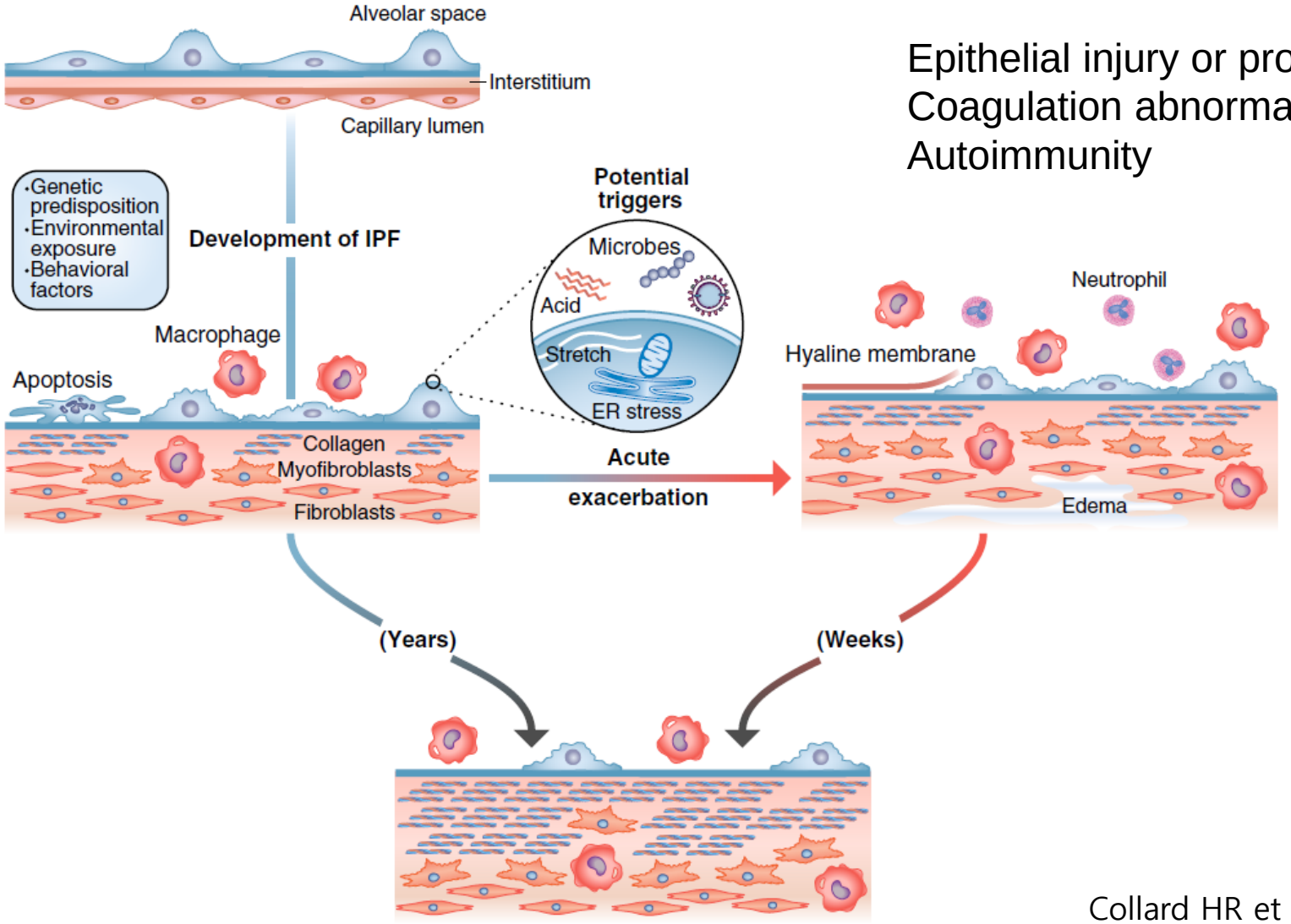
#2 Heterogenicity of fibrotic ILDs

#3 Heterogenicity of causes (triggers)

#4 Heterogenicity of pathology

#5 Risk of side effects

Pathobiological paradigm for AE of IPF



Epithelial injury or proliferation
Coagulation abnormalities
Autoimmunity

Collard HR et al. AJRCCM 2016;194(3):265-75

Triggers

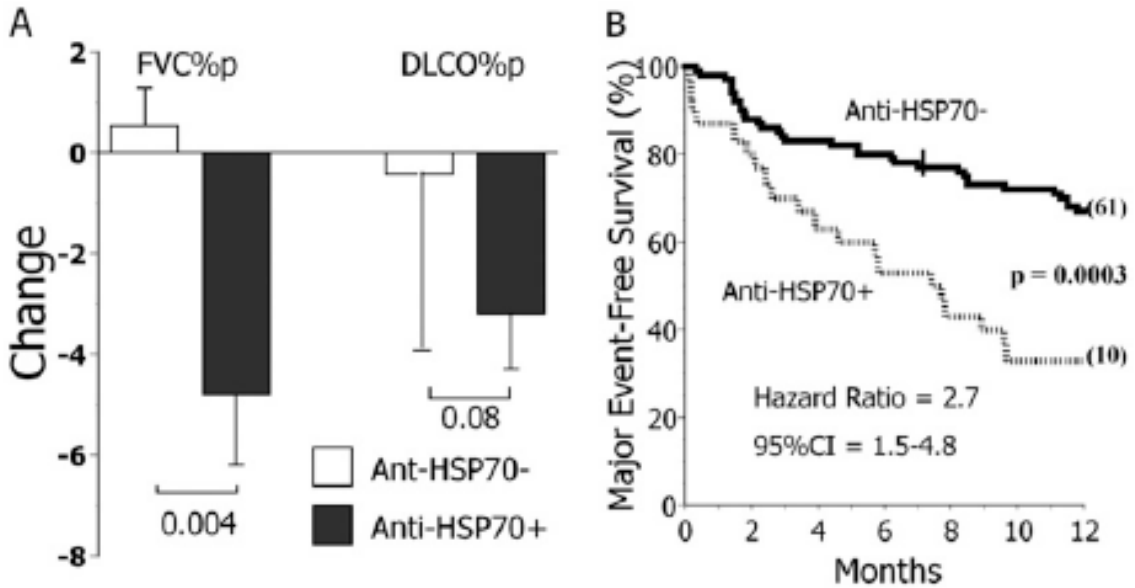
- Autoimmunity
- Infection (viral, bacterial, fungal)
- Microaspiration
- Environmental exposures
- Procedures or surgery
- Drug toxicity

Patients with Idiopathic Pulmonary Fibrosis with Antibodies to Heat Shock Protein 70 Have Poor Prognoses

Rehan A. Kahloon[1*], Jianmin Xue[1*], Arpit Bhargava[1], Eva Csizmadia[2], Leo Otterbein[2], Daniel J. Kass[1], Jessica Bon[1], Makoto Soejima[1], Marc C. Levesque[1], Kathleen O. Lindell[1], Kevin F. Gibson[1], Naftali Kaminski[1], Gunjan Banga[1], Chester V. Oddis[1], Joseph M. Pilewski[1], Frank C. Sciurba[1], Michael Donahoe[1], Yingze Zhang[1], and Steven R. Duncan[1]

[1]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and [2]Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

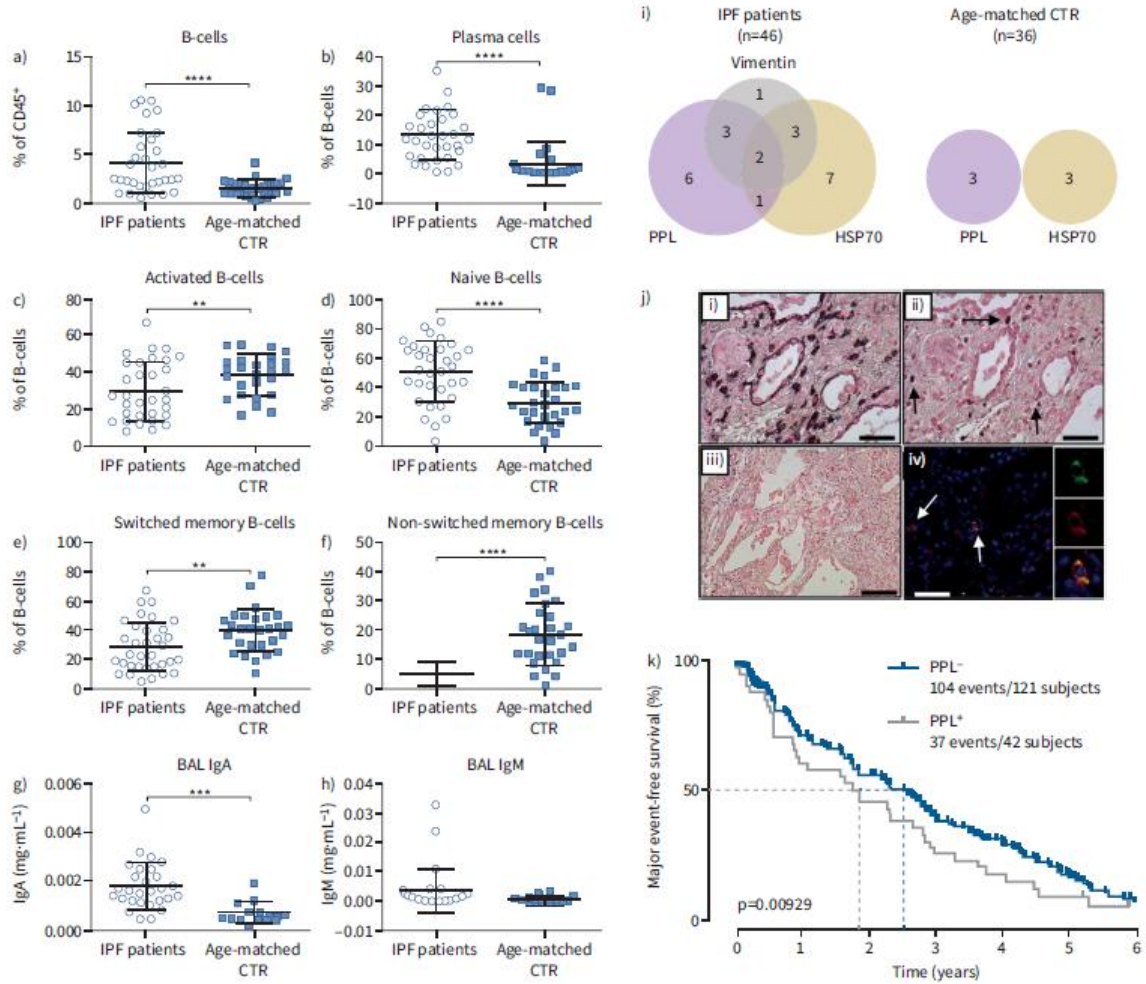
Am J Respir Crit Care Med Vol 187, Iss. 7, pp 768–775, Apr 1, 2013



Autoantibodies are associated with disease progression in idiopathic pulmonary fibrosis

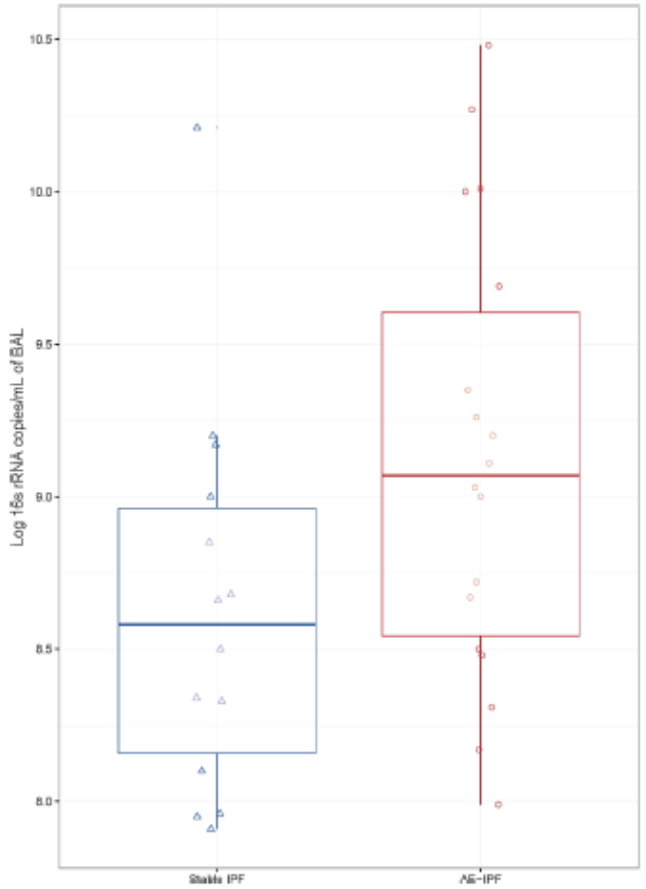
Katerina Koether[1], Valérie Besnard[2], Hilary Sandig[1], Alan Carruthers[1], Elena Miranda[3], Sabine Grootenboer-Mignot[2,4], Camille Taillé[2,5], Sylvie Chevret[6], Dominique Valeyre[7], Hilario Nunes[7], Dominique Israel-Biet[8], Wei Keat Lim[9], Vincent Cottin[10], Dominic Corkill[1], Claire Dobson[11], Maria Groves[11], Franco Ferraro[11], Edouard Guenzi[2,12], Ling Huang[1], Michal Sulikowski[1], Arnaud Mailleux[4], Lynne Anne Murray[1], Thomas Mustelin[13,14], Ian Strickland[1,15], Matthew A. Sleeman[1,15] and Bruno Crestani[2,5,15]

Eur Respir J 2023; 61: 2102381

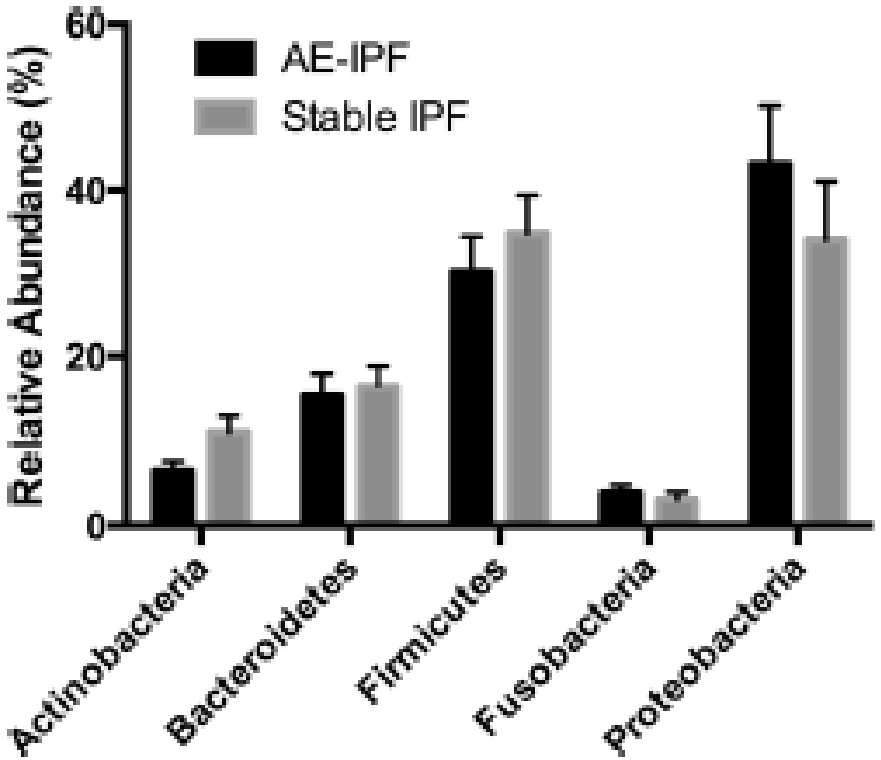


Changes in the respiratory microbiome during acute exacerbations of idiopathic pulmonary fibrosis

Philip L. Molyneaux[1,2], Michael J Cox[1], Athol U. Wells[2], Ho Cheol Kim[3], Wonjun Ji[3], William O. C. Cookson[1], Miriam F. Moffatt[1], Dong Soon Kim[3†] and Toby M. Maher[1,2,4*†]



Bacterial load in AE-IPF compared with stable IPF



Changes in specific bacterial species in AE-IPF compared with stable IPF

Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial

Ganesh Raghu, Carlos A Pellegrini, Eric Yow, Kevin R Flaherty, Keith Meyer, Imre Noth, Mary Beth Scholand, John Cello, Lawrence A Ho, Sudhakar Pipavath, Joyce S Lee, Jules Lin, James Maloney, Fernando J Martinez, Ellen Morrow, Marco G Patti, Stan Rogers, Paul J Wolters, Robert Yates, Kevin J Anstrom, Harold R Collard

	Surgery (n=29)	No surgery (n=29)	p value
Clinical events*			
Acute exacerbation	1 (3%)	4 (16%)	0·19
Respiratory hospitalisation	2 (7%)	6 (21%)	0·25
Non-elective hospitalisation	5 (17%)	8 (28%)	0·35
Lung transplantation	0	1 (3%)	>0·99
Disease progression†			
Death	1 (3%)	4 (18%)	0·13
10% FVC decline or death	2 (9%)	7 (29%)	0·038
10% FVC decline, acute exacerbation, or death	2 (9%)	7 (28%)	0·048
Respiratory hospitalisation or death	2 (9%)	5 (19%)	0·16
Non-elective hospitalisation or death	5 (17%)	7 (26%)	0·50
10% FVC decline, 5 point UCSD Shortness of Breath Questionnaire increase, respiratory hospitalisation, or death	15 (57%)	15 (56%)	0·74

Lancet Respir Med 2018; 6: 707–14

Cons for high-dose steroid in AE-ILD

#1 Uncertainty of efficacy

#2 Heterogenicity of fibrotic ILDs

#3 Heterogenicity of causes (triggers)

#4 Heterogenicity of pathology

#5 Risk of side effects

Autopsy analyses in acute exacerbation of idiopathic pulmonary fibrosis

Keishi Oda[1], Hiroshi Ishimoto[1], Sohsuke Yamada[2], Hisako Kushima[3], Hiroshi Ishii[4], Tomotoshi Imanaga[5], Tatsuhiko Harada[6], Yuji Ishimatsu[6], Nobuhiro Matsumoto[7], Keisuke Naito[1], Kazuhiro Yatera[1], Masamitsu Nakazato[7], Jun-ichi Kadota[3], Kentaro Watanabe[4], Shigeru Kohno[6] and Hiroshi Mukae[1*]

52 patients with AE-IPF

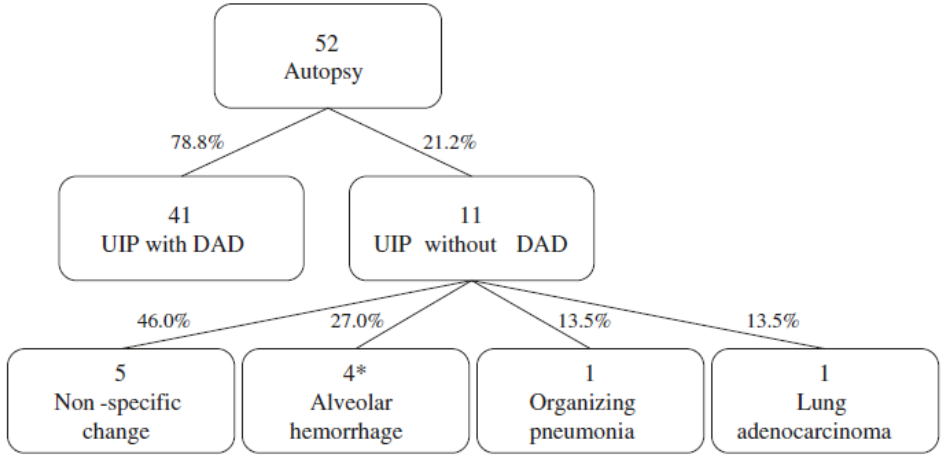


Table 3 The autopsy findings of patients with AE-IPF

Pathological findings	No. (%)
UIP pattern	52 (100)
Diffuse alveolar damage	41 (78.8)
Alveolar hemorrhage	15 (28.8)
Organizing pneumonia	1 (1.9)
Pulmonary thromboembolism	9 (17.3)
Lung cancer	6 (11.5)
Bronchopneumonia	15 (28.8)
Bacterial infection	6 (11.5)
Fungal infection	7 (13.5)
Cytomegalovirus infection	6 (11.5)
Extrapulmonary findings	
Gastrointestinal hemorrhage	13 (25.0)
Right ventricular hypertrophy	18 (34.6)

Abbreviations: AE-IPF Acute exacerbation of idiopathic pulmonary fibrosis, *UIP* Usual interstitial pneumonia.

Table 4 The characteristics of the 15 patients with positive results for infectious causes

Patient, No.	Age	Sex	Time from AE-IPF to death (days)	Prior treatment for IPF	Treatment for AE-IPF	Mechanical ventilation	Bacteria	Virus	Fungus
1	74	M	1	None	None	No	-	-	*Aspergillus* species
2	68	M	8	CS	High dose corticosteroids, CPA	Yes	-	CMV	-
3	66	M	10	None	High dose corticosteroids	Yes	-	-	*Aspergillus* species
4	67	M	12	None	High dose corticosteroids	Yes	GPC	-	-
5	76	F	13	CS	High dose corticosteroids, CPA	Yes	-	-	*Candia albicans*
6	78	M	15	None	High dose corticosteroids	No	GNR	CMV	-
7	68	M	19	None	High dose corticosteroids, CPA	Yes	GPC	-	-
8	83	M	19	CS, CsA	High dose corticosteroids, CsA	No	-	-	*Aspergillus* species
9	71	M	20	CS	High dose corticosteroids	Yes	-	-	*Aspergillus* species
10	68	M	22	None	High dose corticosteroids	Yes	-	CMV	-
11	81	M	35	CS	High dose corticosteroids, CPA	No	-	-	*Aspergillus* species
12	68	F	38	None	High dose corticosteroids, CPA	Yes	-	CMV	-
13	59	M	41	CS, CsA	High dose corticosteroids	No	GPC, GNR	CMV	-
14	76	M	58	None	High dose corticosteroids, CPA	Yes	-	CMV	-
15	80	M	122	CS	High dose corticosteroids	No	GNR	-	*Aspergillus* species

Cons for high-dose steroid in AE-ILD

#1 Uncertainty of efficacy

#2 Heterogenicity of fibrotic ILDs

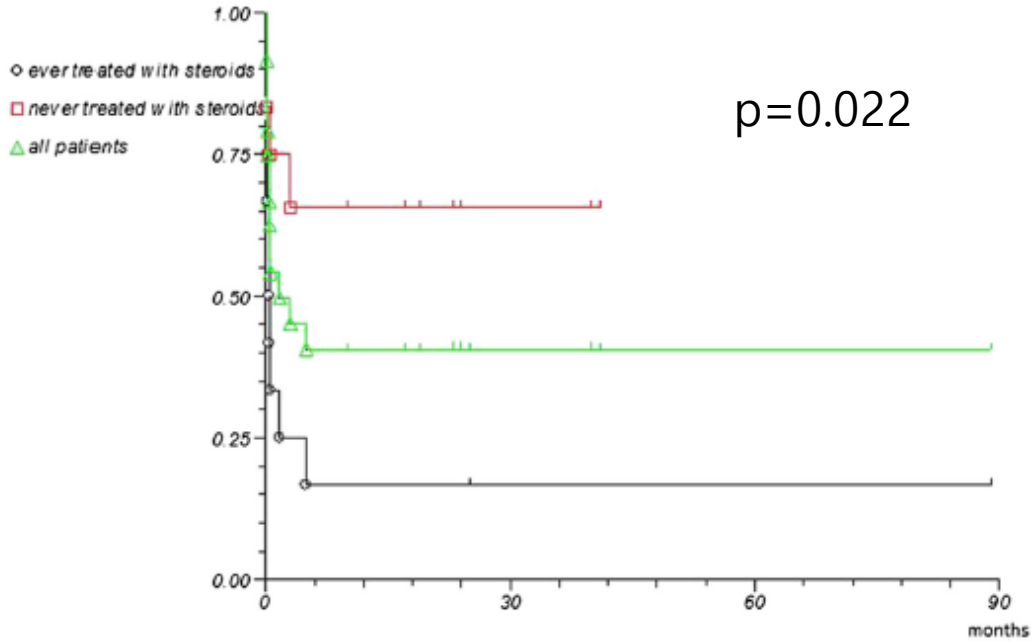
#3 Heterogenicity of causes (triggers)

#4 Heterogenicity of pathology

#5 Risk of side effects

Survival in Idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach

Spyros A Papiris[1*†], Konstantinos Kagouridis[1†], Likurgos Kolilekas[2], Andriana I Papaioannou[1], Aneza Roussou[1], Christina Triantafillidou[3], Katerina Baou[4], Katerina Malagari[5], Stylianos Argentos[1], Anastasia Kotanidou[6], Anna Karakatsani[1] and Effrosyni D Manali[1]



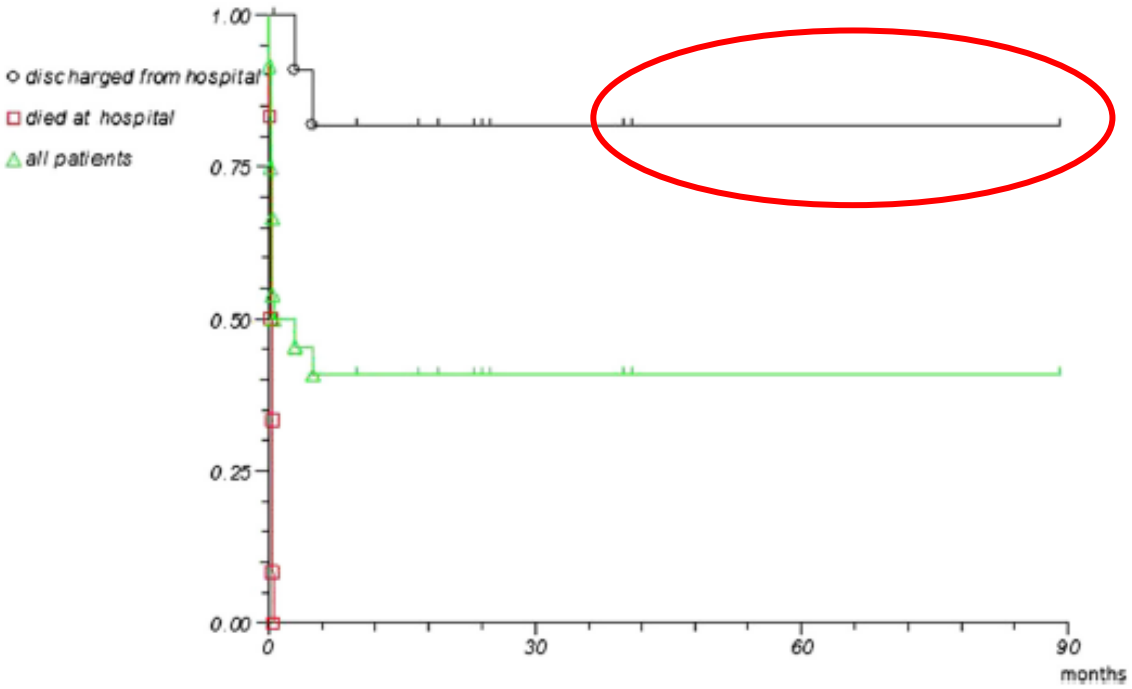
p=0.022

Mortality of patients with IPF
Ever treated vs. never treated with steroid

Study protocol after hospital discharge

Immediate cessation of immunosuppression
Best supportive care
Broad spectrum antimicrobials according to the immune status of each patients

12/24 (50%) survived the exacerbation event



Papiris et al. BMC Pulmonary Medicine (2015) 15:162

Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study

Akbar K Waljee,[1,2,3,4] Mary A M Rogers,[2,4,5] Paul Lin,[2] Amit G Singal,[6] Joshua D Stein,[2,7,8] Rory M Marks,[9] John Z Ayanian,[2,5,8] Brahmajee K Nallamothu[1,2,4,10]

Patients 327,452/1,548,945 (21.1%)

Adverse event	No of participants	Median dose (mg/day)	Median No of days using steroids	5-30 days* Incidence rate ratio† (95% CI)	5-30 days* P value	31-90 days* Incidence rate ratio† (95% CI)	31-90 days* P value
All doses *v* no corticosteroids:							
Sepsis	1556	20	6	5.30 (3.80 to 7.41)	<0.001	2.91 (2.05 to 4.14)	<0.001
Venous thromboembolism	4343	17.5	6	3.33 (2.78 to 3.99)	<0.001	1.44 (1.19 to 1.74)	<0.001
Fracture	20090	19	6	1.87 (1.69 to 2.07)	<0.001	1.40 (1.29 to 1.53)	<0.001
Dose: <20 mg/day *v* 0 mg/day:							
Sepsis	708	17.5	6	4.02 (2.41 to 6.69)	<0.001	2.62 (1.58 to 4.34)	<0.001
Venous thromboembolism	2139	17.5	6	3.61 (2.81 to 4.64)	<0.001	1.27 (0.96 to 1.67)	0.10
Fracture	9941	17.5	6	1.83 (1.60 to 2.10)	<0.001	1.41 (1.24 to 1.59)	<0.001
Dose: 20-39 mg/day *v* 0 mg/day:							
Sepsis	652	32	7	7.10 (4.20 to 12.01)	<0.001	2.91 (1.64 to 5.18)	<0.001
Venous thromboembolism	1713	35	7	2.83 (2.09 to 3.84)	<0.001	1.40 (1.03 to 1.90)	0.03
Fracture	8009	35	7	1.95 (1.66 to 2.30)	<0.001	1.33 (1.15 to 1.54)	<0.001
Dose: ≥40 mg/day *v* 0 mg/day:							
Sepsis	196	60	5	4.98 (1.69 to 14.72)	0.004	5.20 (1.77 to 15.25)	0.003
Venous thromboembolism	491	60	5	4.15 (2.45 to 7.03)	<0.001	2.27 (1.38 to 3.74)	0.001
Fracture	2140	60	5	1.77 (1.31 to 2.39)	<0.001	1.61 (1.26 to 2.05)	<0.001

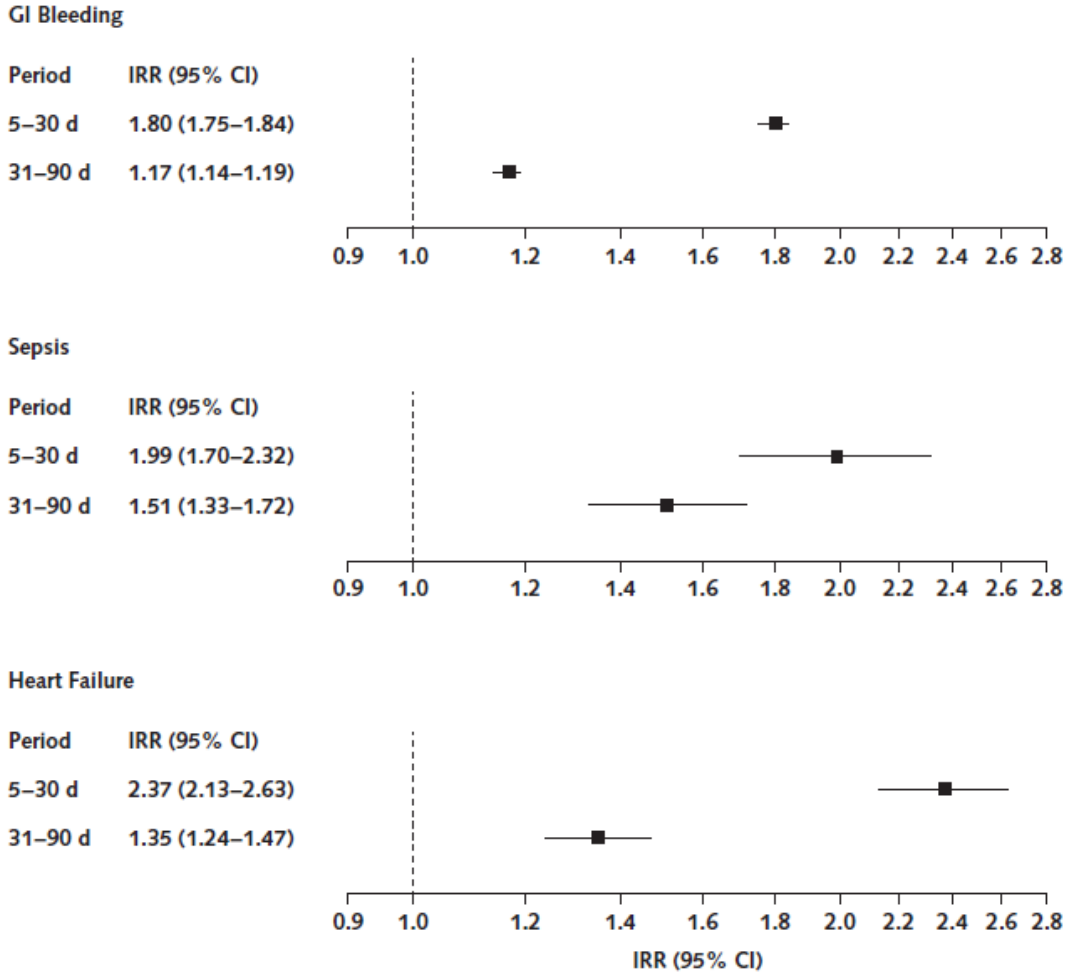
BMJ 2017;357:j1415

Association Between Oral Corticosteroid Bursts and Severe Adverse Events

A Nationwide Population-Based Cohort Study

Tsung-Chieh Yao, MD, PhD; Ya-Wen Huang, MS; Sheng-Mao Chang, PhD; Shun-Yu Tsai, BS; Ann Chen Wu, MD, MPH; and Hui-Ju Tsai, MPH, PhD

Patients 2,623,327/15,859,129



Adverse Event	Steroid Bursts			Non-Steroid Users			Rate Difference per 1000 Person-Years (95% CI)
	Cases, *n*	Person-Years, *n*	Incidence Rate per 1000 Person-Years (95% CI)	Cases, *n*	Person-Years, *n*	Incidence Rate per 1000 Person-Years (95% CI)	
GI bleeding	17 004	628 100	27.1 (26.7-27.5)	458 914	27 360 062	16.8 (16.7-16.8)	10.3 (9.9-10.7)
Sepsis	969	637 622	1.5 (1.4-1.6)	39 512	28 023 082	1.4 (1.4-1.4)	0.1 (0.01-0.2)
Heart failure	846	637 751	1.3 (1.2-1.4)	10 195	28 053 806	0.4 (0.4-0.4)	1.0 (0.9-1.1)

Ann Intern Med. 2020;173:325-330. doi:10.7326/M20-0432

Treatment options beyond corticosteroids

- Immunomodulatory therapy
- Antifibrotics
- Thrombomodulin alfa
- Lung transplantation

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

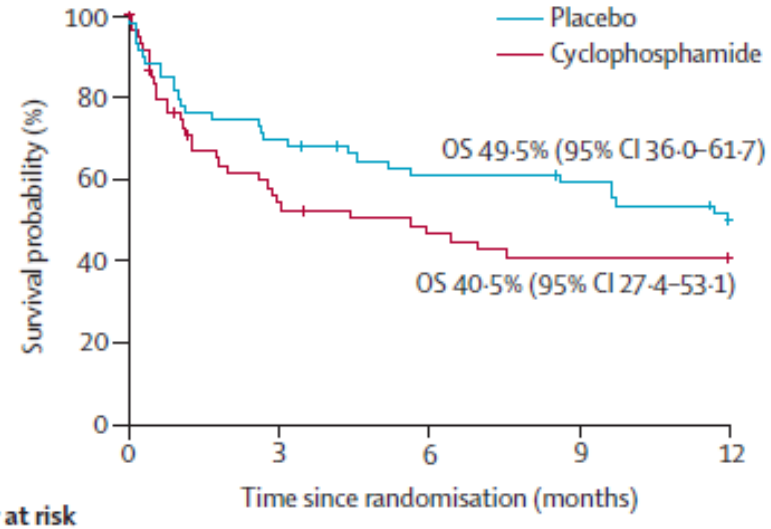
*Jean-Marc Naccache, Stéphane Jouneau, Morgane Didier, Raphaël Borie, Marine Cachanado, Arnaud Bourdin, Martine Reynaud-Gaubert, Philippe Bonniaud, Dominique Israël-Biet, Grégoire Prévot, Sandrine Hirschi, François Lebargy, Sylvain Marchand-Adam, Nathalie Bautin, Julie Traclet, Emmanuel Gomez, Sylvie Leroy, Frédéric Gagnadoux, Frédéric Rivière, Emmanuel Bergot, Anne Gondouin, Elodie Blanchard, Antoine Parrot, François-Xavier Blanc, Alexandre Chabrol, Stéphane Dominique, Aude Gibelin, Abdellatif Tazi, Laurence Berard, Pierre Yves Brillet, Marie-Pierre Debray, Alexandra Rousseau, Mallorie Kerjouan, Olivia Freynet, Marie-Christine Dombret, Anne-Sophie Gamez, Ana Nieves, Guillaume Beltramo, Jean Pastré, Aurélie Le Borgne-Krams, Tristan Dégot, Claire Launois, Laurent Plantier, Lidwine Wémeau-Stervinou, Jacques Cadranel, Cécile Chenivesse, Dominique Valeyre, Bruno Crestani, Vincent Cottin, Tabassome Simon, Hilario Nunes, on behalf of the EXAFIP investigators and the OrphaLung network**

Baseline antifibrotic therapy before acute exacerbation of IPF
→ lower risk of death at 3 months
(OR 0.33 [0.13-0.82]

Lancet Respir Med 2022;
10: 26–34

All patients: methylprednisolone 10mg/kg per for 3days followed by a progressive tapering to 10mg or 7.5mg at month 6

Cyclophosphamide or placebo on days 0, 15, 30, and 60.



	Cyclophosphamide (n=60)	Placebo (n=59)
Any adverse event between month 0 and month 6	25 (42%)	30 (51%)
Haemorrhagic cystitis	0	0
Leukopenia	1 (2%)	0
Neutropenia	3 (5%)	0
Lymphopenia	0	1 (2%)
Anaemia	1 (2%)	0
Thrombopenia	0	2 (3%)
Nausea or vomiting	4 (7%)	3 (5%)
Diarrhoea	7 (12%)	4 (7%)
Newly developed diabetes	0 (0%)	1 (2%)
Newly developed hypertension	2 (3%)	2 (3%)
Infectious disease	20 (33%)	21 (36%)
Any serious adverse event between 0 and 12 months	53 (88%)	50 (85%)
Serious adverse event excluding progression of IPF between 0 and 12 months	26 (43%)	29 (49%)
Serious infectious disease	9 (15%)	15 (25%)
Cardiac disorder	6 (10%)	10 (17%)

IPF=idiopathic pulmonary fibrosis.

Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis

A Systematic Review and Meta-Analysis

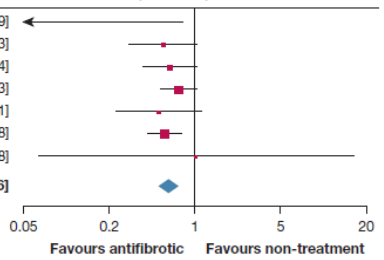
Tananchai Petnak, MD; Ploypin Lertjitbanjong, MD; Charat Thongprayoon, MD; and Teng Moua, MD

12,956 patients across 26 studies

A

Study or Subgroup	log[Relative Risk]	SE	Antifibrotic Total	Non-treatment Total	Weight	Relative Risk IV, Random, 95% CI
Azuma 2005	−3.1048	1.463	72	35	0.4%	0.04 [0.00, 0.79]
Richeldi 2011	−0.5621	0.3019	343	85	9.1%	0.57 [0.32, 1.03]
Richeldi 2014	−0.4427	0.2441	638	423	14.0%	0.64 [0.40, 1.04]
Zurkova 2019	−0.2853	0.1611	383	218	32.1%	0.75 [0.55, 1.03]
Feng 2020	−0.635	0.3767	36	31	5.9%	0.53 [0.25, 1.11]
Kang 2020	−0.5335	0.1476	474	474	38.2%	0.59 [0.44, 0.78]
Lancaster 2020	0.0177	1.4016	56	57	0.4%	1.02 [0.07, 15.88]
Total (95% CI)			**2,002**	**1,323**	**100.0%**	**0.63 [0.53, 0.76]**

Heterogeneity: Tau² = 0.00; χ² = 5.14, *df* = 6 (*P* = .53); I² = 0%
Test for overall effect: Z = 5.02 (*P* < .00001)



0.63 (0.53-0.76)

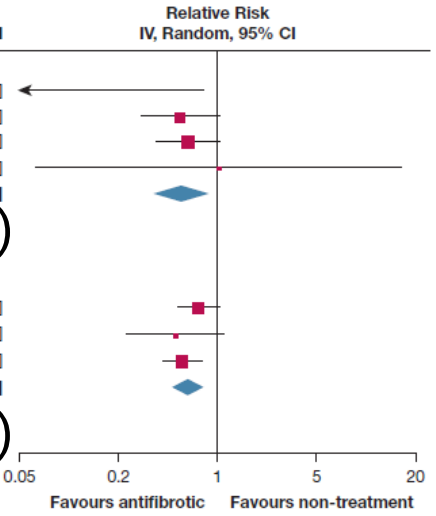
Relative risk for acute exacerbation

B

Study or Subgroup	log[Relative Risk]	SE	Antifibrotic Total	Non-treatment Total	Weight	Relative Risk IV, Random, 95% CI
RCTs						
Azuma 2005	−3.1048	1.463	72	35	2.2%	0.04 [0.00, 0.79]
Richeldi 2011	−0.5621	0.3019	343	85	40.3%	0.57 [0.32, 1.03]
Richeldi 2014	−0.4427	0.2441	638	423	55.1%	0.64 [0.40, 1.04]
Lancaster 2020	0.0177	1.4016	56	57	2.4%	1.02 [0.07, 15.88]
Subtotal (95% CI)			**1,109**	**600**	**100.0%**	**0.58 [0.38, 0.89]**
Heterogeneity: Tau² = 0.03; χ² = 3.39, *df* = 3 (*P* = .34); I² = 11%						
Test for overall effect: Z = 2.47 (*P* = .01)						
Cohorts						
Zurkova 2019	−0.2853	0.1611	383	218	42.1%	0.75 [0.55, 1.03]
Feng 2020	−0.635	0.3767	36	31	7.7%	0.53 [0.25, 1.11]
Kang 2020	−0.5335	0.1476	474	474	50.2%	0.59 [0.44, 0.78]
Subtotal (95% CI)			**893**	**723**	**100.0%**	**0.65 [0.53, 0.79]**
Heterogeneity: Tau² = 0.00; χ² = 1.59, *df* = 2 (*P* = .45); I² = 0%						
Test for overall effect: Z = 4.18 (*P* < .0001)						
Test for subgroup differences: χ² = 0.18, *df* = 1 (*P* = .67), I² = 0%						

0.58 (0.38-0.89)

0.65 (0.53-0.79)



C

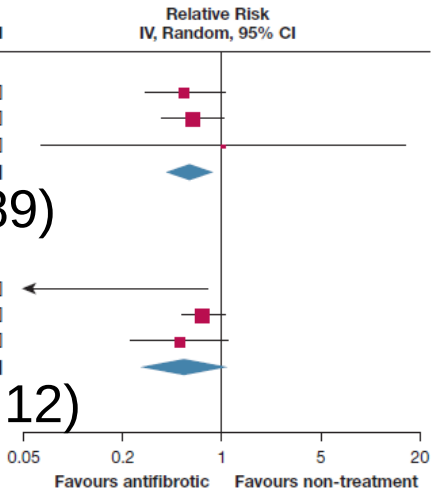
Study or Subgroup	log[Relative Risk]	SE	Antifibrotic Total	Non-treatment Total	Weight	Relative Risk IV, Random, 95% CI
Nintedanib						
Richeldi 2011	−0.5621	0.3019	343	85	38.8%	0.57 [0.32, 1.03]
Richeldi 2014	−0.4427	0.2441	638	423	59.4%	0.64 [0.40, 1.04]
Lancaster 2020	0.0177	1.4016	56	57	1.8%	1.02 [0.07, 15.88]
Subtotal (95% CI)			**1,037**	**565**	**100.0%**	**0.62 [0.43, 0.89]**
Heterogeneity: Tau² = 0.00; χ² = 0.22, *df* = 2 (*P* = .89); I² = 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: Tau² = 0.18; χ² = 4.27, *df* = 2 (*P* = .12); I² = 53%						
Test for overall effect: Z = 1.62 (*P* = .10)						
Test for subgroup differences: χ² = 0.04, *df* = 1 (*P* = .84), I² = 0%						

Nintedanib

0.62 (0.43-0.89)

Pirfenidone

0.57 (0.29-1.12)



CHEST 2021; 160(5):1751-1763

Effect of nintedanib on acute exacerbations of fibrosing interstitial lung diseases: a national database study in Japan

Hirokazu Urushiyama[1], Taisuke Jo[1,2], Wakae Hasegawa[1], Akira Yokoyama[1], Takahiro Ando[1], Yukiyo Sakamoto[1], Ryosuke Kumazawa[3], Kazuaki Uda[3], Nobuaki Michihata[2], Nobuyasu Awano[4], Matsui Hiroki[3], Kiyohide Fushimi[5], Hideo Yasunaga[3] and Takahide Nagase[1]

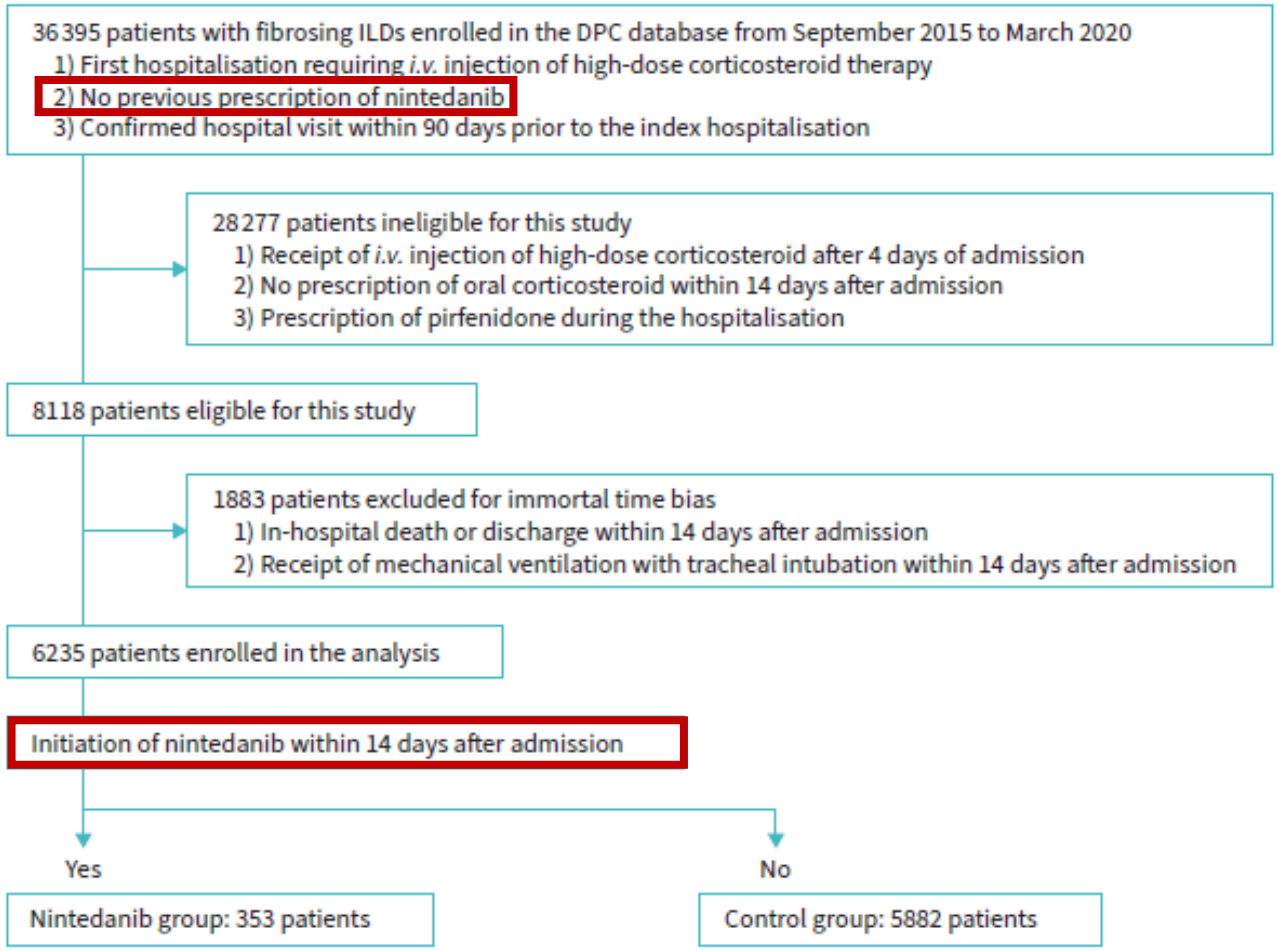


FIGURE 2 Flow diagram of the study. ILD: interstitial lung disease; DPC: Diagnosis Procedure Combination.

Retrospective cohort study

TABLE 3 Outcomes with or without nintedanib in the original and adjusted cohorts

	Original cohort			Adjusted cohort		
	Control group (n=5882)	Nintedanib group (n=353)	p-value	Control group (n=3118)	Nintedanib group (n=3118)	p-value
In-hospital death	804 (13.7)	21 (6.0)	<0.001	471 (15.1)	222 (7.1)	<0.001
Length of hospital stay (days)	39.9±22.2	30.4±12.6	<0.001	37.5±19.0	30.7±13.7	<0.001

Data are presented as n (%) or mean±SD, unless otherwise stated. After overlap propensity score weighting, nintedanib treatment was significantly associated with lower in-hospital mortality in the adjusted cohort (OR 0.43, 95% CI 0.27–0.70; p=0.001).

In-hospital mortality
IPF patients
Nintedanib 8.9% vs. control 14%, p<0.001

Non-IPF patients
Nintedanib 2.8% vs. control 17.7%, p<0.001

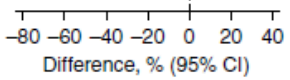
ERJ Open Res 2022; 8: 00209-2022

Thrombomodulin Alfa for Acute Exacerbation of Idiopathic Pulmonary Fibrosis

A Randomized, Double-Blind Placebo-controlled Trial

Yasuhiro Kondoh[1], Arata Azuma[2], Yoshikazu Inoue[3], Takashi Ogura[4], Susumu Sakamoto[5], Kenji Tsushima[6], Takeshi Johkoh[7], Kiminori Fujimoto[8], Kazuya Ichikado[9], Yasuo Matsuzawa[10], Takefumi Saito[11], Kazuma Kishi[5], Keisuke Tomii[12], Noriho Sakamoto[13], Masahiro Aoshima[14], Jun Araya[15], Shinyu Izumi[16], Machiko Arita[17], Mitsuhiro Abe[18], Hiroyoshi Yamauchi[19], Joe Shindoh[20], Takafumi Suda[21], Masaki Okamoto[22], Masahito Ebina[23], Yoshihito Yamada[24], Yuji Tohda[25], Tetsuji Kawamura[26], Yoshio Taguchi[27], Hiroshi Ishii[28], Naozumi Hashimoto[29], Shinji Abe[30], Hiroyuki Taniguchi[1], Jun Tagawa[31], Koji Bessho[31], Natsuki Yamamori[31], and Sakae Homma[32]

Subgroup	No. of subjects		Survival proportion on Day 90 No. (%)		Favors	Favors	Difference in Survival proportion
	Placebo	ART-123	Placebo	ART-123	Placebo	ART-123	Percentage points (95% CI)
Overall	37	40	33 (89.2)	29 (72.5)			−16.7 (−33.8, 0.4)
Sex							
Male	30	37	27 (90.0)	27 (73.0)			−17.0 (−34.9, 0.9)
Female	7	3	6 (85.7)	2 (66.7)			−19.0 (−78.4, 40.3)
Age (y)							
< 65	5	8	5 (100.0)	7 (87.5)			−12.5 (−35.4, 10.4)
≥ 65	32	32	28 (87.5)	22 (68.8)			−18.8 (−38.5, 1.0)
IPF stage of JRS							
I, II	10	9	10 (100.0)	7 (77.8)			−22.2 (−49.4, 4.9)
III, IV	14	20	11 (78.6)	12 (60.0)			−18.6 (−49.0, 11.8)
Unknown	13	11	12 (92.3)	10 (90.9)			−1.4 (−23.7, 20.9)
Anti-fibrotic drugs (underlying IPF before AE-IPF)							
Yes	17	20	16 (94.1)	12 (60.0)			−34.1 (−58.3, −9.9)
No	20	20	17 (85.0)	17 (85.0)			0.0 (−22.1, 22.1)
Supplemental oxygen (underlying IPF before AE-IPF)							
Yes	7	16	6 (85.7)	8 (50.0)			−35.7 (−71.4, −0.0)
No	30	24	27 (90.0)	21 (87.5)			−2.5 (−19.5, 14.5)
PaO_2/FiO_2 ratio							
≤ 250	11	19	9 (81.8)	14 (73.7)			−8.1 (−38.3, 22.1)
> 250	26	21	24 (92.3)	15 (71.4)			−20.9 (−42.7, 1.0)
HRCT score							
< 245	33	28	30 (90.9)	23 (82.1)			−8.8 (−26.0, 8.5)
≥ 245	4	12	3 (75.0)	6 (50.0)			−25.0 (−76.0, 26.0)
CRP (mg/dL)							
< 5	22	17	19 (86.4)	14 (82.4)			−4.0 (−27.1,19.1)
≥ 5	15	23	14 (93.3)	15 (65.2)			−28.1 (−51.3, −4.9)
D-dimer (mg/L)							
< 2	18	21	17 (94.4)	17 (81.0)			−13.5 (−33.3, 6.4)
≥ 2	19	19	16 (84.2)	12 (63.2)			−21.1 (−48.2, 6.1)



AE of IPF: coagulation abnormalities and endothelial damage

- Thrombomodulin alfa, a recombinant human soluble thrombomodulin

anticoagulant and anti-inflammatory effects

Am J Respir Crit Care Med Vol 201, Iss 9, pp 1110–1119, May 1, 2020

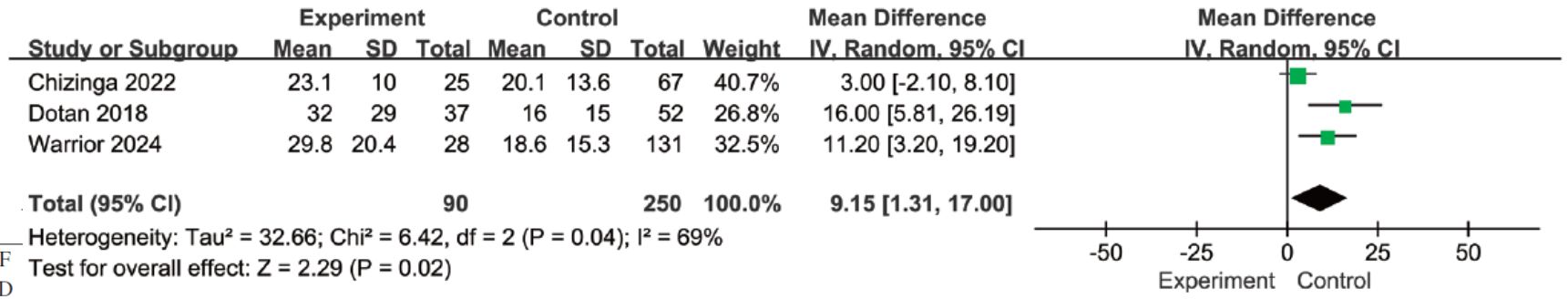
Prognosis of Lung Transplantation in Patients with Acute Exacerbations of Interstitial Lung Disease: A Meta-Analysis Based on Cohort Studies

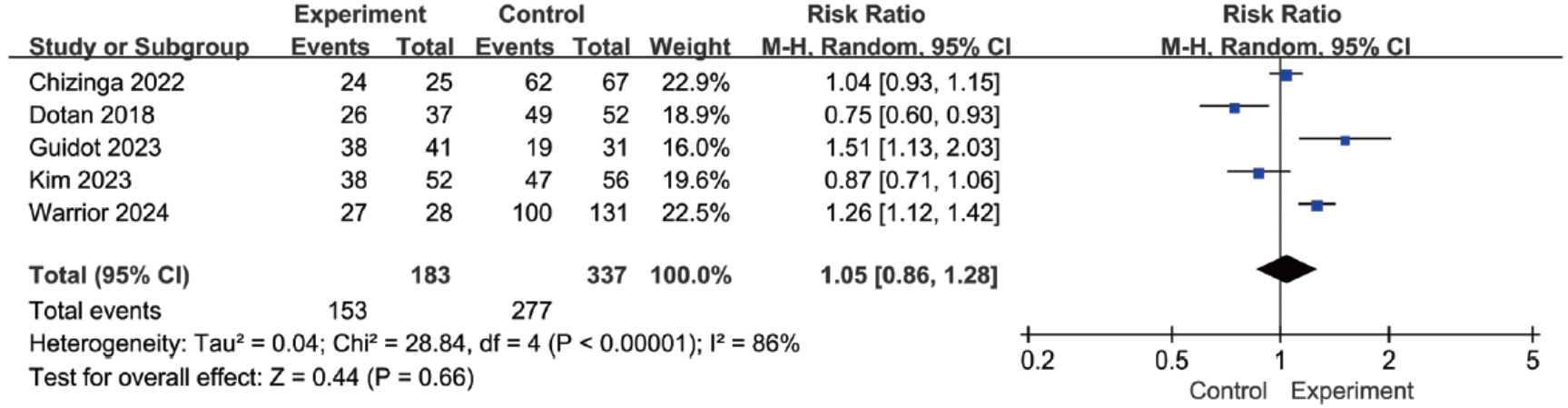
Lei Yang,[1] Zhiyi Xiang,[2] Min Dai,[3] Qiufeng Zhang,[2] and Ying Zhou[2]

Ann Thorac Cardiovasc Surg 2024: 30; 24–00086

Author	Year	Recruitment time	Country	Experiment	Control
Dotan	2018	2012.1-2016.9	America	AE-IPF	Stable-IPF
Chizinga	2022	2015.1-2018.12	America	AE-ILD	Stable-ILD
Kim	2022	2008.10-2022.1	Korea	AE-ILD	Stable-ILD
Guidot	2023	2005.5-2019.4	America	AE-ILD	Stable-ILD
Warrior	2024	2005.7-2020.7	America	AE-IPF	Stable-IPF

Five cohort studies
183 patients in AE-ILD
337 patients in stable ILD





Take home message

Does high-dose steroid therapy improve prognosis in AE-ILD?

- Evidence is limited
  - No clear survival benefit has been demonstrated
  - High mortality is observed regardless of high-dose steroid use

- High heterogeneity
  - Steroid response differs by ILD subtypes, triggers, and underlying pathologies

- Potential risks
  - Infections, fracture, venous thromboembolism, GI bleeding

High-dose steroid use should be individualized with careful consideration