IPF 의 급성악화
새 정의와 치료

경희의료원
호흡기내과
최혜숙

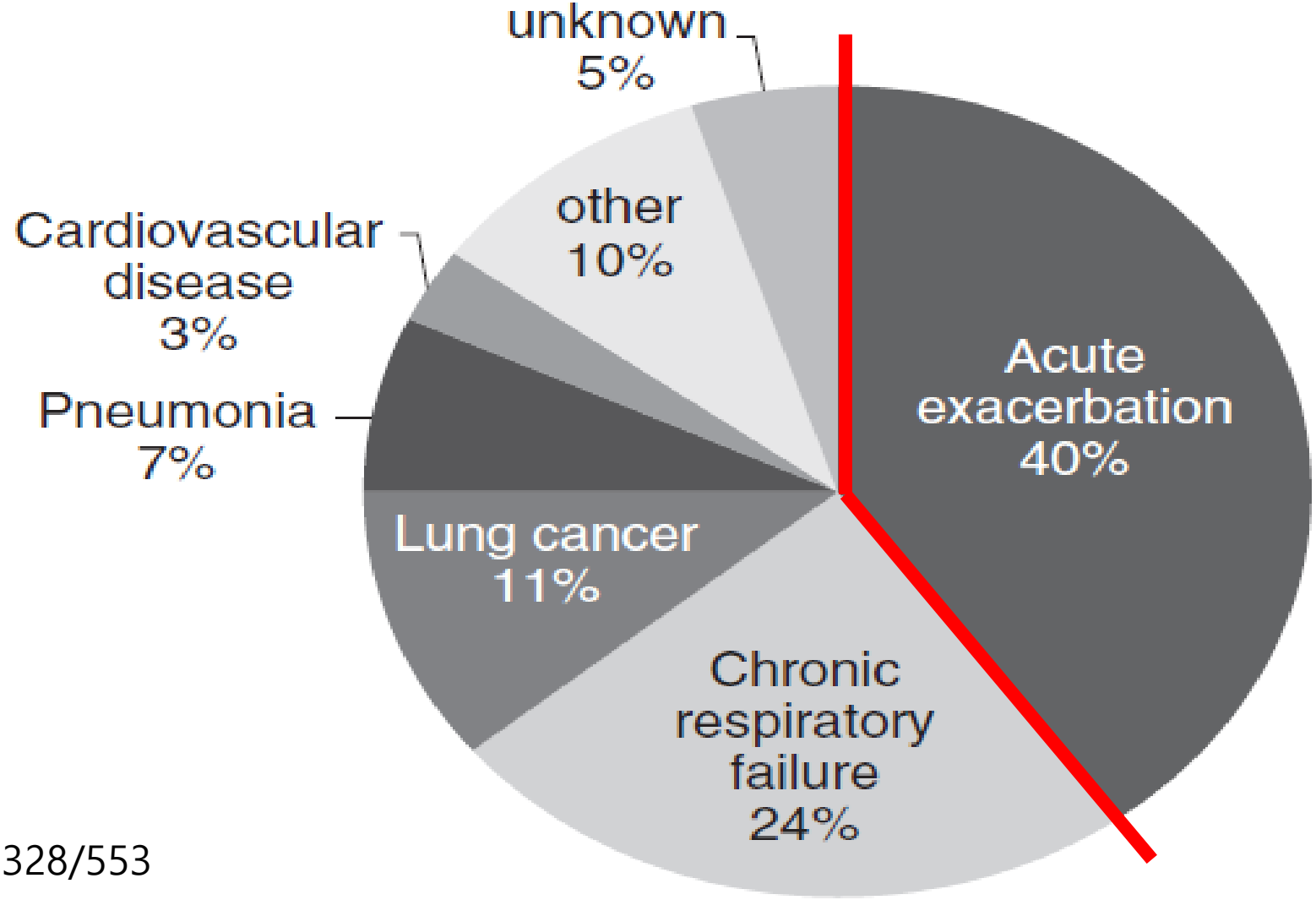
ILD School

- ✓IPF 에서 급성악화의 의미
- ✓IPF 급성악화 위험인자, 예후
- ✓IPF 급성악화 새 정의
- ✓IPF 급성악화 치료

➢**오늘**

- 2015~2019 저널
- AE of IPF
  : 새 정의 와 치료

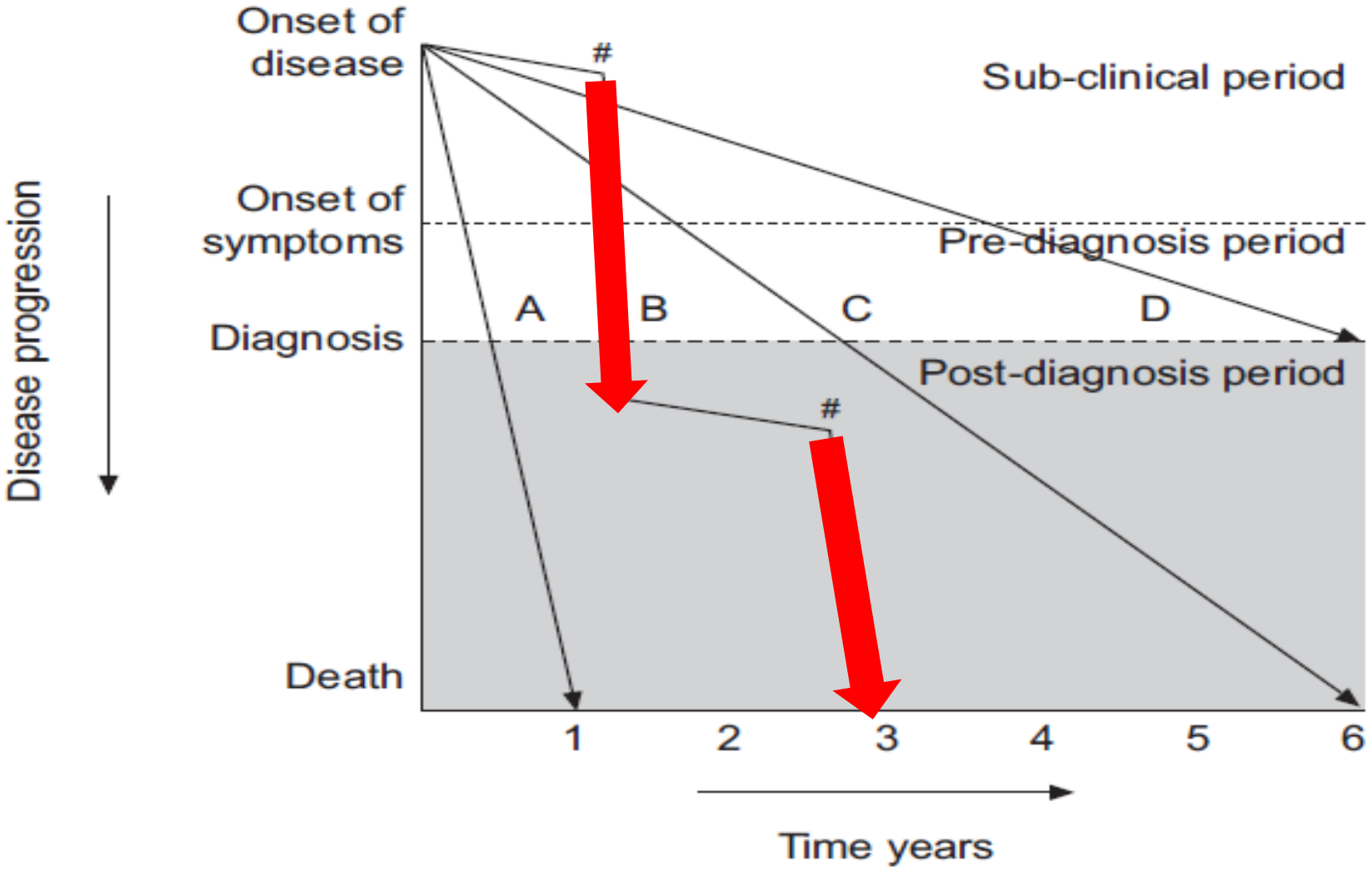
Causes of death in patients with IPF



N=328/553

AJRCCM 2014 Oct 1;190(7):773-9.

Clinical courses of IPF



AJRCCM 2011 Feb 15;183(4):431-40

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

➢ acute exacerbation

➢ **Clinical manifestation**

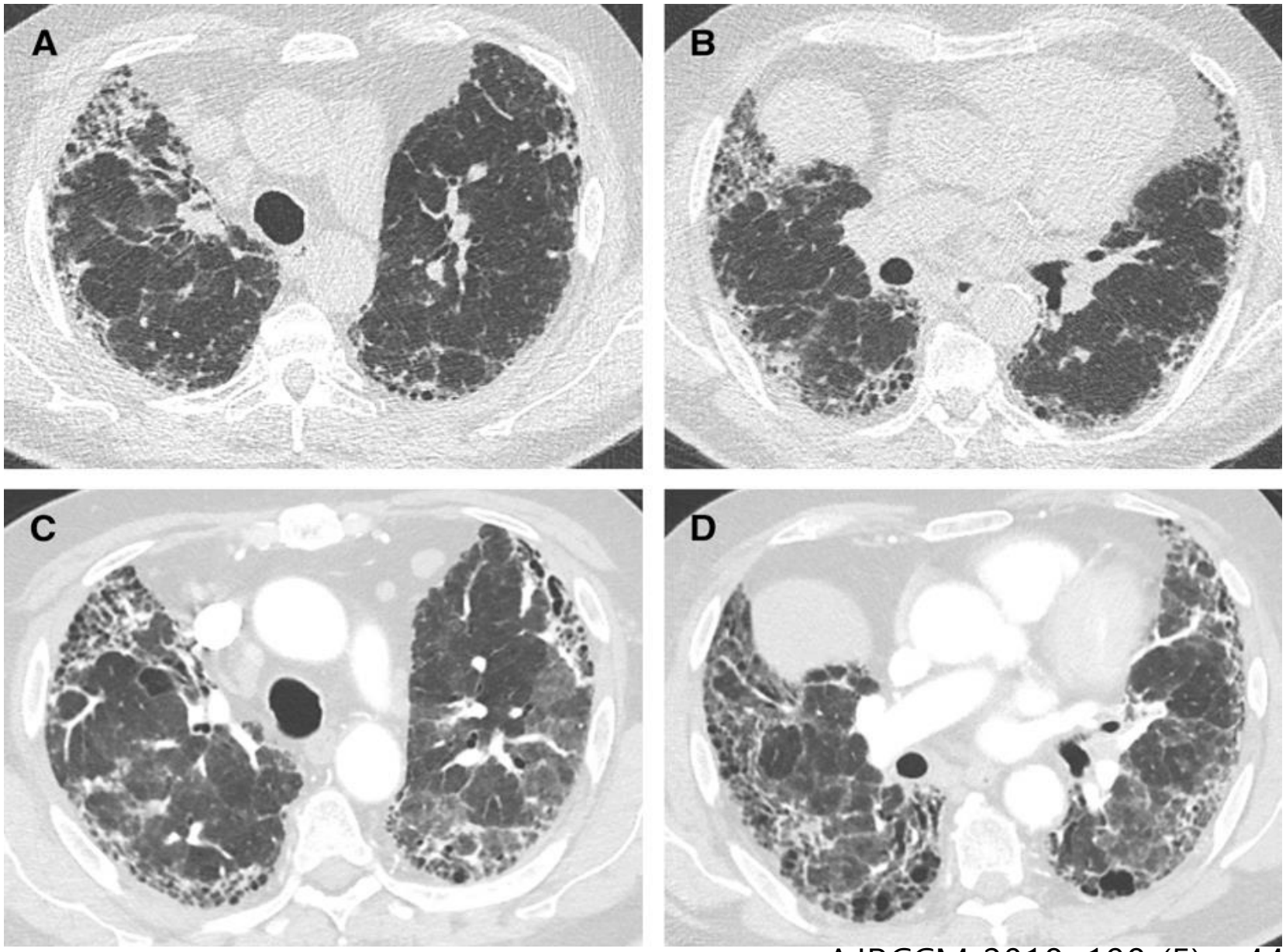
worsening of dyspnea over a few weeks and

new GGO on HRCT scan with a background of lower lobe fibrotic lung disease

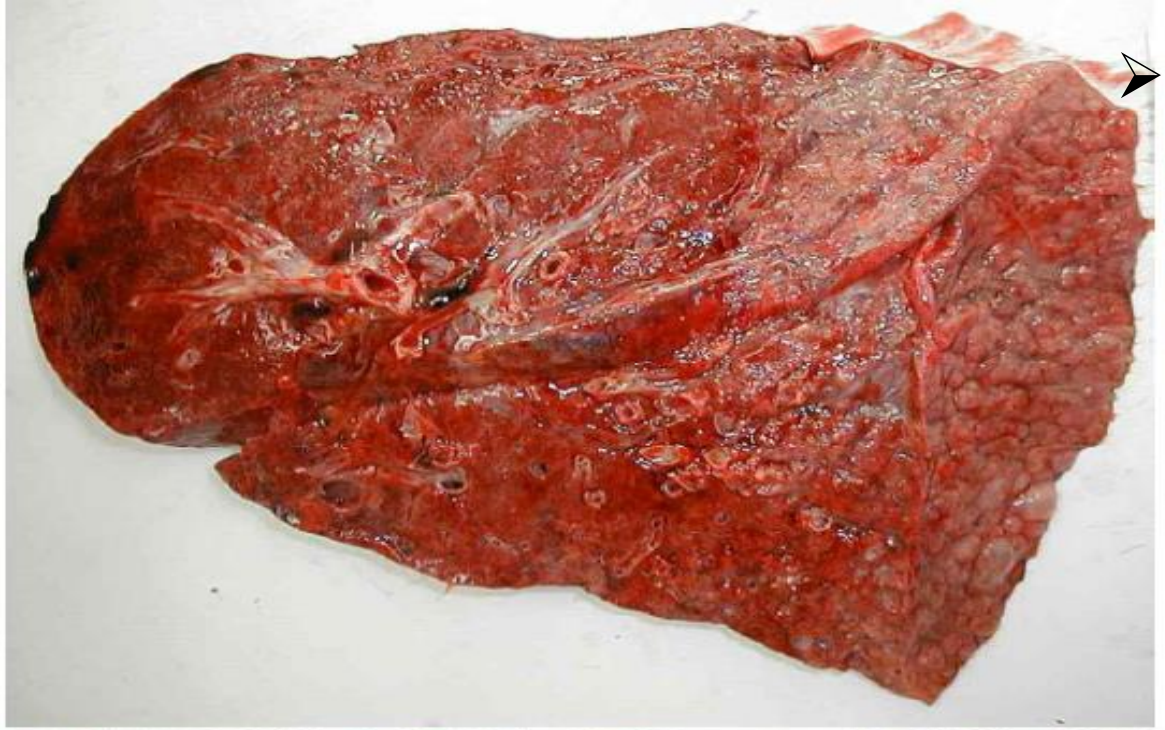
➢ **Diagnosis, HRCT technique**

AJRCCM 2018: 198 (5), e44–e68

CT findings in the presence of an AE

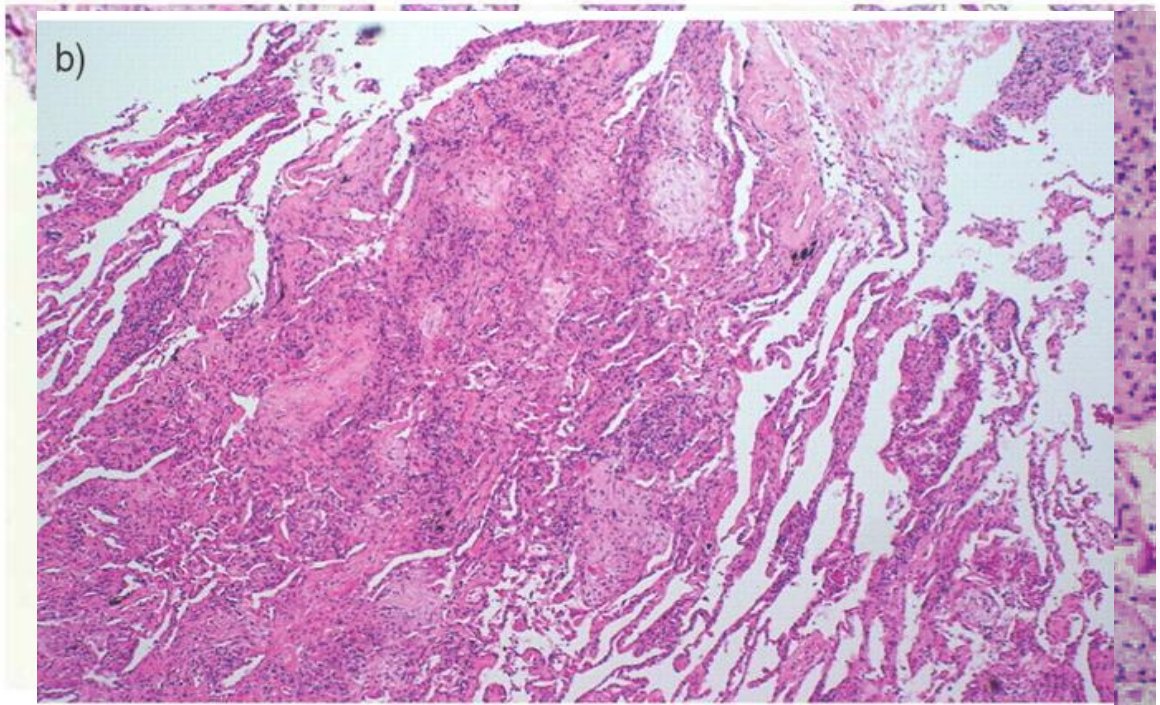


AJRCCM 2018: 198 (5), e44–e68



➢ Histopathologic pattern

A: dense, liver-like aspect of the lung, with reticulation on the surface



B. **UIP pattern** with honeycombing and cyctic changes and **DAD** with hyperplastic pneumocityes

± **hyaline membrane**

or **COP**

Intern Emerg Med 2015; 10; 401-411

Chest. 2005 Nov;128(5):3310-5.

Eur Respir J. 2006 Jan;27(1):143-50

Epidemiology of AE

TABLE 1 Incidence of acute exacerbation (AE) and rapid deterioration (RD)

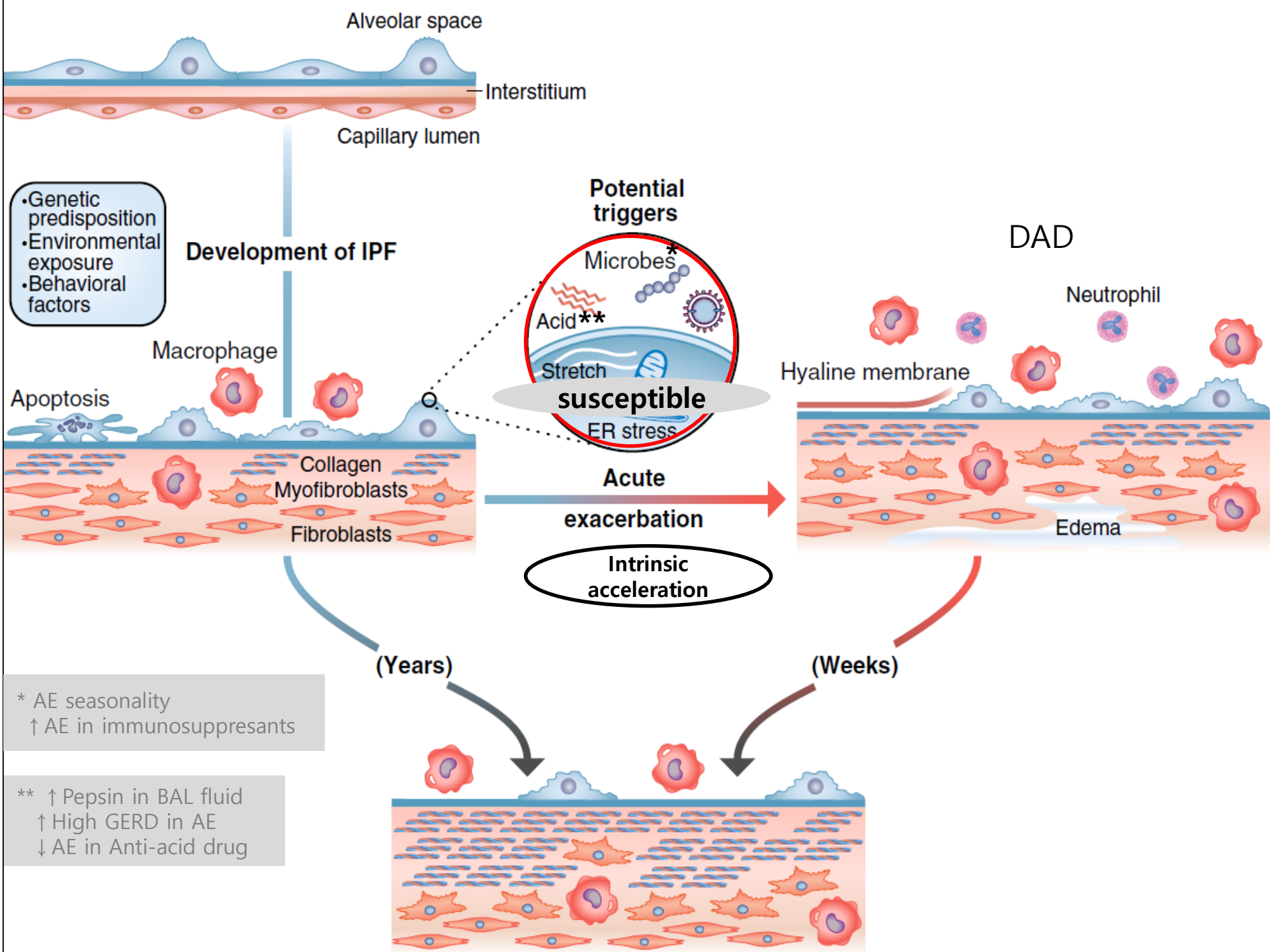
Incidence[#]	AE[¶]	RD
1-yr	58 (14.2)	97 (23.0)
2-yr	71 (18.8)	124 (31.2)
3-yr	75 (20.7)	134 (35.4)

Data are presented as n (%). The cumulative incidences of AE, excluding patients first presented at the time of AE, are 11.6% (1-yr), 16.3% (2-yr) and 18.2% (3-yr). [#]: first event; [¶]: 14 patients first presented at the time of AE.

Song *et al.*, 2011 (13)	461	IPFnet	14.2% incidence at 1 yr; 20.7% incidence at 3 yr
Sugino *et al.*, 2015 (11)	64	IPFnet	28% incidence at 3 yr; 43% incidence at 5 yr
Tomassetti *et al.*, 2013 (53)	122	IPFnet	19% incidence over median follow up of 2.5 yr

AJRCCM 2016;194(3):265-75

Eur Respir J 2011 37: 356-363


Alveolar space
Interstitium
Capillary lumen
•Genetic predisposition
•Environmental exposure
•Behavioral factors
Development of IPF
Macrophage
Apoptosis
Collagen
Myofibroblasts
Fibroblasts
Potential triggers
Microbes*
Acid**
Stretch
susceptible
ER stress
Acute
exacerbation
Intrinsic acceleration
DAD
Neutrophil
Hyaline membrane
Edema
(Years)
(Weeks)
* AE seasonality
↑ AE in immunosuppresants
** ↑ Pepsin in BAL fluid
↑ High GERD in AE
↓ AE in Anti-acid drug

Risk Factors of AE

- Low FVC
- low DLCO
- Low 6MWD
- Pulmonary hypertension
- poor baseline oxygenation
- increased dyspnea
- Recent decline in FVC

➢physiologically and functionally **advanced disease**

➢comorbid coronary artery disease…..

➢higher BMI

➢Prior history of AE

➢elevated serum level of Krebs von Lungen-6 (KL-6)

AJRCCM 2016;194(3):265-75

Prognosis of AE

- lower baseline **FVC and DLCO**
- more extensive **CT** abnormalities at the time of AE
- Worse **oxygenation**
- BAL **neutrophil** and lymphocyte percentages
- LDH, CRP, KL-6, fibrocytes, HSP 70, Ferritin
- Dyspnea duration
- Treatment delay

AJRCCM 2016;194(3):265-75

2007 Definition and Diagnostic Criteria for AE of IPF

Definition	An acute, clinically significant, respiratory deteriorartion of unidentifiable cause
Diagnostic criteria	
– Previous diagnosis	Previous or concurrent diagnosis of IPF
– Clinical presentation	Unexplained worsening or development of dyspnea within 30 days
– Computed tomography findings	New bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with UIP pattern
– Exclusion of differential diagnosis	Exclusion of alternative causes, including left heart failure, pulmonary embolism and an identifiable cause of acute lung injury
– Concomitant Infection	No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage

Definite VS. Suspected AE

AJRCCM 2007;176:636-643

Table 2 24-week mortality by acute worsening status

Group	Number of deaths	Number at risk	24-week mortality
Acute Exacerbation of IPF *	8	17	47%
Other Acute Worsening	6	13	46%
No Acute Worsening	1	150	1%

* Combined definite and suspected cases. Two deaths were in the definite acute exacerbation group (50% mortality rate at 24 weeks) and six deaths were in the suspected acute exacerbation group (46% mortality rate at 24 weeks).
Abbreviations: *IPF*, idiopathic pulmonary fibrosis.

Definite AE 50% ≒ Suspected AE 46%

Respir Res. 2013 Jul 13;14:73

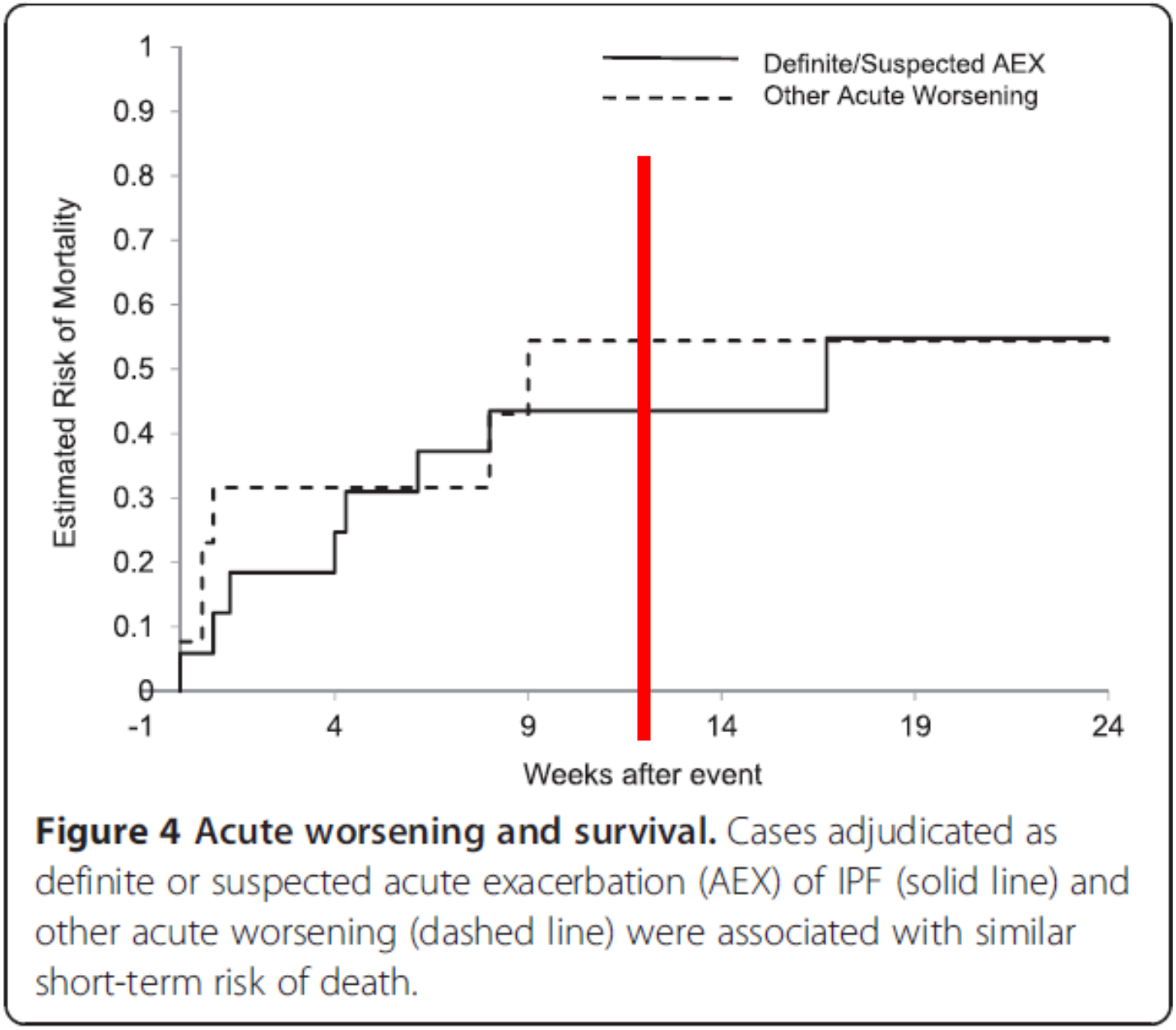
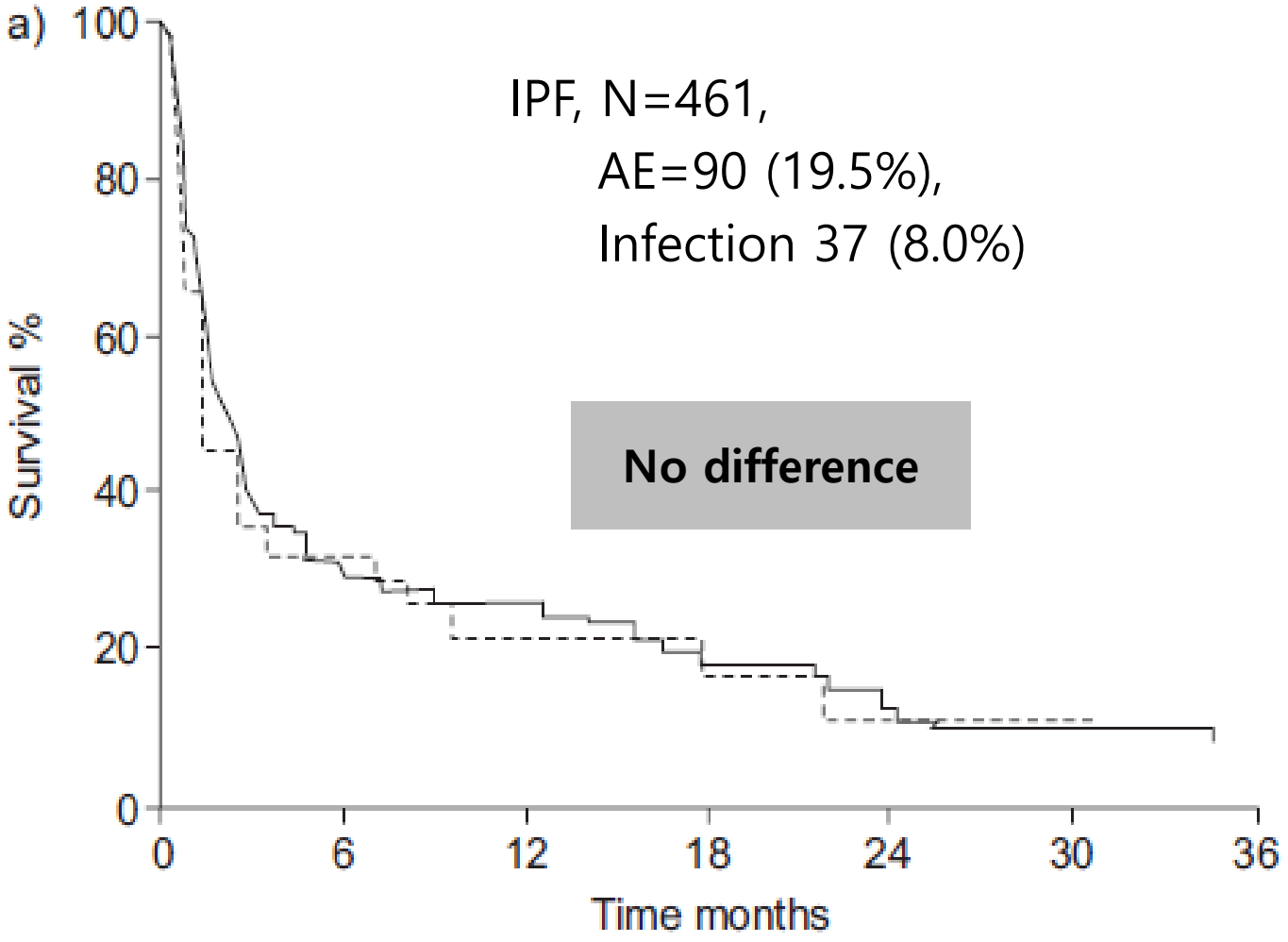


Figure 4 Acute worsening and survival. Cases adjudicated as definite or suspected acute exacerbation (AEX) of IPF (solid line) and other acute worsening (dashed line) were associated with similar short-term risk of death.

Respir Res. 2013 Jul 13;14:73

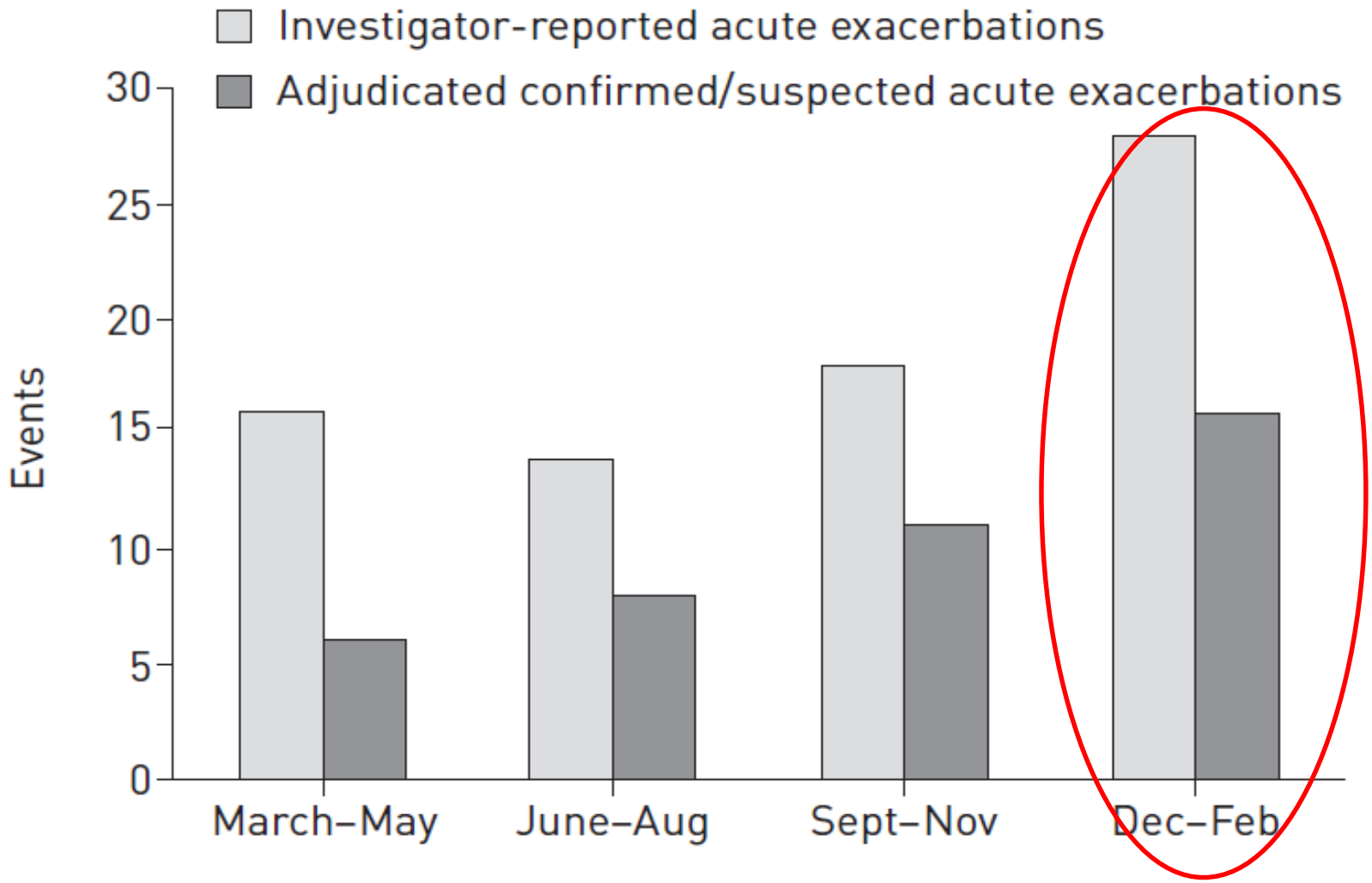
Comparison of Survival Curves between AE and Infection from onset of rapid deterioration



Eur Respi J 2011 37: 356-363

Seasonality of AE

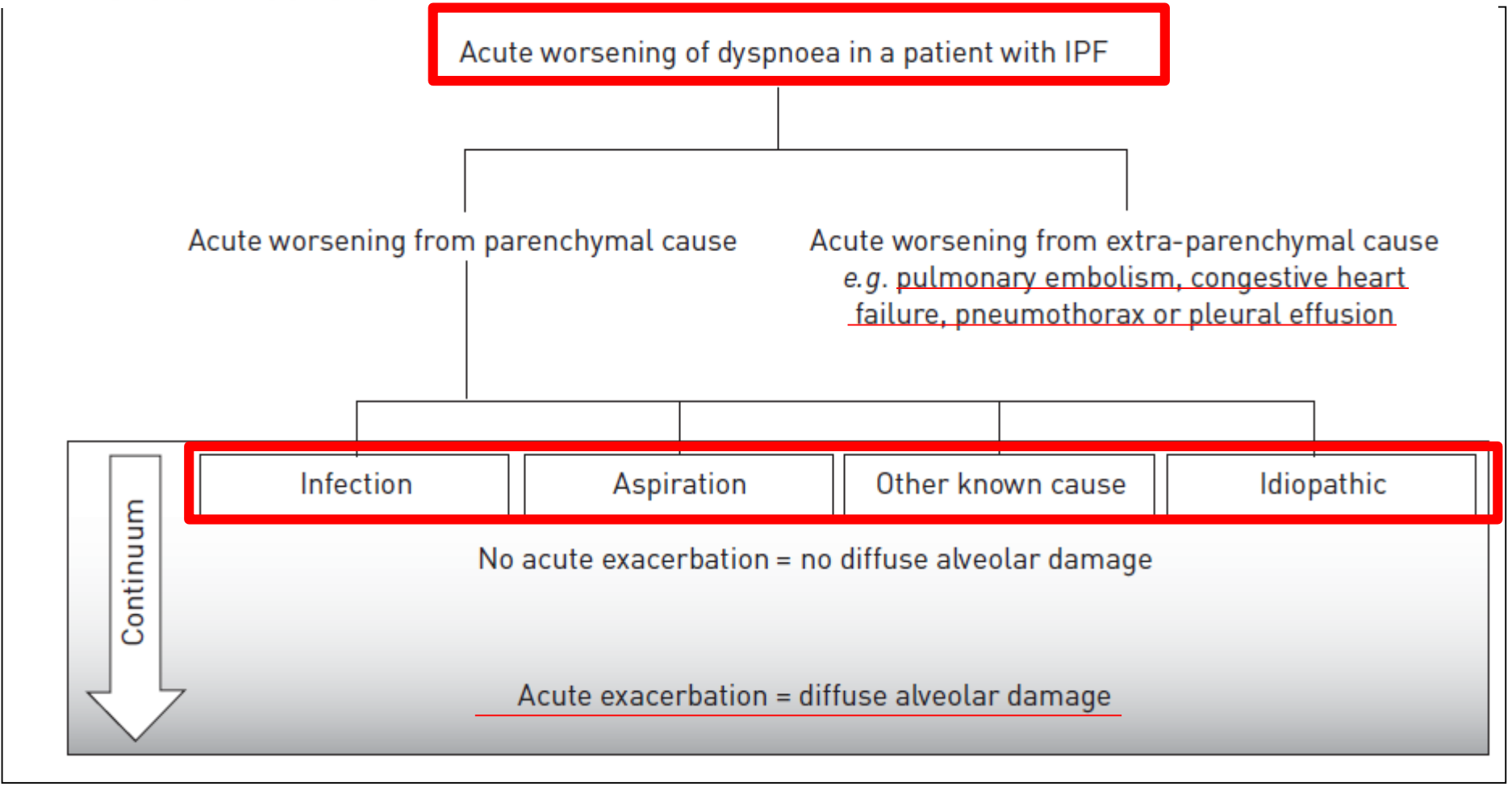
in the INPULSIS trials of nintedanib



Eur Respir J 2017; 49: 1601339

Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm

Christopher J. Ryerson[1], Vincent Cottin[2], Kevin K. Brown[3] and Harold R. Collard[4]



Eur Respir J 2015; 46: 243–249.

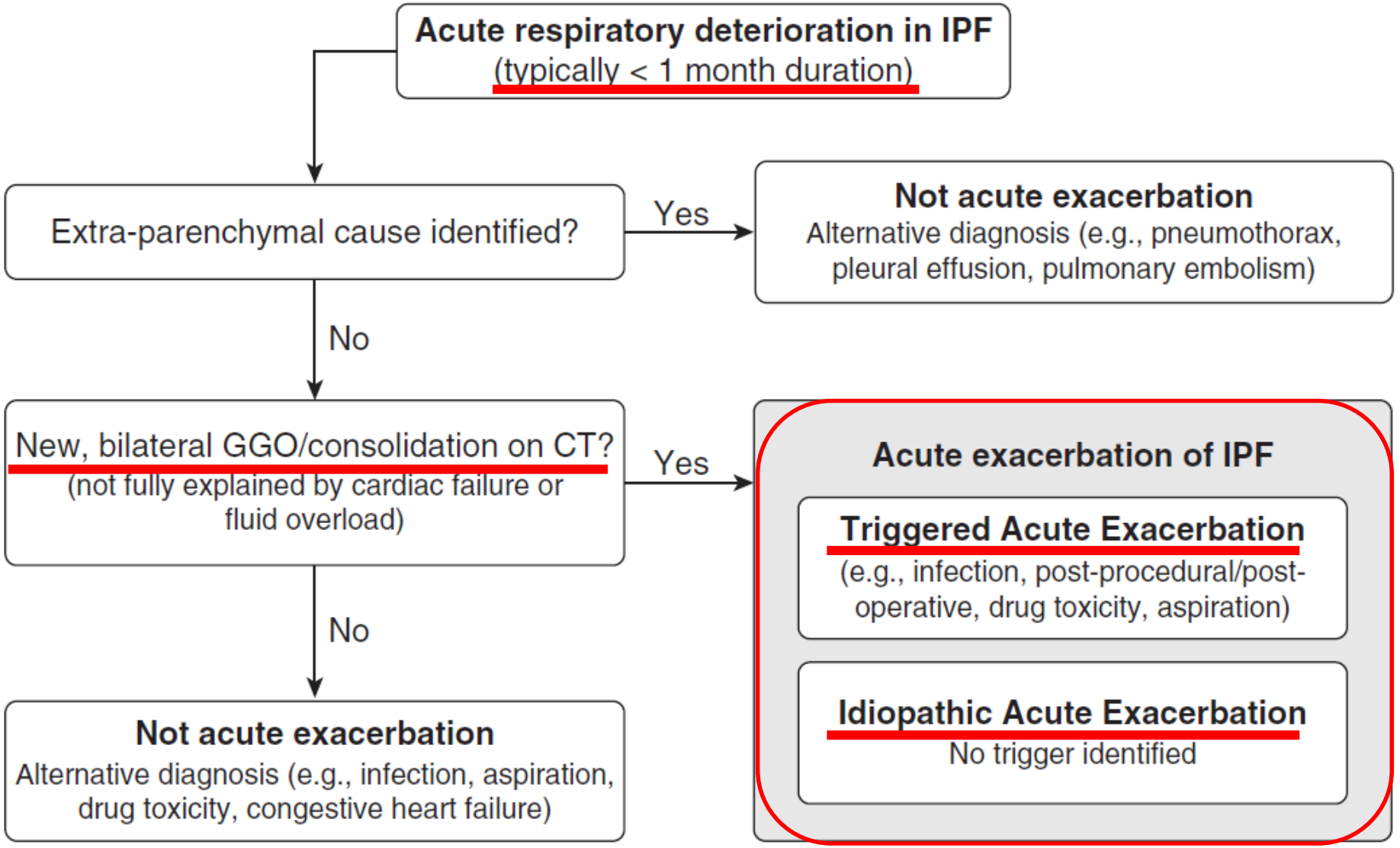
Acute Exacerbation of Idiopathic Pulmonary Fibrosis

An International Working Group Report

Database inception ~February 14, 2016

AJRCCM **2016**;194(3):265-75

Proposed conceptual framework for evaluation of acute respiratory deterioration in IPF



AJRCCM 2016;194(3):265-75

Proposed Revised Definition and Diagnostic Criteria for AE of IPF

Revised definition

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

Revised 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 usual interstitial pneumonia pattern†
- Deterioration not fully explained by cardiac failure or fluid overload

Suspected AE ≤3 criteria owing to missing CT

AJRCCM 2016;194(3):265-75

BMJ Open Respiratory Research

Acute exacerbation of idiopathic pulmonary fibrosis: a 10-year single-centre retrospective study

Masatoshi Yamazoe, Hiromi Tomioka

2008-2017 JAPAN
Using new definition of AE

BMJ Open Resp Res 2018;5:e000342

Table 1 Comparison of patients' characteristics in idiopathic and triggered groups in AE-IPF

	Total (n=64)	Idiopathic (n=42)	Triggered (n=22)	P values
Treatments after AE-IPF				
Intravenous high-dose steroids	42 (65.6)	31 (73.8)	11 (50)	0.06
Antibiotic therapy	52 (81.3)	32 (76.2)	20 (90.9)	0.19
Azithromycin	12 (18.8)	9 (21.4)	3 (13.6)	0.52
Mechanical ventilation	2 (3.1)	0	2 (9.1)	0.11
Length of hospital stay, median (range; days)	27.5 (2–119)	26 (2–91)	28 (3–119)	0.46
In-hospital death	35 (54.7)	22 (52.4)	13 (59.1)	0.61

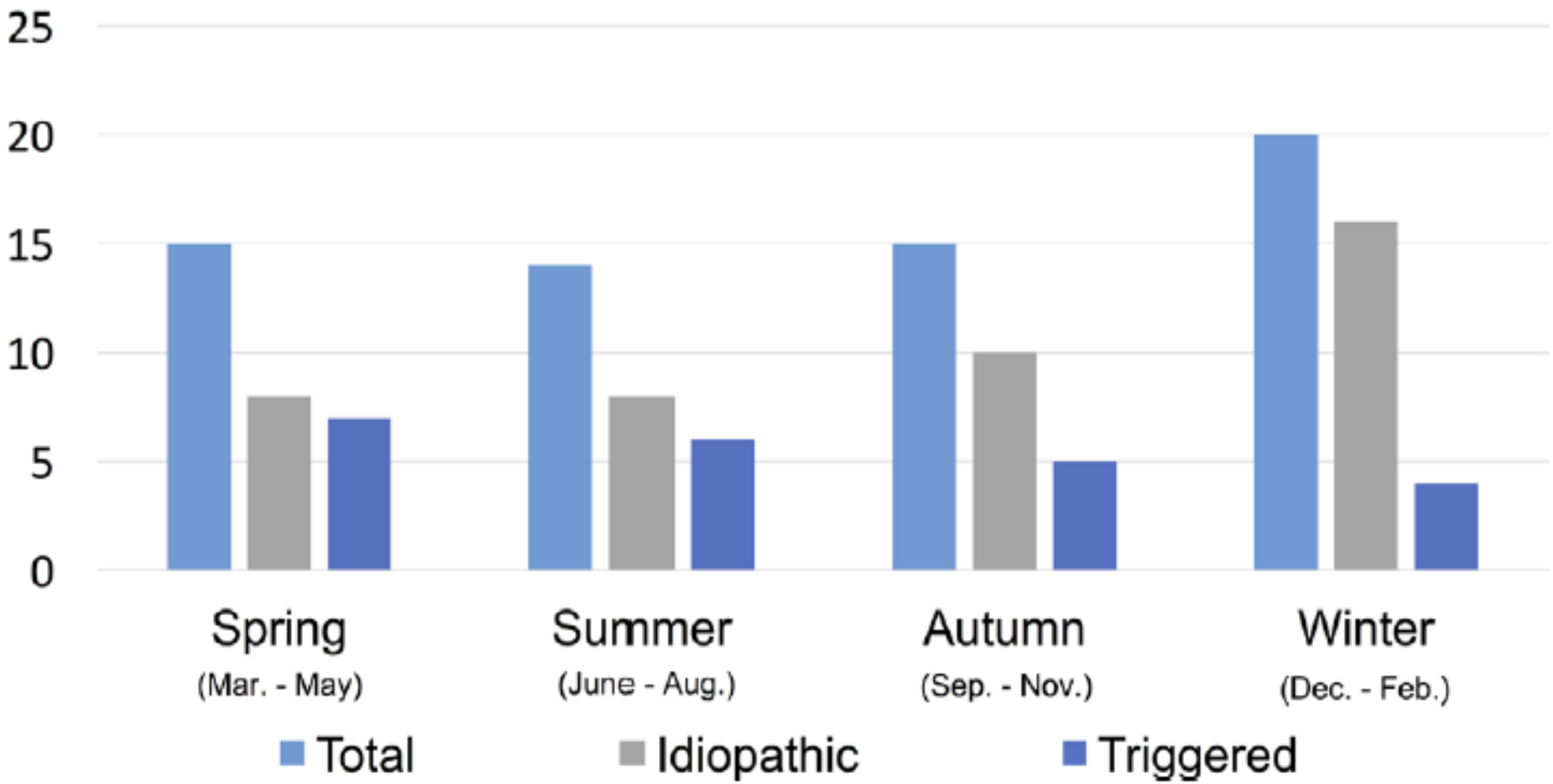


Figure 2 Seasonal variation in the occurrence of AE-IPF. AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis.

BMJ Open Resp Res 2018;5:e000342

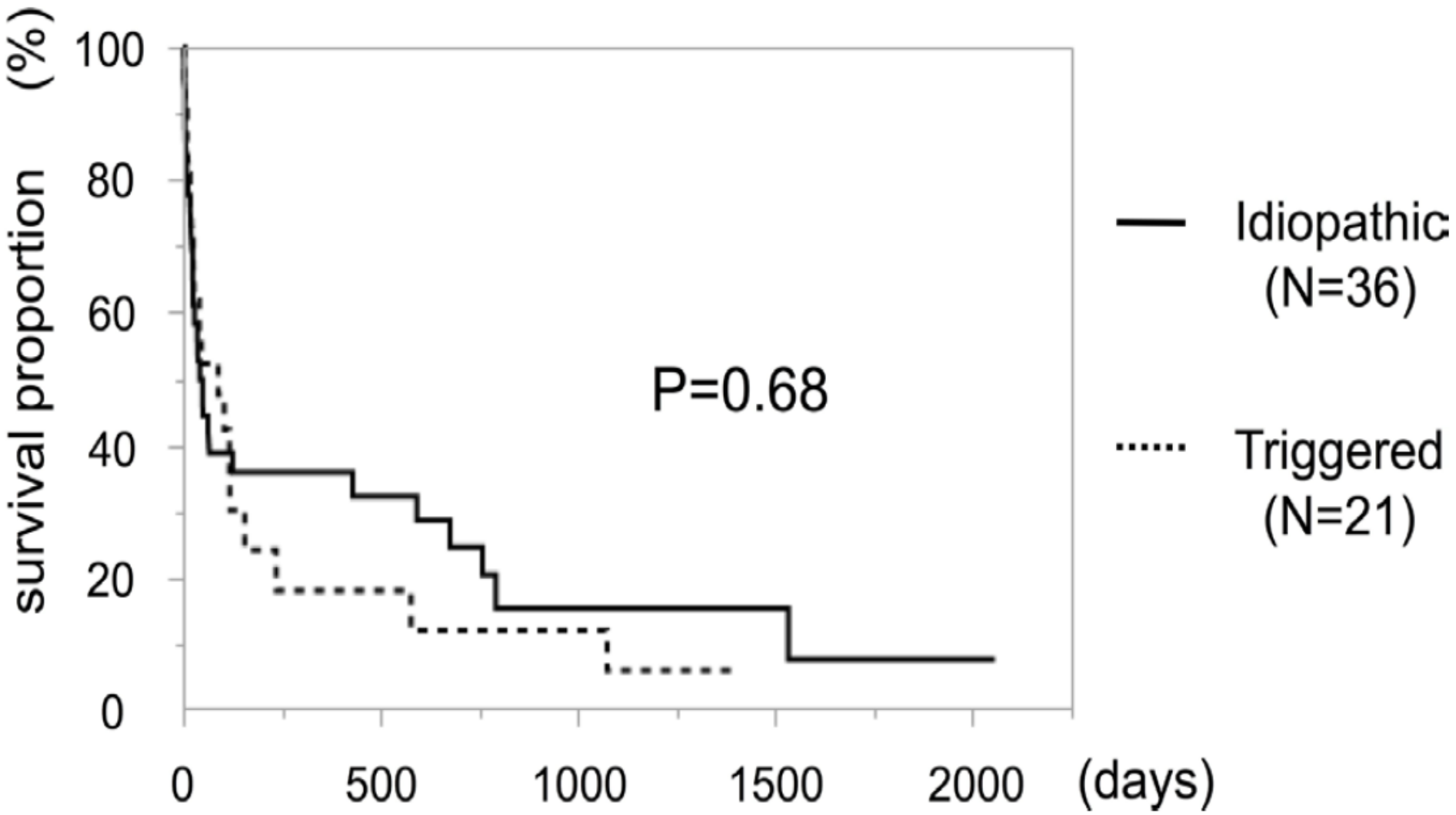


Figure 3 Survival after hospitalisation, idiopathic AE versus triggered AE. AE, acute exacerbation.

BMJ Open Resp Res 2018;5:e000342

Management of AE

- No proven, effective therapies for AE of IPF.

consider

- supportive care and unproven interventions.

AJRCCM 2016;194(3):265-75

MV with ARF in IPF

Table 1 Outcome studies on IPF patients ventilated in ICU

Study (period observed)	Number of IPF patients ventilated	Hospital mortality	Overall short-term mortality
Blivet et al.,[11] France (1989–1998)	15		
Molina-Molina et al.,[12] Spain (1986–2002)	14		
Saydain et al.,[13] USA (1995–2000)	19		
Nava and Rubini,[14] Italy	7		
Stern et al.,[15] France (1991–1999)	23	22	
Al-Hameed and Sharma,[16] Canada (1988–2000)	25	24	24
Fumeaux et al.,[17] Switzerland (1996–2001)	11	11	11
Kim et al.,[10] South Korea (1990–2003)	9	7	8
Pitsiou et al.,[18] Greece (2001–2005)	12	12	12
Total	135	118	127

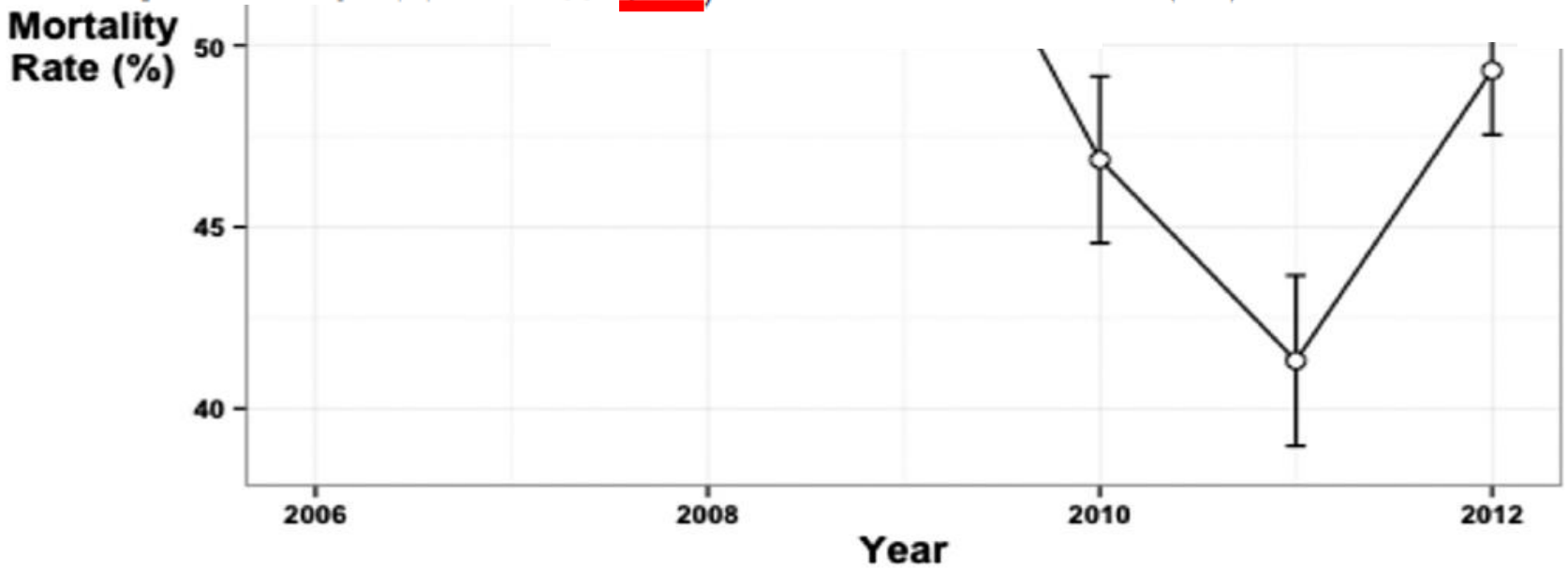
87%

3Mo.
94%

Respir Med 2008;102:1355–1359

Hospital Mortality in MV patients of AE-IPF by year

	Mechanical ventilation (n = 1703)	Non invasive ventilation (n = 778)	p-value
Age in years, mean (SD)	66.3 (12.8)	70.2 (12.9)	<0.0001
Length of Stay in days, Median (IQR)	13.3 (16)	6.5 (7)	<0.0001
Total Hospital mortality, n(%)	887 (51.9)	241 (30.9)	<0.0001



Respiratory Medicine 2016 :111; 72e76

Therapies for AE of IPF

Potential Therapy*	Study	Summary
Randomized controlled clinical trials		
Nintedanib (preventative therapy)	Richeldi *et al.*, 2011 (75); Richeldi *et al.*, 2014 (15)	Richeldi (2011): 432 patients. Highest dose of nintedanib resulted in lower incidence of acute exacerbation than placebo (2.4 vs. 15.7 per 100 patient-years, $P = 0.02$) Richeldi (2014): Two parallel trials, 1,066 patients. In the first, no significant difference in time to first investigator-reported acute exacerbation was found (HR, 1.15; $P = 0.67$). In the second, there was a significant benefit (HR, 0.38; $P = 0.005$)
Pirfenidone (preventative therapy)	Azuma *et al.*, 2005 (76); Taniguchi *et al.*, 2010 (47)	Azuma: 107 patients. Acute exacerbation occurred exclusively in the placebo group (5 events vs. no events, $P = 0.0031$) Taniguchi: 275 patients. No significant difference in acute exacerbation seen between treatment groups (5.6 vs. 5.5 vs. 4.8%)
Cohort studies		
Anti-acid therapy (preventative therapy)	Controlled: Lee *et al.*, 2013 (23) Uncontrolled: none	Lee: 124 patients compared with 118 control subjects, all from placebo arms of clinical trials. Incidence of acute exacerbation was 0 vs. 8% favoring anti-acid therapy
Corticosteroid monotherapy	Controlled: none Uncontrolled: Akira *et al.*, 1997 (69); Al-Hameed *et al.*, 2004 (51); Suzuki *et al.*, 2011 (30); Tachikawa *et al.*, 2012 (68)	Total of 75 cases reported without control subjects
Cyclophosphamide	Controlled: none Uncontrolled: Akira *et al.*, 2008 (50); Fujimoto *et al.*, 2012 (55); Tachikawa *et al.*, 2012 (68); Yokoyama *et al.*, 2010 (70)	Approximately 128 cases reported without control subjects
Cyclosporine	Controlled: Homma *et al.*, 2005 (64); Inase *et al.*, 2003 (63); Sakamoto, *et al.* 2010 (65) Uncontrolled: Fujimoto *et al.*, 2012 (55); Yokoyama *et al.*, 2010 (70)	Homma: 9 patients compared with historical control subjects. Mean survival, 9.9 mo vs. 1.7 mo in control subjects Inase: 7 patients compared with 5 control subjects. Survival, 3 of 7 vs. 0 of 5 Sakamoto: 11 patients compared with 11 control subjects. Survival, 9 of 11 vs. 5 of 11 Approximately 11 cases reported without control subjects
Polymyxin-B immobilized fiber column hemoperfusion	Controlled: none Uncontrolled: Abe *et al.*, 2011 (71); Abe *et al.*, 2012 (56); Oishi *et al.*, 2013 (72); Seo *et al.*, 2006 (73); Tachibana *et al.*, 2011 (74)	Total of 127 cases reported without control subjects
Rituximab, plasma exchange and intravenous immunoglobulin	Controlled: Donahoe *et al.*, 2015 (66)	Donahoe: 11 patients compared with 20 historical control subjects; 1-year survival, 46 vs. 0% favoring rituximab and plasma exchange

Procalcitonin-Guided Antibiotic Use in AE of IPF

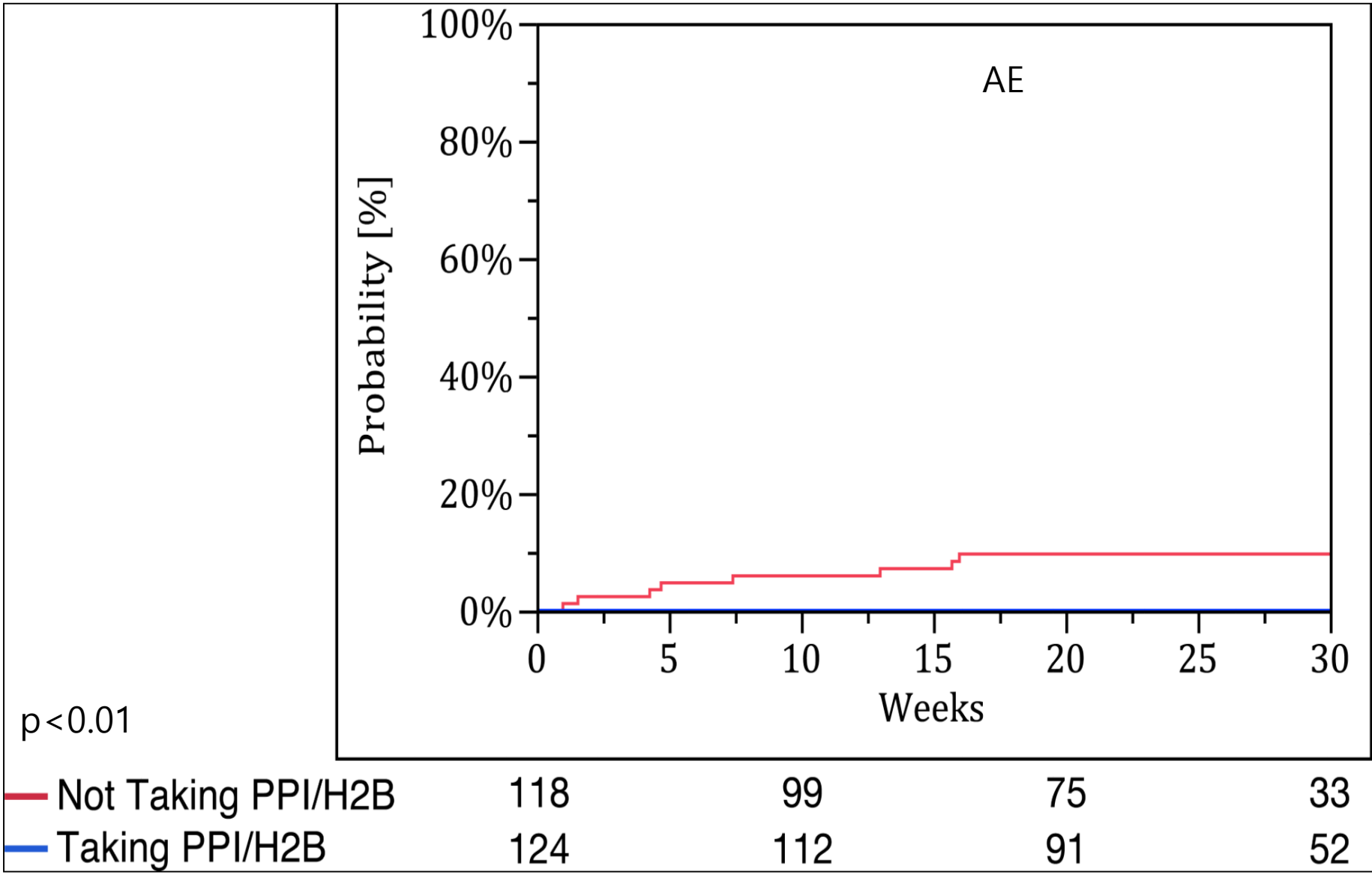
Table 1. Characteristics of patients with acute exacerbation of idiopathic pulmonary fibrosis.

Characteristics	PCT Group (33 cases)	Routine treatment Group (35 cases)	*P* value
Age (years)	72.3±5.5	73.0±6.30	0.63
Male sex, n (%)	19(57.6)	19(54.3)	0.61
Smoker	20	26	0.92
Duration of disease (months)	12±8.6	11.6±8.7	0.85
Dry cough	23	24	0.71
Clubbing	16	20	0.30
Inspiratory crackles	26	24	0.20
Fever	8	13	0.13
Duration of Corticosteroid therapy (months)	8.6±8.7	7.6±7.3	0.50
Duration of Immunosuppressive therapy (months)	1.7±3.2	2.1±3.4	0.60
PaO_2 (mmHg)	52.1±2.7	52.0±2.8	0.89
WBC ($\times 10^9$)	10.3±3.2	9.7±3.2	0.41
Neut (%)	67.9±7.7	69.7±7.5	0.33
Patients exposed to antibiotics treatment	26	35	<0.001
Duration of antibiotic treatment (days)*	8.7±6.6	14.5±5.2	<0.001
Duration of mechanical ventilation (days)*	14.3±7.4	15.7±8.2	0.49
Mortality (%)	21(63.6)	20(57.1)	0.42

*clinical outcomes at 30 day follow up in patients with AE-IPF. Definition of abbreviations: WBC = white blood cell; Neut = neutrophil.

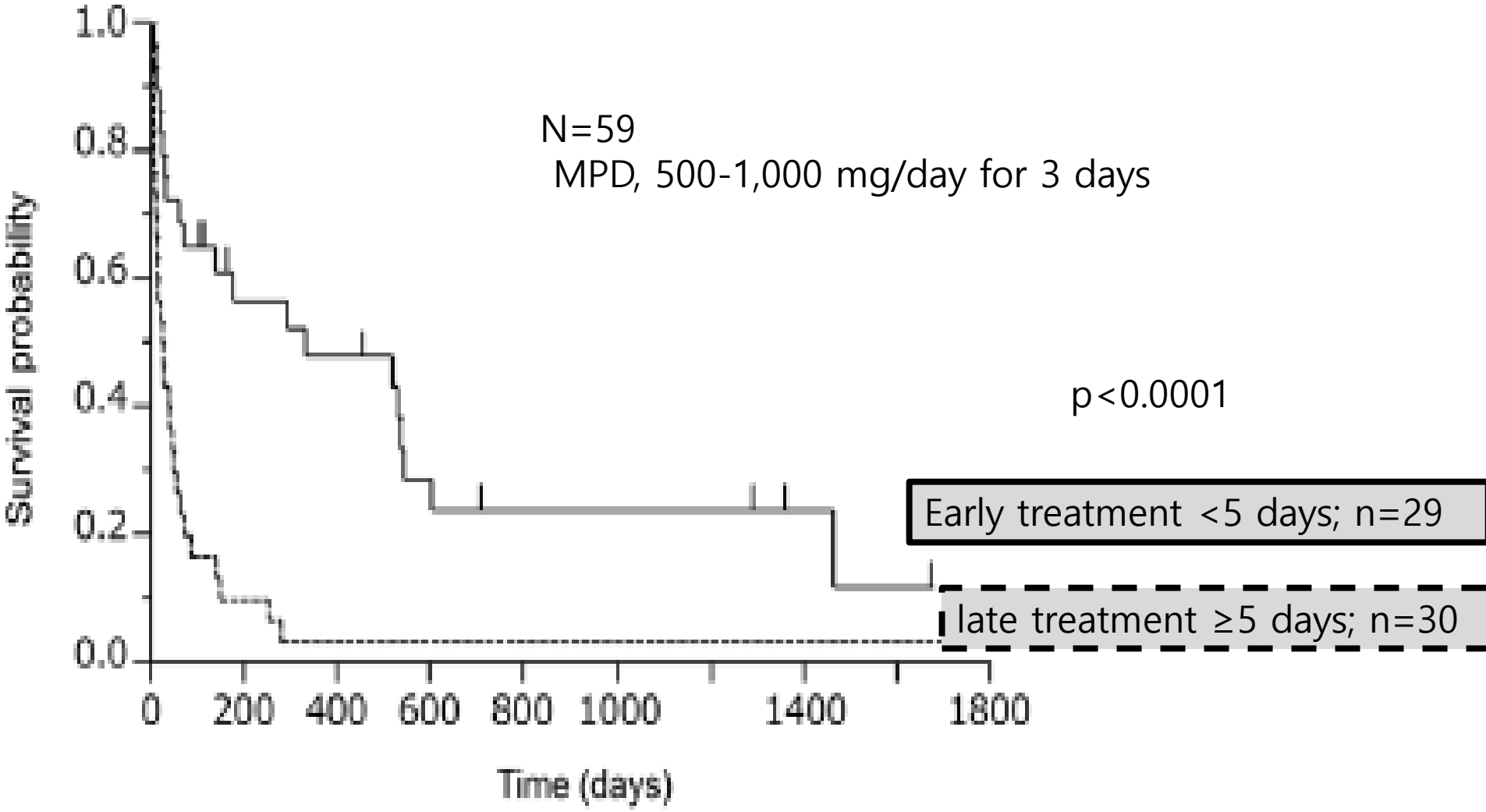
Ding et al. Int J Med Sci. 2013 May 20;10(7):903-7

Anti-acid therapy effect on AE



Lancet Respir Med 2013;1: 369–76

The initiation of **corticosteroid pulse therapy** may be an independent prognostic factor in IPF-AE



Intern Med 2018:57: 655-661

High-dose prednisolone: a significant predictor of good prognosis of AE-IPF without PPV

AE-IPF=63

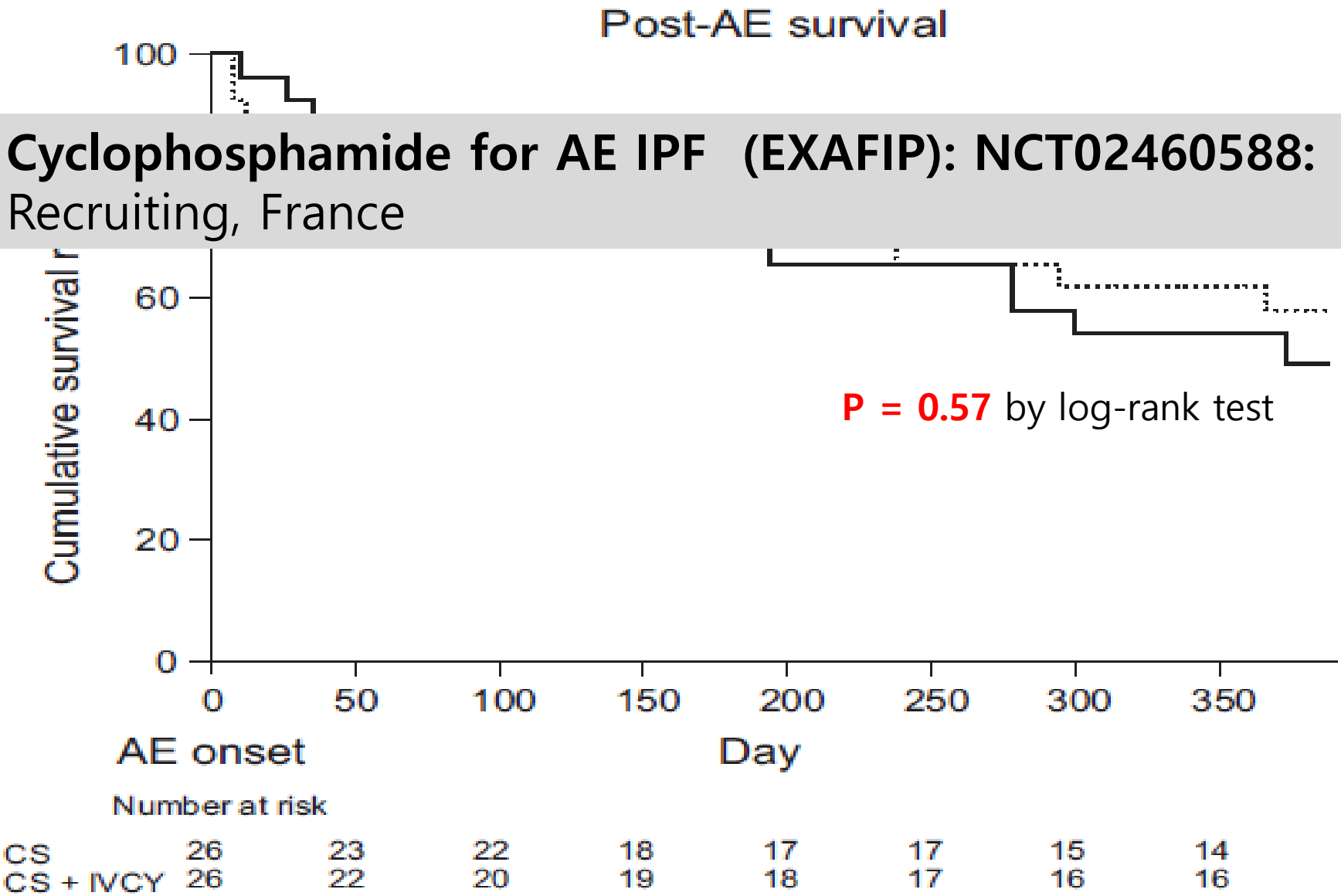
Parameters	HR	95% CI	*P*-value
LTOT before AE, Yes	2.158	1.06–4.393	0.034
IgG × 100 mg/dL	0.923	0.874–0.976	0.005
Prednisolone dose, ≥0.6 mg/kg	0.429	0.204–0.902	0.026

†High-dose PSL ≥0.6 mg/kg, after i.v. high-dose MPD (0.5-1g/d, 3d)

Arai et al. Respirology (2017) 22, 1363–1370

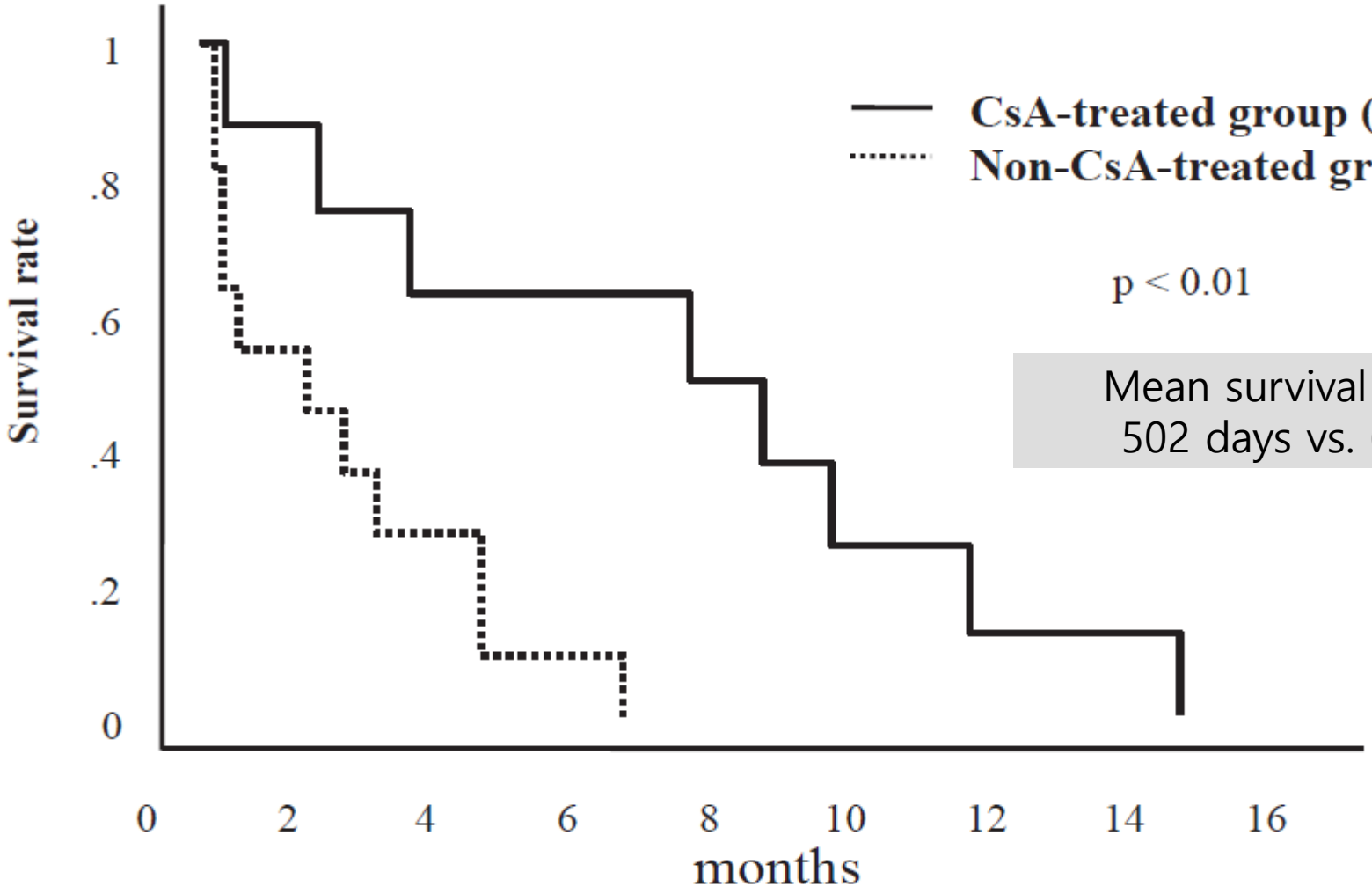
Efficacy of **corticosteroid** and intravenous **cyclophosphamide** in AE-IPF: A propensity score-matched analysis

Cyclophosphamide for AE IPF (EXAFIP): NCT02460588: Recruiting, France



Respirology. 2019 Feb 25

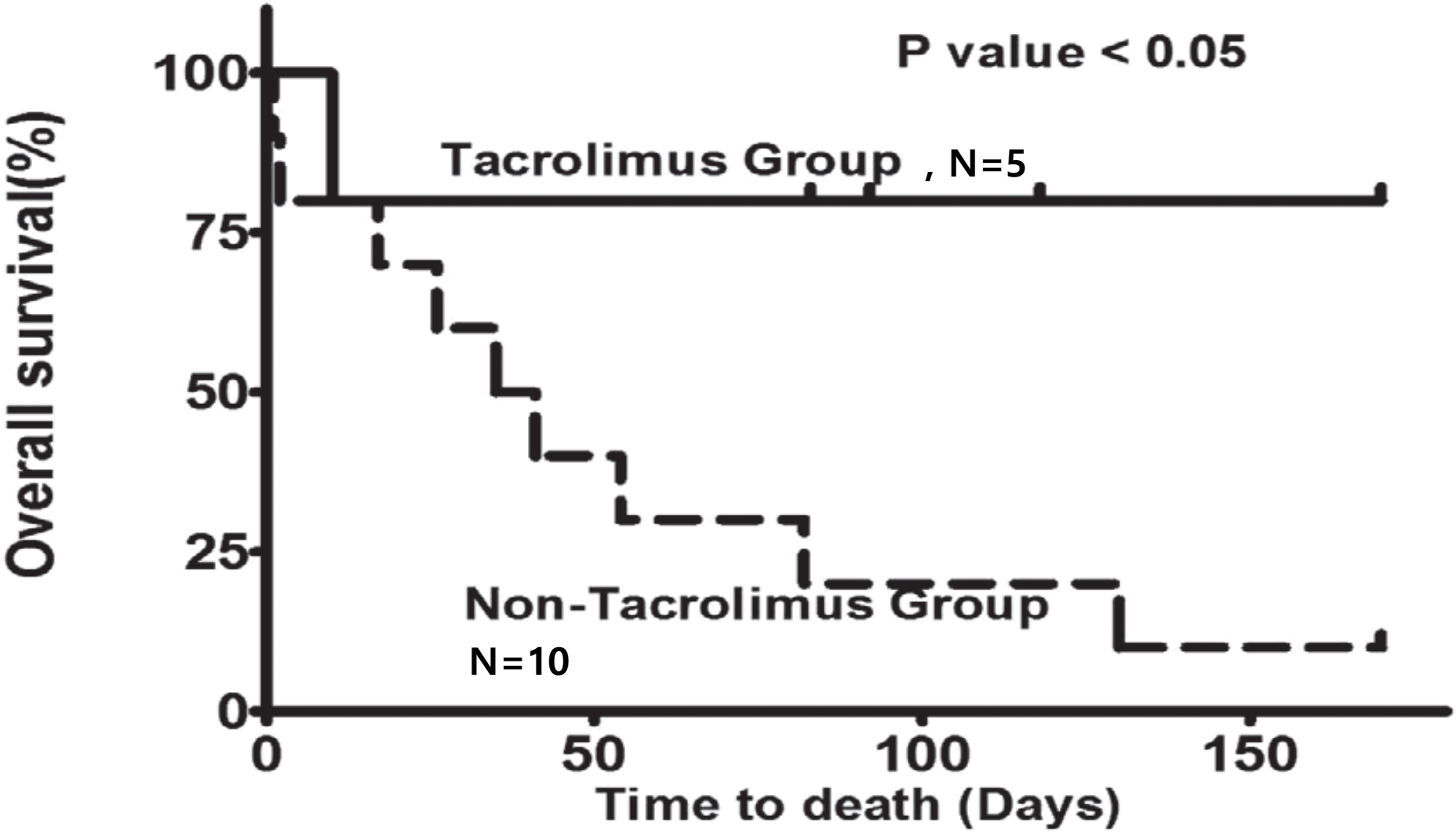
Cyclosporin A in the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis



Mean survival after AE
502 days vs. 60 days

Sakamoto et al. Intern Med. **2010**;49(2):109-15.

Tacrolimus and Steroid Treatment for Acute Exacerbation of Idiopathic Pulmonary Fibrosis



Horita et al. Intern Med 50: 189-195, 2011

Effect of **Polymyxin B-immobilized Fiber Column (PMX)** on P/F in Interstitial Pneumonia with **AE:**

a multicenter retrospective analysis; 160 IP patients (including 73 IPF)

	pre-PMX	end of 1st PMX	end of 2nd PMX
all patients	148.9±87.2	177.7±108.7*	175.1±92.5*
IPF	173.9±105.4	205.4±122.1#	195.2±106.8##

Data are given as mean ± SD (Torr)

*p<0.0001 compared to pre-PMX

#p=0.001 compared to pre-PMX, ##p=0.003 compared to pre-PMX

Abe et al. Intern Med. 2012;51(12):1487-91

Table 6. Effect of PMX on P/F in Interstitial Pneumonia (all and IPF) Patients with Acute Exacerbation: Comparison of 3-Month-survivors and Non-survivors

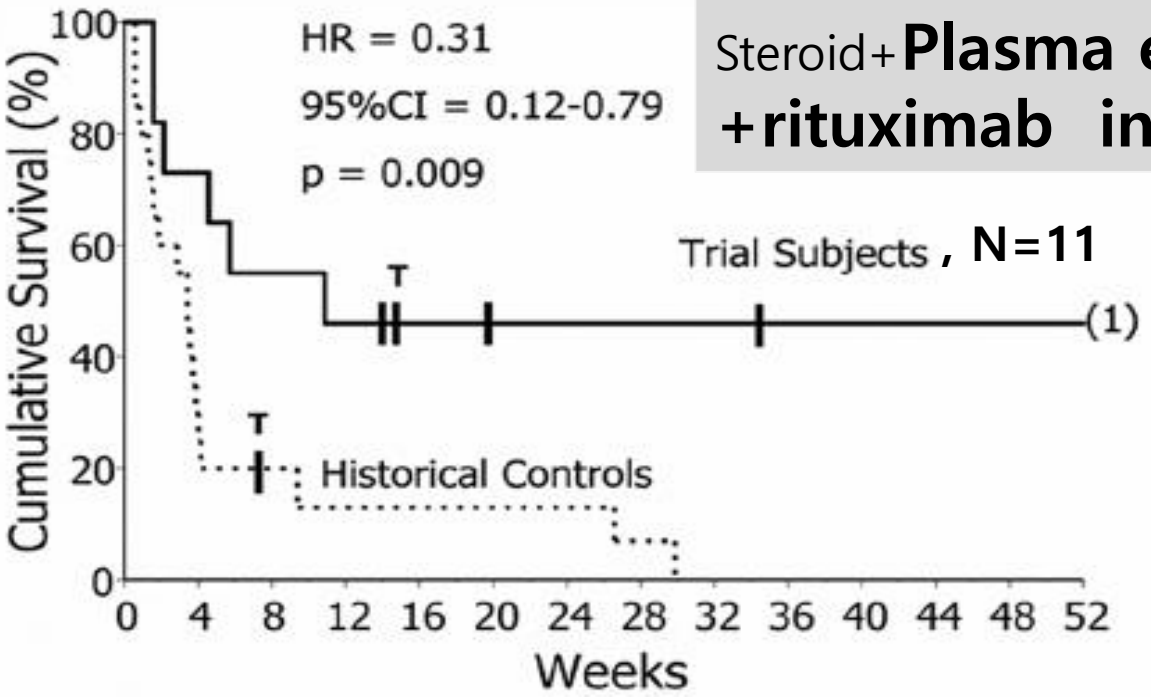
		pre-PMX	end of 2nd PMX
all patients	survivors	167.1 ± 95.3	208.1 ± 120.8*
	non-survivors	135.0 ± 83.1	149.5 ± 71.0
IPF	survivors	166.0 ± 97.1	216.2 ± 108.9#
	non-survivors	133.9 ± 70.9	152.4 ± 91.5

Data are given as mean ± SD

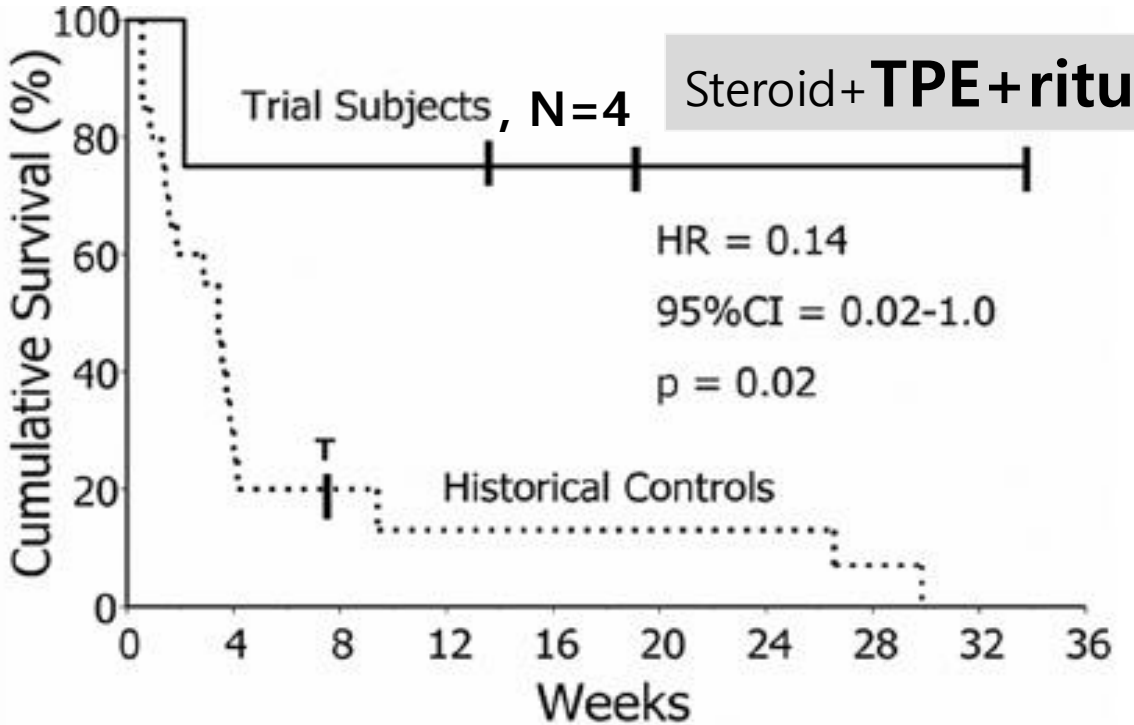
*p=0.04 compared to pre-PMX, #p=0.03 compared to pre-PMX

Abe et al. Intern Med. 2012;51(12):1487-91

Steroid+**Plasma exchanges (TPE) +rituximab in AEIPF**

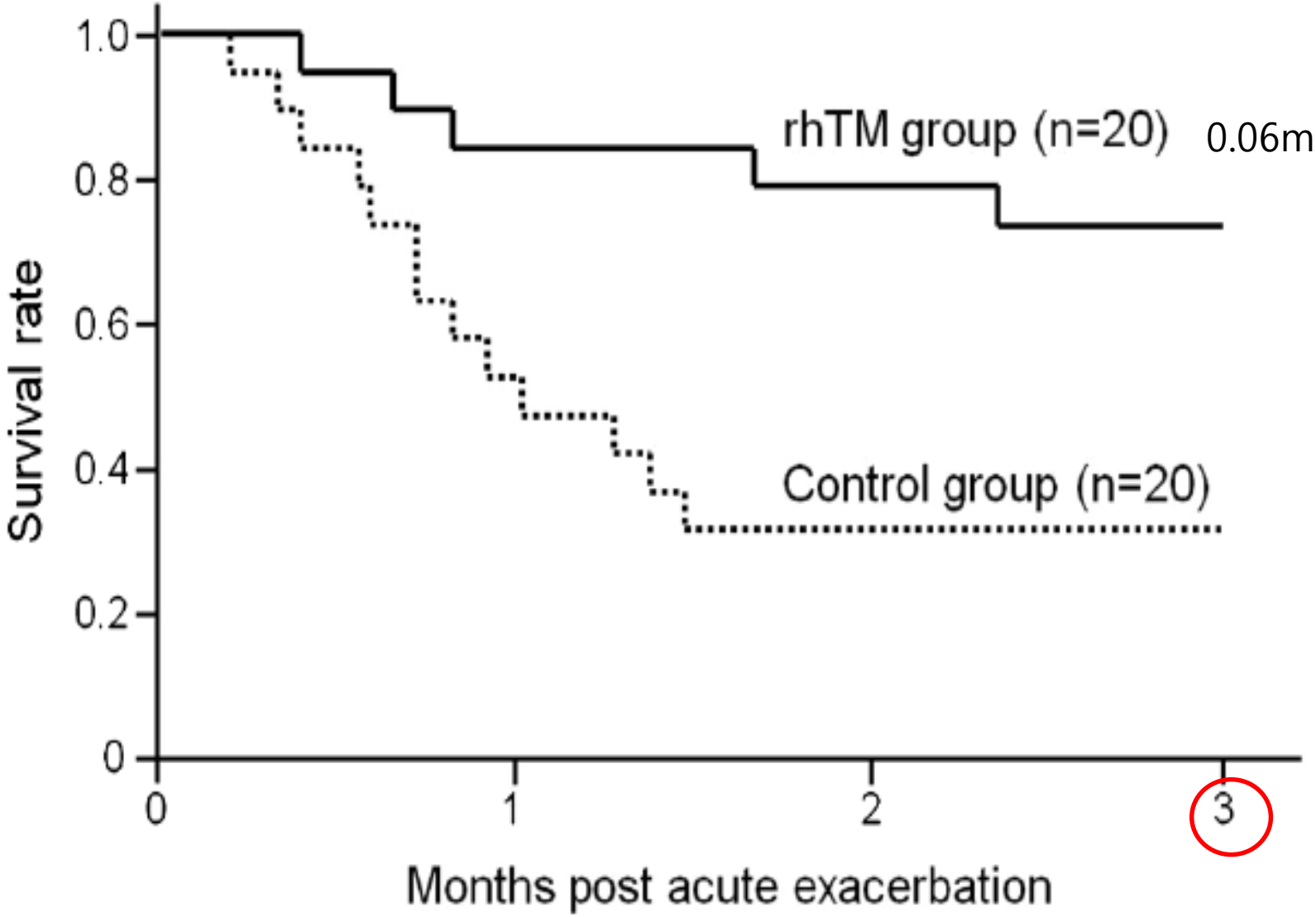


Steroid+**TPE+rituximab +IVIG in AEIPF**



ahoe et al. Plos One 2015;10: e0127771

Recombinant Human Thrombomodulin in Acute Exacerbation of Idiopathic Pulmonary Fibrosis



Kataoka et al. Chest. 2015 Aug;148(2):436-443.

Concurrent treatments with high-dose corticosteroids in a rapid progression of respiratory failure (MV) IPF.

Prognostic factors for survival

Variable		Multivariate logistic analysis		
	N (%)	OR	95 % CI	*p*-value
Age, years	209			
<60	17 (8.1)	ref		
≥80	42 (20.1)	2.94	1.044–8.303	0.041
Performing bronchoscopy	20 (9.6)	0.25	0.079–0.798	0.019
Intravenous high-dose cyclophosphamide	32 (15.3)	3.17	1.101–9.148	0.033
Antibiotic therapy	206 (98.6)			
Co-trimoxazole	115 (55.0)	0.28	0.132–0.607	0.001
Macrolides	48 (23.0)	0.37	0.155–0.867	0.033

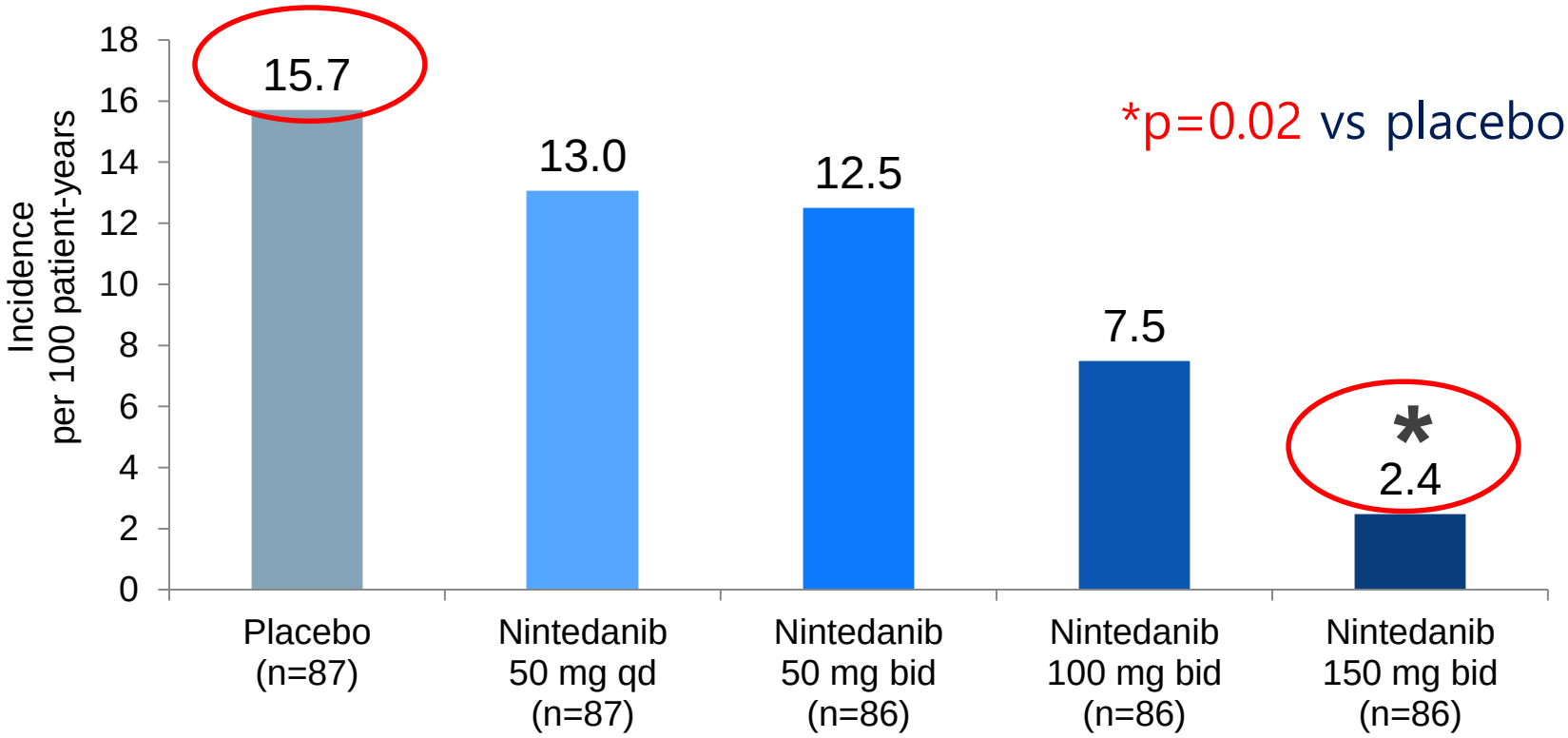
high-dose corticosteroids: MPD >0.5g/d

Oda et al. BMC Pulmonary Medicine (2016) 16:91

Nintedanib: Acute exacerbations

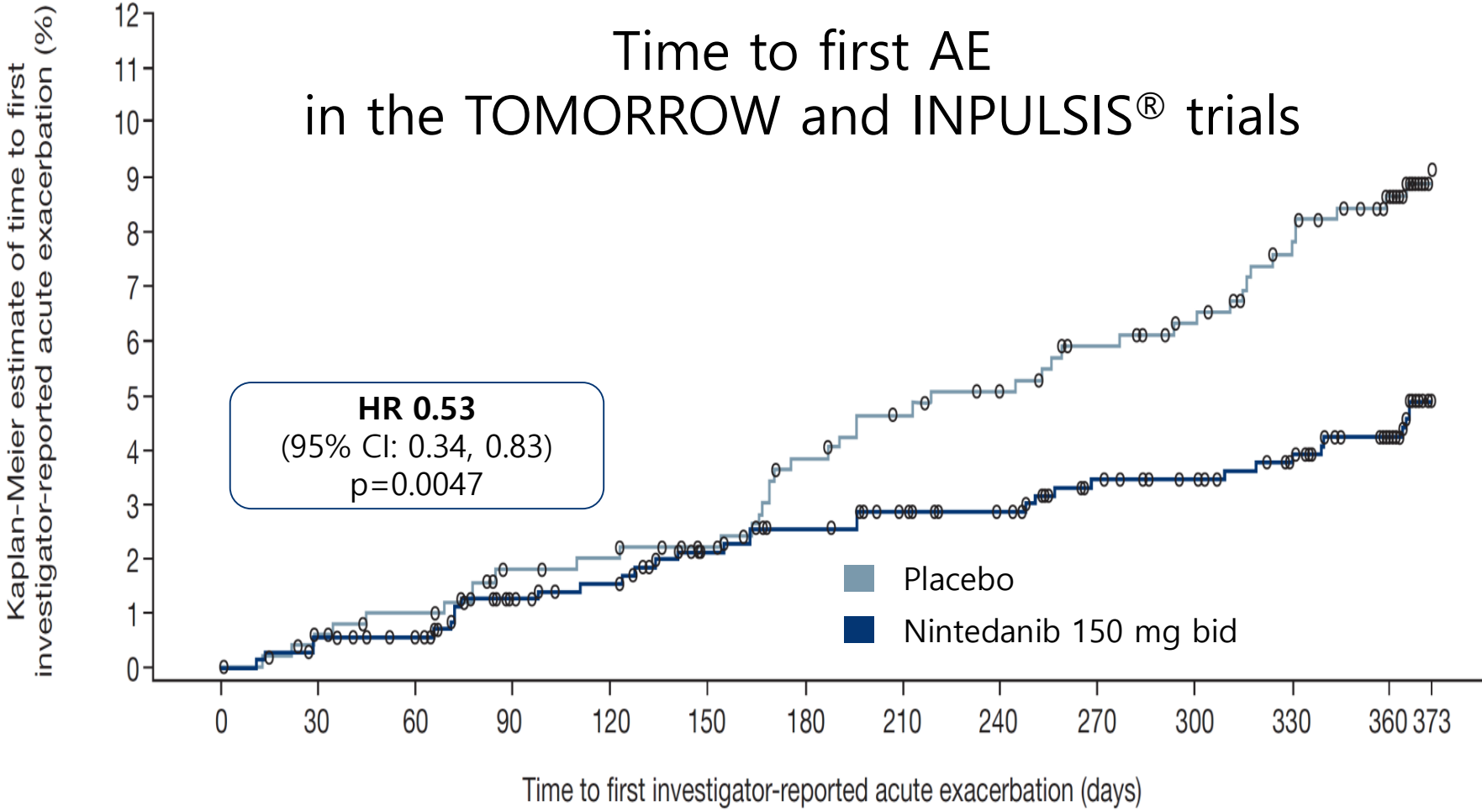
TOMORROW trial

N= 432, 150 mg of nintedanib twice a day vs. placebo



Richeldi L, et al. NEJM 2011;365:1079–1087

Time to first AE in the TOMORROW and INPULSIS® trials



No. of patients

Nintedanib 150 mg bid	723	717	712	693	687	674	667	659	654	641	632	623	598 513
Placebo	508	502	497	488	486	481	470	464	460	452	446	436	417 353

	Nintedanib 150 mg bid (n=723)	Placebo (n=508)
Patients with ≥1 acute exacerbation, %	4.6	8.7

Richeldi et al. Respiratory Medicine 2016: 113:74-79

Mortality following onset of AE from INPULSIS trials

N (%)	Investigator-reported AE		Adjudicated as confirmed or suspected AE *		Adjudicated as not AE†	
	Nintedanib (n=34)	Placebo (n=35)	Nintedanib (n=14)	Placebo (n=25)	Nintedanib (n=23)	Placebo (n=13)
Mortality						
30-day	7 (20.6)	14 (40.0)	3 (21.4)	9 (36.0)	4 (17.4)	5 (38.5)
90-day	10 (29.4)	15 (42.9)	5 (35.7)	12 (48.0)	6 (26.1)	7 (53.9)
180-day	12 (35.3)	20 (57.1)	6 (42.9)	15 (60.0)	7 (30.4)	7 (53.9)

*Analysis based on patients who had ≥1 confirmed or suspected acute exacerbation. †Analysis based on patients who had ≥1 event that was adjudicated and all events adjudicated as not acute exacerbations.

Collard HR et al. Eur Respir J 2017;49:1601339

Double-blind, Placebo-controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Arata Azuma, Toshihiro Nukiwa, Eiyasu Tsuboi, Moritaka Suga, Shosaku Abe, Koichiro Nakata, Yoshio Taguchi, Sonoko Nagai, Harumi Itoh, Motoharu Ohi, Atsuhiko Sato, and Shoji Kudoh for the members of the Research Group for Diffuse Lung Diseases in Japan; and Ganesh Raghu

Reason for Discontinuation	Pirfenidone Number of Patients (%)	Placebo Number of Patients (%)	p Value*
Acute exacerbation	0 (0.0)	5 (13.9)	0.0032

Azuma et al. Am J Respir Crit Care Med 2005; 171: 1040–1047

Pirfenidone in idiopathic pulmonary fibrosis

H. Taniguchi*, M. Ebina#, Y. Kondoh*, T. Ogura¶, A. Azuma+, M. Suga§, Y. Taguchif, H. Takahashi**, K. Nakata##, A. Sato¶¶, M. Takeuchi++, G. Raghu§§, S. Kudoh+ and T. Nukiwa#, and the Pirfenidone Clinical Study Group in Japanff

Pirfenidone dosage	high-dose 1,800 mg/day N=108	low-dose 1,200 mg/day N=55	Placebo N=104	P
AE incidence	6 (5.6%),	3 (5.5%)	5 (4.8%)	NS

Taniguchi H et. al. Eur Respir J. 2010 Apr;35(4):821-9

Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials

Paul W Noble, Carlo Albera, Williamson Z Bradford, Ulrich Costabel, Marilyn K Glassberg, David Kardatzke, Talmadge E King Jr, Lisa Lancaster, Steven A Sahn, Javier Szwarcberg, Dominique Valeyre, Roland M du Bois, for the CAPACITY Study Group

Noble PW, et al. Lancet. 2011 May 21;377(9779):1760-9.

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

: ASCEND trial

King TE Jr, et al. N Engl J Med. 2014 May 29;370(22):2083-9.

CrossMark

Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials

- Pooled data of CAPACITY(004, 006) and ASCEND trials

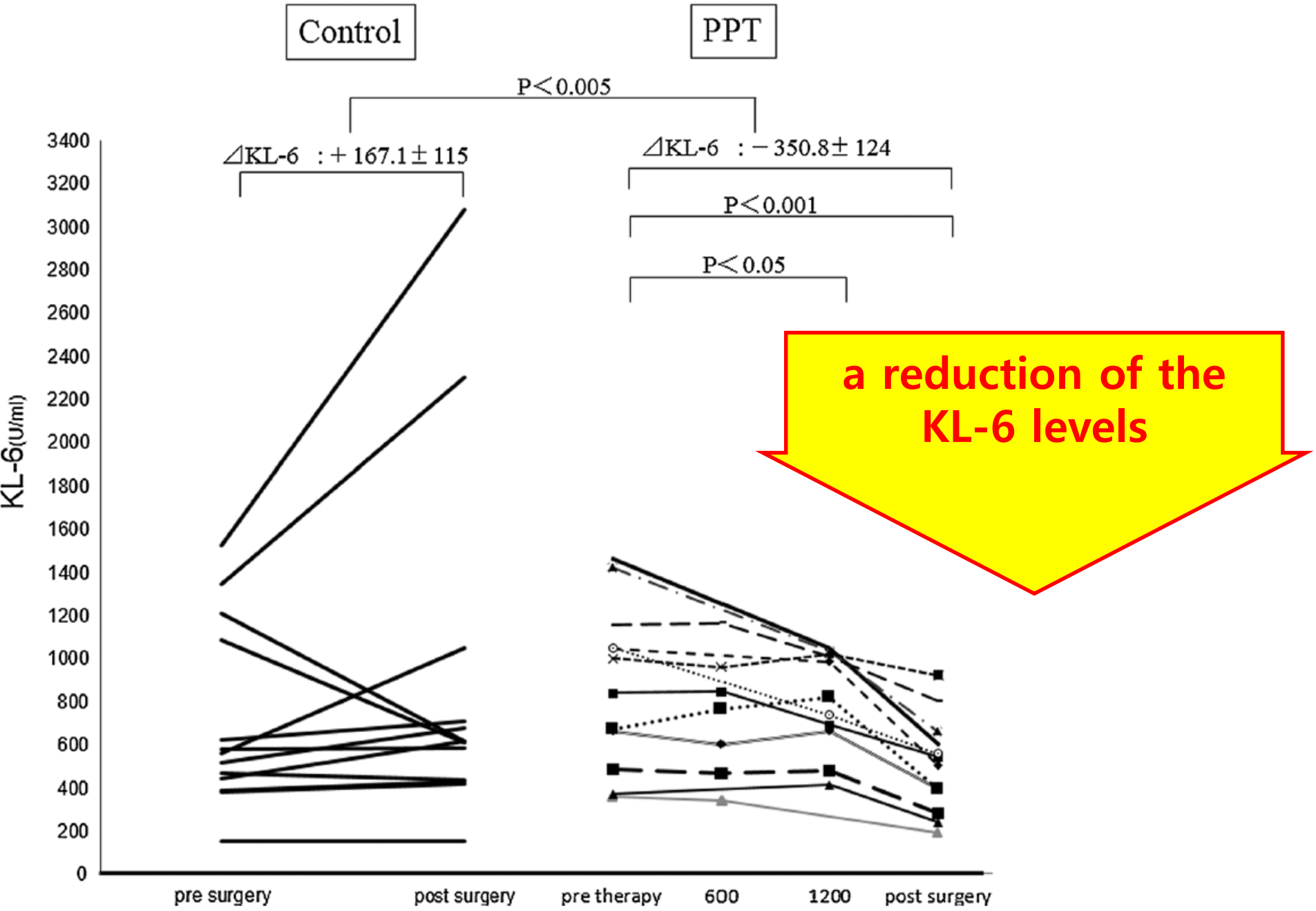
Noble PW, et al. Eur Respir J. 2016 Jan;47(1):243-53.

Experience with perioperative pirfenidone for lung cancer surgery in patients with idiopathic pulmonary fibrosis

Complications

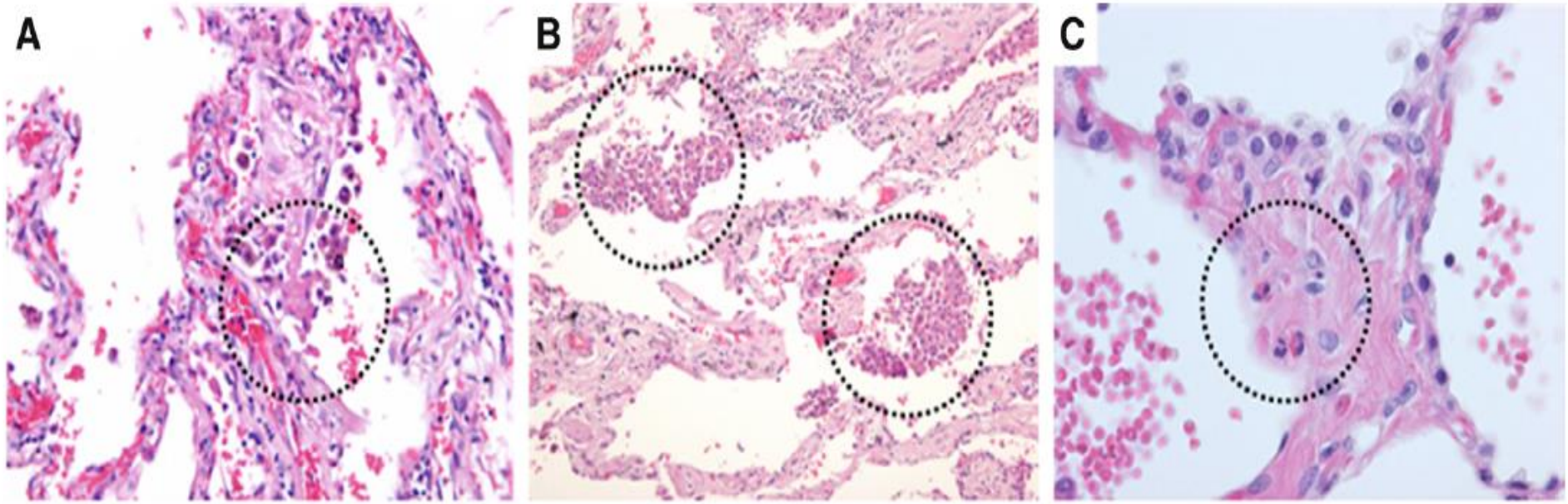
Variable	PPT ($n = 12$)		Control ($n = 16$)		P*
AE-IPF	Perioperative period	0	Perioperative period	1	0.3778
	Entire observation period	0	Entire observation period	6	0.0167

Surg Today. 2015 Oct;45(10):1263-70



a reduction of the KL-6 levels

Surg Today. 2015 Oct;45(10):1263-70



Category	Pathological Score (mean ± SD)		p value
	PPT (n=8)	Control (n=16)	
A: Alveolar fibrin exudation	0.13 ± 0.35	0.50 ± 0.73	0.187
B: Alveolar pink macrophage accumulation	1.50 ± 1.07	2.38 ± 1.03	0.065
C: Interstitial neutrophils and eosinophils *	0.86 ± 0.64	1.81 ± 0.66	0.003
Total Score *	2.50 ± 1.85	4.69 ± 2.12	0.021

Histopathological sections of specimens

Surg Today. 2015 Oct;45(10):1263-70

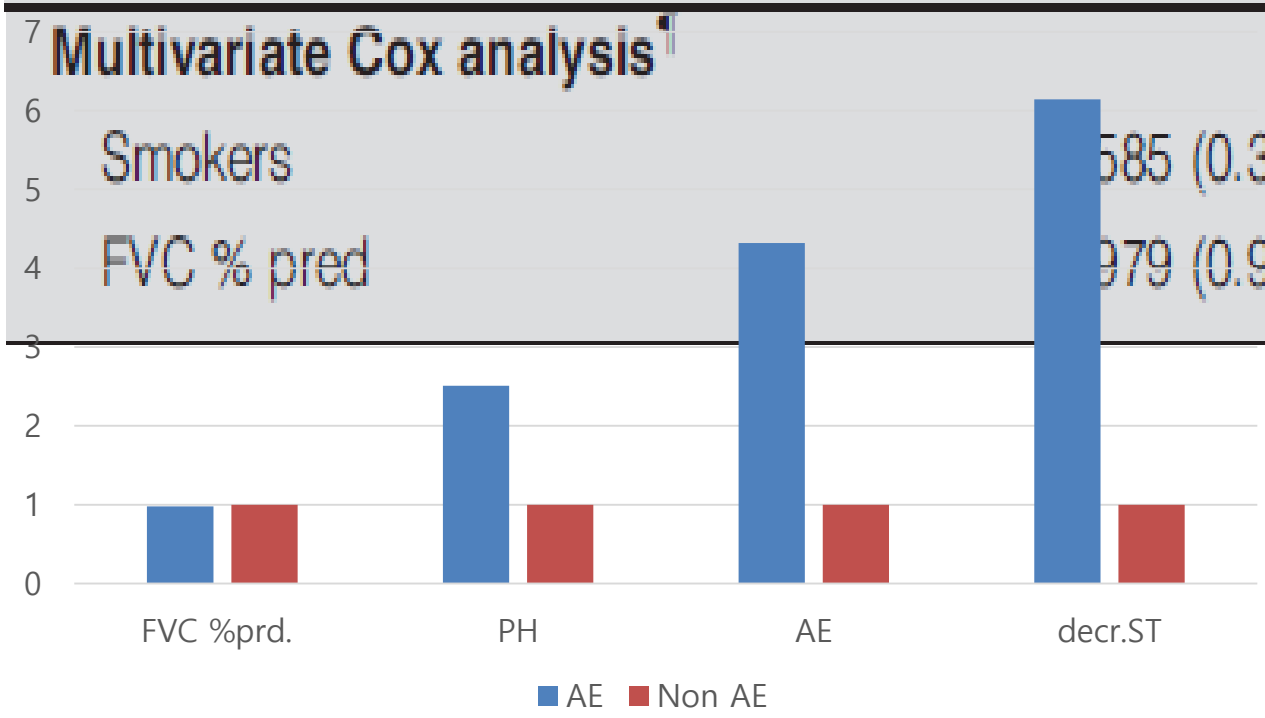
Take Home Messeges

- ✓ AE-IPF mortality: high mortality rate
- ✓ New definition of AE-IPF
  - : idiopathic and triggered AE
  - : help conduct well designed clinical trials
- ✓ Therapies
  - : lack of evidence based therapy options
  - cf. steroid, CsA, CY, tacrolimus, rituximab, rhTM, PMX, antibiotics
- ✓ Prevention
  - cf. Nintedanib, Anti-acid, pirfenidone

Risk factors of AE-IPF

TABLE 4 Risk factors for acute exacerbation compared to no episodes of rapid deterioration (RD) at the time of initial diagnosis

Parameters		HR (95% CI)	p-value
Multivariate Cox analysis[¶]			
Smokers		585 (0.342–1.001)	0.050
FVC % pred		979 (0.964–0.995)	0.011



ERJ 2011 37: 356-363

TABLE 3 Risk factors at initial assessment for acute exacerbation

Parameter	HR (95% CI)	p-value
Multivariate Cox analysis		
Male	0.587 (0.398–1.139)	0.182
PH	2.510 (1.119–5.628)	0.026

Eur Respir J. 2012 Jul;40(1):93-100

- AE was associated with high risk of subsequent AE and substantially decreased survival time.

	HR	95% CI
Acute exacerbation	4.32	2.33-7.98
Decreased survival time	6.14	4.03-9.34

Eur Respir J 2014;43:1124–1131

Table 3 – Univariate analysis using Cox's proportional hazards models of predictors for acute exacerbation

Variables	*p*-Value	Hazard Ratio	95% Confidence interval	
			Lower	Upper
Sex	0.4893	1.505	0.472	4.801
Age	0.6420	0.982	0.912	1.059
BMI	0.4601	0.935	0.782	1.118
Smoking status, yes[a]	0.1683	0.464	0.155	1.384
Hugh-Jones classification	0.1676	1.763	0.788	3.947
PaO_2	0.1097	0.955	0.904	1.099
$AaDO_2$	0.0691	1.047	0.996	1.099
%VC	0.0777	0.971	0.941	1.003
%DLCO	0.7140	0.994	0.965	1.025
KL-6	0.6980	1.000	0.999	1.001
SP-A	0.7764	0.998	0.988	1.004
SP-D	0.8745	1.000	0.997	1.004
>10% decline in %VC within 6 mo. (absolute)	0.0011	6.432	2.095	19.751
>10% decline in %VC within 6 mo. (relative)	0.0079	4.406	1.475	13.163
Pirfenidone	0.7318	1.211	0.406	3.613

- Respir Investig 2015;53:271–278

Respiratory Medicine 113 (2016) 74–79

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journal homepage: www.elsevier.com/locate/rmed

Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS® trials

Luca Richeldi [a, *], Vincent Cottin [b], Roland M. du Bois [c], Moisés Selman [d], Toshio Kimura [e], Zelie Bailes [f], Rozsa Schlenker-Herceg [g], Susanne Stowasser [e], Kevin K. Brown [h]

Respiratory Medicine 2016: 113:74-79

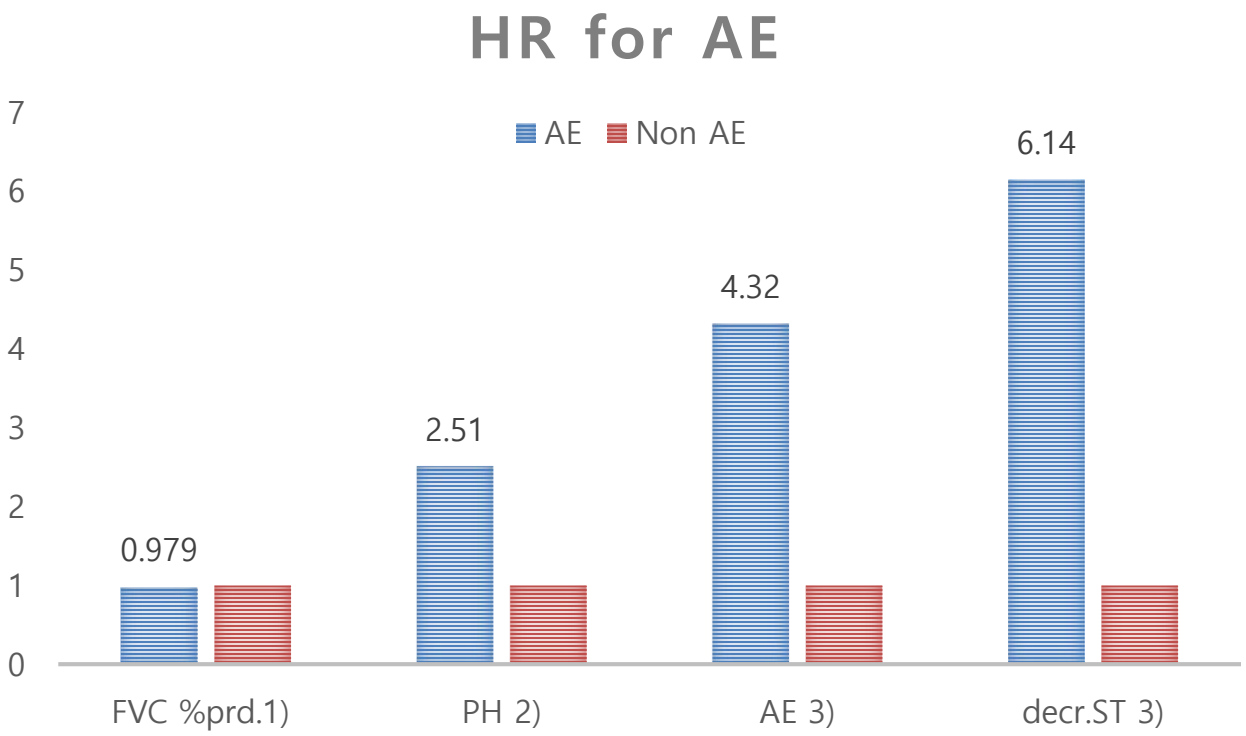
Risk factor of AE

Risk factors of AEIPF

Variable	Acute exacerbation *N = 17	Other acute worsening N = 13	No acute worsening N = 150	AE vs. Non AE	Any acute worsening vs. No acute worsening P-value
Age, years	71	69	69	[illegible]	0.30
Male gender	17 (100%)	11 (85%)	122 (81%)	0.08	0.11
Disease duration, years	2.01	2.97	1.86	0.74	0.19
Body mass index	28.3	29.3	29.0	0.64	0.75
Ever smoker	10 (59%)	11 (85%)	116 (77%)	0.13	0.39
HRCT UIP pattern	14 (82%)	13 (100%)	121 (81%)	>0.99	0.22
Biopsy proven disease	7 (41%)	5 (39%)	75 (50%)	0.80	0.76
6MWD meters				**<0.001**	<0.001
FVC % pred.				**0.03**	0.04
FEV1/FVC ratio	0.77	0.77	0.77	0.45	0.63
DLCO, % pred.				**<0.001**	<0.001
PaO_2				**0.01**	<0.001
UCSD				**0.03**	0.003
SF-36 physical score	33.47	28.21	34.58	0.44	0.03
SF-36 mental score	50.87	49.20	51.71	0.83	0.43
SGRQ total score	55.64	64.60	51.80	0.28	0.01
Sildenafil use **	8 (47%)	5 (39%)	76 (51%)	0.78	0.46
PPI use	3 (18%)	7 (54%)	68 (45%)	0.09	0.45
Prednisone use	7 (41%)	2 (15%)	28 (19%)	0.05	0.01

Respir Res. 2013 Jul 13;14:73.

Risk factors of AE-IPF



1)ERJ 2011 37: 356-363

2)Eur Respir J. 2012 Jul;40(1):93-100

3)Eur Respir J 2014;43:1124–1131

Table 8 Multivariable Cox proportional hazards regression on suspected acute exacerbation in the subsequent period

	Suspected Acute Exacerbation[a]	
	Hazard Ratio (95 % CI)	*P*-value*
Race		
White vs. non-white	0.63 (0.45–0.88)	0.007*
Lung-function decline group		
Marginal decline vs. stable	2.02 (1.13–3.59)	0.011*
Significant decline vs. stable	2.86 (1.69–4.85)	<0.001*
BMI		
25–30 vs. <25	0.82 (0.53–1.26)	0.362
≥30 vs. <25	0.75 (0.45–1.23)	0.245
Comorbidities		
Cardiac disorder vs. no cardiac disorder	1.57 (1.04–2.37)	0.031*
Pulmonary hypertension vs. no pulmonary hypertension	1.65 (1.03–2.63)	0.036*
Emphysema vs. no emphysema	1.89 (1.02–3.50)	0.043*
Gastroesophageal reflux disease vs. no gastroesophageal reflux disease	1.07 (0.74–1.54)	0.736
Smoking status		

BMC Pulm Med. 2015 Dec 29;15:167

Stepwise multivariate analysis with Cox proportional hazards regression models of predictors of acute exacerbation of idiopathic pulmonary fibrosis

Stepwise multivariate analysis	Hazard Ratio	95% CI	P Value
modified MRC scale, 2 and above	2.93	1.46-5.85	0.002
BMI	1.20	1.03-1.40	<0.001
10% decline in FVC at 6 months, yes	2.60	1.01-7.45	0.049

n=70, because only patients for whom all data were available werelysis

Sarcoidosis Vasc Diffuse Lung Dis 2010;27:103–110

Prognosis of AE

AJRCCM 2016;194(3):265-75

Prognostic Factors in the Acute Exacerbation of Idiopathic Pulmonary Fibrosis: A Retrospective Single-center Study

Table 2. Clinical Characteristics of the Patient Series at the Onset of IPF-AE.

Variables	Overall (n=59)		Survivors (n=27)		Non-survivors (n=32)		p value*	
Body temp (°C)	37.0	(36.6-37.7)	37.0	(36.6-38.0)	36.9	(36.6-37.4)	0.231	
LDH (U/L)	336	(287-413)	310	(266-382)	382	(311-437)	0.034	*
KL-6 (U/mL)	1,583	(1,007-2,288)	1,583	(798-2,288)	1,655	(1,133-2,399)	0.451	
SP-D (ng/mL)	281	(148-413)	308	(161-433)	274	(144-383)	0.589	
CRP (mg/dL)	9.7	(5.9-15.1)	9.2	(5.7-14.8)	9.9	(6.0-16.0)	0.612	
D-dimer (mg/mL)	2.7	(1.7-6.8)	3.3	(1.6-9.4)	2.6	(1.8-5.2)	0.654	
$PaCO_2$ (Torr)	34.4	(31.1-38.3)	35.0	(31.4-38.1)	33.9	(30.6-39.0)	0.731	
A-aDO_2 (Torr)	215	(88-436)	155	(84-431)	216	(103-451)	0.433	
P/F ratio (Torr)[a]	174	(97-253)	195	(97-268)	140	(96-238)	0.398	
HRCT score[b]	200	(181-216)	190	(180-209)	209	(185-229)	0.042	*
Treatment option								
Symptom duration (day)[c]	6.0	(3.0-9.0)	3.0	(2.0-6.0)	6.5	(5.0-10.0)	0.003	*
Mechanical ventilation[d]	24		5		19		0.002	*
PMX-DHP[e]	21		10		11		1.000	
Immunosuppressants[f]	28		12		16		0.798	

Intern Med 57: 655-661, 2018

TABLE 6 Prognostic factors for in-hospital mortality of patients with acute exacerbation

Parameters	OR (95% CI)	p-value
Univariate logistic analysis		
Age	1.022 (0.969–1.078)	NS
Male sex	1.455 (0.543–3.895)	NS
Disease duration	0.994 (0.977–1.011)	NS
Steroid with/without cytotoxic agent use[#]	0.828 (0.353–1.943)	NS
Duration[¶]	1.142 (0.932–1.399)	NS
Last dose[¶]	1.034 (0.990–1.081)	NS
Duration of dyspnoea	0.939 (0.902–0.978)	0.003
Documented fever	2.364 (0.799–6.989)	NS
Sputum production	1.705 (0.684–4.252)	NS
$P_{a,O_2}/F_{I,O_2}$	0.989 (0.983–0.996)	0.001
CRP	1.087 (1.009–1.172)	0.029
BAL		
Total cells	0.998 (0.992–1.003)	NS
Lymphocytes	0.905 (0.826–0.992)	0.033
Neutrophils	1.055 (0.996–1.118)	0.070
Multivariate logistic analysis		
CRP	2.467 (1.030–5.911)	0.043
BAL lymphocytes	0.869 (0.737–1.024)	0.093

P_{a,O_2}: arterial oxygen tension; F_{I,O_2}: inspiratory oxygen fraction; CRP: C-reactive protein; BAL: bronchoalveolar lavage; NS: nonsignificant. [#]: within 30 days prior to rapid deterioration; [¶]: steroid treatment.

N=461

ERJ 2011 37: 356-363;

Table 3. Univariate analysis of clinical, laboratory, HRCT scan, and treatment data comparing survivors and nonsurvivors (n = 37)

	Survivors (n = 27)	Nonsurvivors (n = 10)	p value
Characteristics of patients			
Age at IPF diagnosis, years (n = 30)	65 (51–77)	66 (29–72)	0.57
Age at AEx, years (n = 30)	68 (60–81)	69 (31–75)	0.46
Males/females, n (%)	23 (85)/4 (15)	8 (80)/2 (20)	0.59
Clinical course of IPF before AEx			
Time between IPF diagnosis and AEx, months	47 ± 27.5	40 ± 48.0	0.08
Pulmonary function test			
FVC, % pred	65 ± 18	51.2 ± 12.3	0.01*
DLCO, % pred	34 ± 9.1	21.7 ± 9.3	0.01*
Previous AEx	9 (31)	2 (20)	0.50
Characteristics of AEx			
Duration of symptoms, days	15 ± 9.4	10.0 ± 9.33	0.11
LDH, IU/l	544.6 ± 155.4	801.0 ± 163.7	0.002*
Neutrophil count, /mm^3	8,591 ± 3,214	7,581 ± 3,794	0.21
D-dimers, ng/ml	852.15 ± 793	1,623.9 ± 1,727.0	0.46
CRP, mg/l	69.7 ± 72.8	46.8 ± 61.0	0.79
Nt-proBNP, ng/l	2,837 ± 3,282	1,997 ± 2,684	0.71
Pulmonary hypertension[1]	12 (44)	6 (60)	0.92
Combined IPF and emphysema, n (%)	13 (48)	6 (60)	0.71
CT pattern[2], n (%)	19 (79)/5 (21)	8 (89)/1 (11)	0.62
Treatment option			
Delay before initiating therapy, days	3.1 ± 2.6	6.0 ± 4.1	0.04*
Anticoagulant therapy, n (%)	14 (48)	5 (50)	0.54
Cyclophosphamide pulse, n (%)	9 (33)	0 (0)	0.07

Respiration. 2012;83(1):28-35.

Table 6 Point assignment for AE staging

Definition	Point
LDH	
<280	0
≧280	1
KL-6	
<1,000	0
≧1,000	1
P/F ratio	
≧100	0
<100	1
Ground-glass opacity + consolidation score	
<20	0
≧20	1

LDH lactate dehydrogenase, *KL-6* sialylated carbohydrate antigen KL-6, *P/F ratio* ratio of partial pressure of oxygen and fraction of inspiratory oxygen concentration

Table 8 Staging system for patients with AE of IPF patients

	Points
Limited exacerbation ($n = 22$)	0–2
Extensive exacerbation ($n = 36$)	≧3

Lung. 2014 Feb;192(1):141-9.

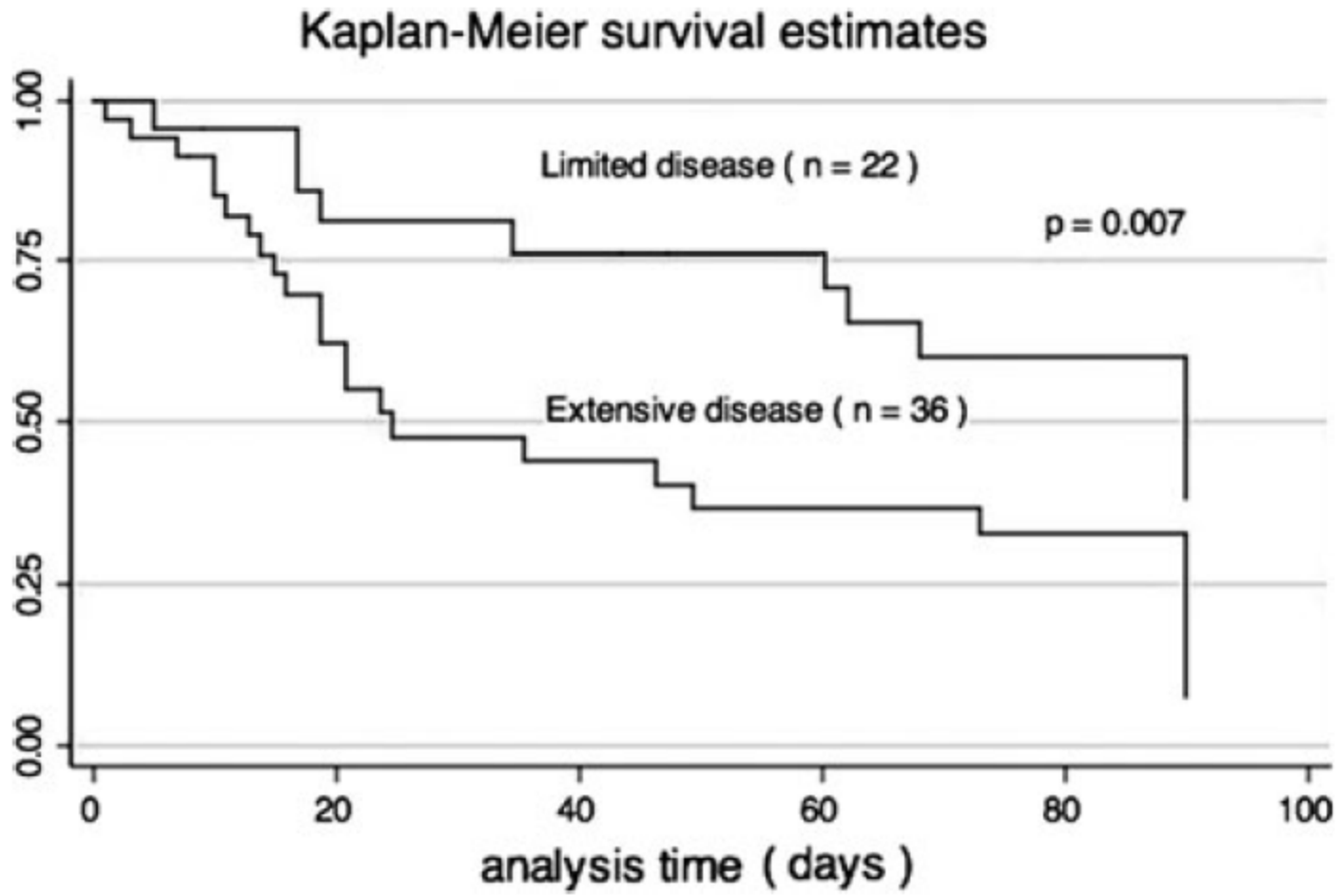


Fig. 3 3-month survival curve according to disease stage. The extensive disease stage group showed high mortality compared with that of the limited disease stage group

Lung. 2014 Feb;192(1):141-9.

Prognostic Factors in the Acute Exacerbation of Idiopathic Pulmonary Fibrosis: A Retrospective Single-center Study

Table 3. Prognostic Factors of Acute Exacerbation of Idiopathic Pulmonary Fibrosis.

	Per unit for HR[a]	HR	95% CI[b]	p value	
Univariate Cox analysis[c]					
Age	1 year	1.00	0.98-1.05	0.551	
Sex (Male)	Male	0.78	0.37-1.92	0.566	
Brinkman Index[d]	200	0.95	0.88-1.02	0.176	
IPF Stage[e]	1	1.50	1.17-1.94	0.0013	*
GAP Index[f]	1	1.45	1.10-1.93	0.0090	*
Regular use of steroid	Positive	1.23	0.50-2.58	0.630	
Regular use of pirfenidone	Positive	1.13	0.53-2.23	0.739	
LDH	10 IU/L	1.02	0.99-1.04	0.237	
KL-6	200 U/mL	1.03	0.97-1.07	0.340	
SP-D	20 ng/mL	0.99	0.96-1.03	0.761	
P/F ratio[g]	10 Torr	0.97	0.94-1.00	0.091	
HRCT score[h]	10	1.24	1.08-1.42	0.0021	*
Symptom duration[i]	1 day	1.11	1.05-1.17	0.0010	*
Immunosuppressants[j]	Positive	1.10	0.62-1.97	0.735	
Multivariate Cox analysis[k]					
IPF Stage	1	1.44	0.91-2.36	0.1211	
GAP Index	1	0.98	0.62-1.51	0.9108	
HRCT score	10	1.18	0.99-1.39	0.0532	
Symptom duration	1 day	1.11	1.01-1.15	0.0427	*

Intern Med 57: 655-661, 2018

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The use of mechanical ventilation in patients with idiopathic pulmonary fibrosis in the United States: A nationwide retrospective cohort analysis

Barret Rush [a, b, *], Katie Wiskar [a], Landon Berger [a, c], Donald Griesdale [a, c, d]

[a] Division of Critical Care Medicine, Department of Medicine, Vancouver General Hospital, University of British Columbia, Room 2438, Jim Pattison Pavilion, 2nd Floor, 855 West 12th Avenue, Vancouver, BC, V5Z 1M9, Canada
[b] Harvard T.H. Chan School of Public Health, Harvard University, 677 Huntington Ave, Boston, MA 02115, USA
[c] Department of Anesthesia, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada
[d] Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute, Vancouver, BC, Canada

Respiratory Medicine 2016 :111; 72e76

Experience with perioperative pirfenidone for lung cancer surgery in patients with idiopathic pulmonary fibrosis

Characteristics[a]	Total	PPT	Control	*P***
Patients, no.	28	12	16	
Gender (male/female)	28/0	12/0	16/0	–
Age	67.9 ± 1.7 (43–83)	68.3 ± 2.7 (55–82)	67.6 ± 2.3 (43–83)	0.415
Pack-years	55.0 ± 4.85 (18–126)	59.6 ± 7.5 (25–84)	51.5 ± 6.4 (18–126)	0.211
% FVC	99.8 ± 3.1	94.7 ± 4.7	103.7 ± 4.0	0.076
% DL_{co}	77.5 ± 4.6	71.0 ± 6.5	83.5 ± 6.2	0.089
PaO_2 (Torr)	89.4 ± 2.4	84.9 ± 3.5	92.7 ± 2.9	0.052
KL-6 (U/ml)	756.2 ± 76.7	831 ± 113	692 ± 105	0.187

PPT perioperative pirfenidone treatment

Surg Today. 2015 Oct;45(10):1263-70

Experience with perioperative pirfenidone for lung cancer surgery in patients with idiopathic pulmonary fibrosis

The surgical procedure

Variable[a]	Total $N = 28$	PPT $N = 12$	Control $N = 16$	P**
Operation				
Lobectomy	19	4	15	
Method				
Segmentectomy	2	2	0	0.003
Wedge resection	7	6	1	
Length of operation (min)	186.3 ± 14.6	166.3 ± 22.1	201.3 ± 18.9	0.121
Blood loss (g)	130.4 ± 23.4	53.8 ± 30.5	187.9 ± 26.0	0.001

PPT perioperative pirfenidone treatment

Surg Today. 2015 Oct;45(10):1263-70

Management of AE

- **Little argument**
  - supportive care, focused on palliation of symptoms and correction of hypoxemia with supplemental oxygen
- **Debate**
  - lengths to which supportive care should extend

    : MV

AJRCCM 2016;194(3):265-75

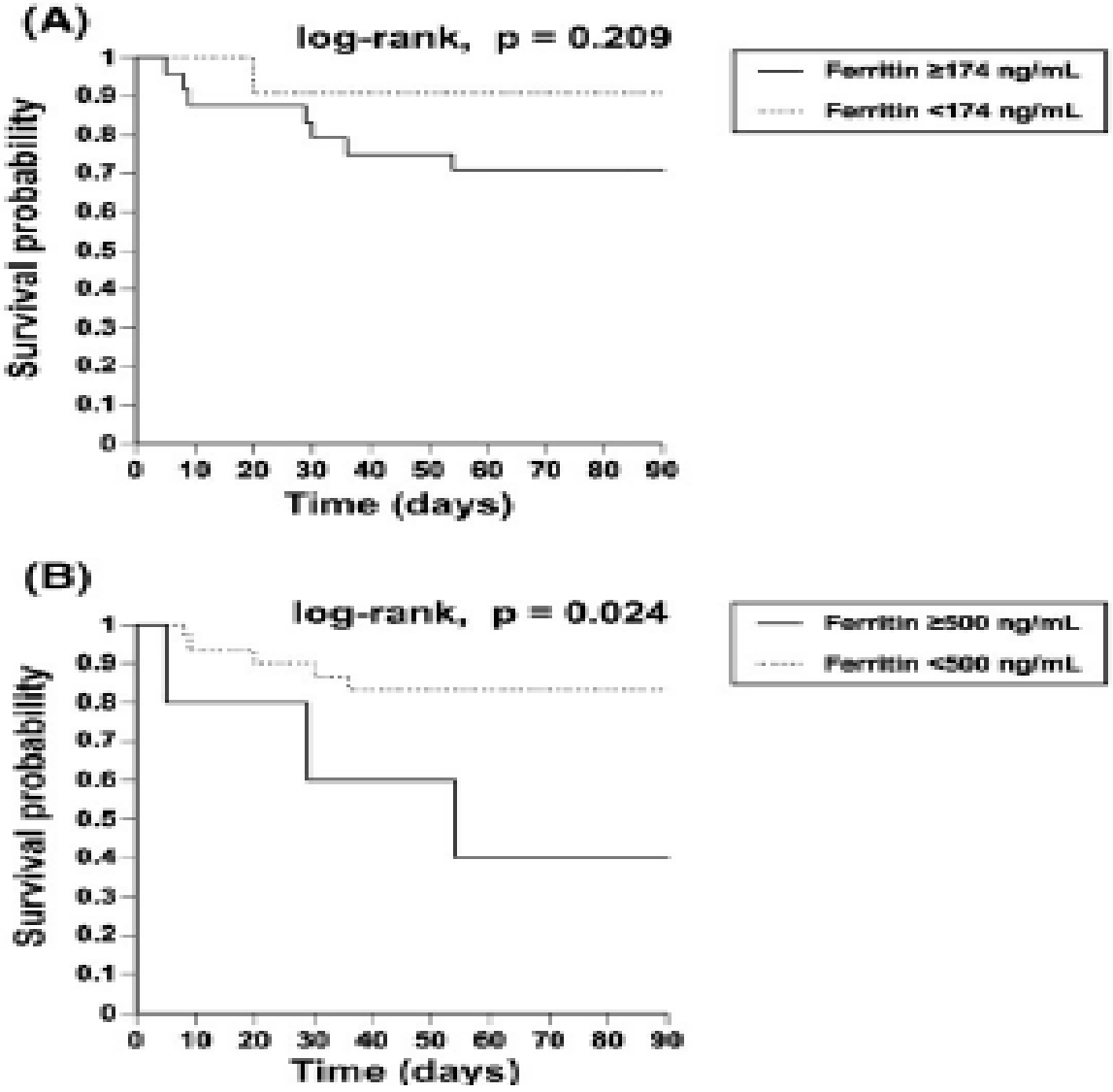
MV with ARF in IPF

- Discussion with patients and their caregivers regarding goals of care
- Decision is best made by the patient, clinician, and family ahead of time
  - AJRCCM 2011: 183. pp 788–824

Al-Hameed and Sharma,[16] Canada (1988–2000)	25	24	24
Fumeaux et al.,[17] Switzerland (1996–2001)	11	11	11
Kim et al.,[10] South Korea (1990–2003)	9	7	8
Pitsiou et al.,[18] Greece (2001–2005)	12	12	12
Total	135	118	127

Respir Med 2008;102:1355–1359

Higher serum ferritin may be related to a worse prognosis in patients with AE-IPF.



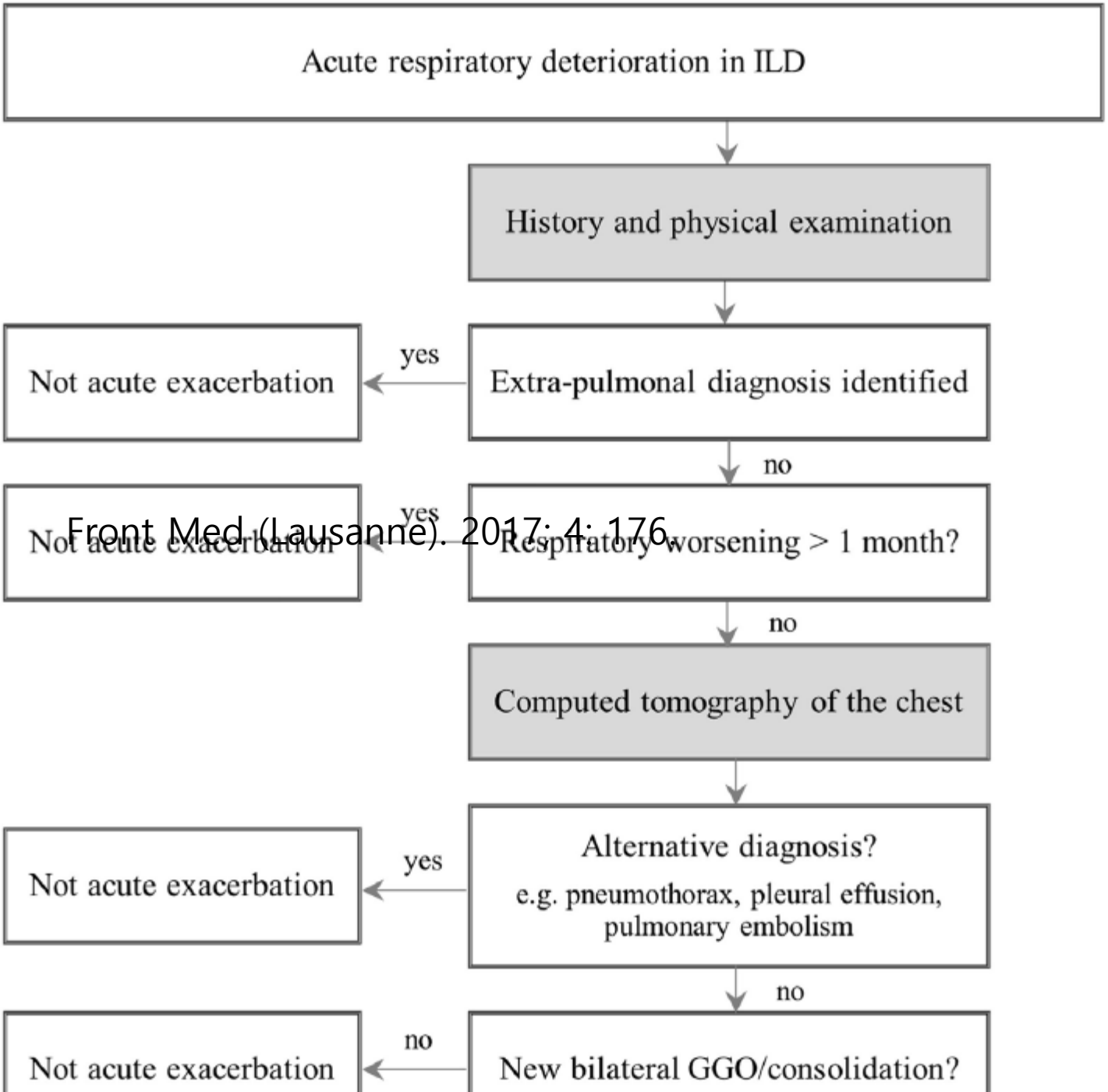
Clin Respir J. 2018;12:2378–2389.

TABLE 1 | Revised and previous definitions and diagnostic criteria for AE-IPF.

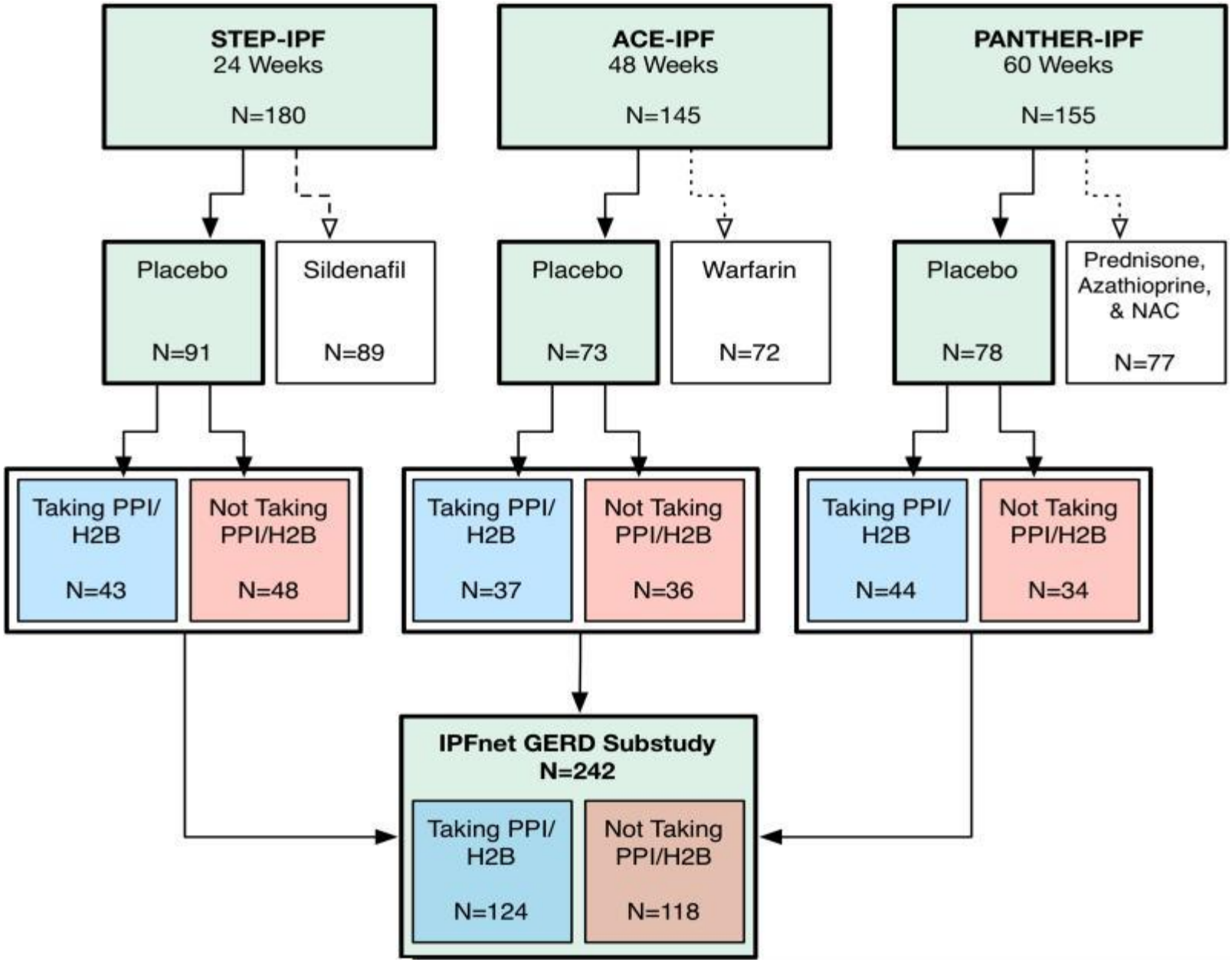
Diagnosis of AE-IPF	Revised diagnosis	Previous diagnosis
Definition		
	An acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormalities	An acute, clinically significant, respi unidentifiable cause
Diagnostic criteria		
– Previous diagnosis	Previous or concurrent diagnosis of IPF	Previous or concurrent diagnosis o
– Clinical presentation	Acute worsening or development of dyspnea typically of less than 1 month	Unexplained worsening or develop 30 days
– Computed tomography findings	New bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia (UIP) pattern	New bilateral ground-glass abnorm superimposed on a background re consistent with UIP pattern
– Exclusion of differential diagnosis	Deterioration not fully explained by cardiac failure or fluid overload	Exclusion of alternative causes, inc pulmonary embolism and an identi
– Concomitant Infection		No evidence of pulmonary infection bronchoalveolar lavage

AEIPF, acute exacerbation of idiopathic pulmonary fibrosis; IPF, idiopathic pulmonary fibrosis.

Front Med (Lausanne). 2017; 4: 176.



Front Med (Lausanne). 2017; 4: 176



Lancet Respir Med 2013;1: 369–76

Management Considerations of AE

- Look carefully for extraparenchymal causes (e.g., pulmonary embolism, pneumothorax, pleural effusion)
- Determine if there are radiologic features
  :HRCT
- Histopathologic features
  :TBLB, SLB
- BAL, Bronchoscopic cryobiopsy

AJRCCM 2016;194(3):265-75

Risk factors associated with **in-hospital deaths in AE-IPF**

	†OR	95% ‡CI	*P* value
Age (year)	0.96	0.87–1.07	0.46
‡PaO_2/§FiO_2	1.00	0.99–1.01	0.87
**WBC ($\times 10^3/\mu L$)	1.38	1.04–1.83	0.03
††Hb (mg/dL)	0.51	0.30–0.85	0.01
‡‡CRP (mg/dL)	1.00	0.90–1.13	0.94
Antibiotic therapy	4.89	0.39–60.56	0.22

BMJ Open Resp Res 2018;5:e000342

Risk factors associated with **in-hospital deaths in idiopathic** group.

	*OR	95% †CI	*P* value
Age (year)	0.99	0.76-1.32	0.95
‡PaO_2/§FiO_2	1.01	0.98-1.05	0.44
**WBC ($\times 10^3/\mu L$)	1.87	1.09-4.95	0.01
††Hb (mg/dL)	0.26	0.04-0.78	0.01
‡‡BUN (mg/dL)	1.02	0.88-1.30	0.86
§§CRP (mg/dL)	0.98	0.79-1.20	0.83
Antibiotic therapy	13.35	0.40-450.58	0.95

BMJ Open Resp Res 2018;5:e000342

Initial prednisolone dose ≥ 0.6 mg/kg is a good prognostic factor of AE-IIP

multivariate Cox proportional hazard regression analysis, AE-IPF=63, AE-non-IPF=22

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

†High-dose PSL **≥0.6 mg/kg,** after i.v. high-dose MPD (0.5-1g/d, 3d)

Respirology (2017) 22, 1363–1370

Prognosis of AE

AJRCCM 2016;194(3):265-75

IPF, N=88

IPF 사망의 46%가 AE에 의함

Table 3 Causes of death in patients with IPF ($n = 50$).

Cause of death	Number of patients (%)
Respiratory failure	34 (68%)
Acute exacerbation	23
Slow progression	11
Infection	7 (14%)
HAP	4
CAP	2
Wound infection	1
Lung cancer	4 (8%)
Pulmonary embolism	1 (2%)
Cardiovascular disease	1 (2%)
Variceal bleeding	1 (2%)
Unknown	2 (4%)

HAP, hospital-acquired pneumonia; CAP, community-acquired pneumonia.

Respir Med. 2006 Mar;100(3):451-7

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

- Scanning to evaluate acute respiratory worsening in a patient known to have ILD. A second major goal is to detect new ground-glass changes that raise the probability of **acute exacerbation.**

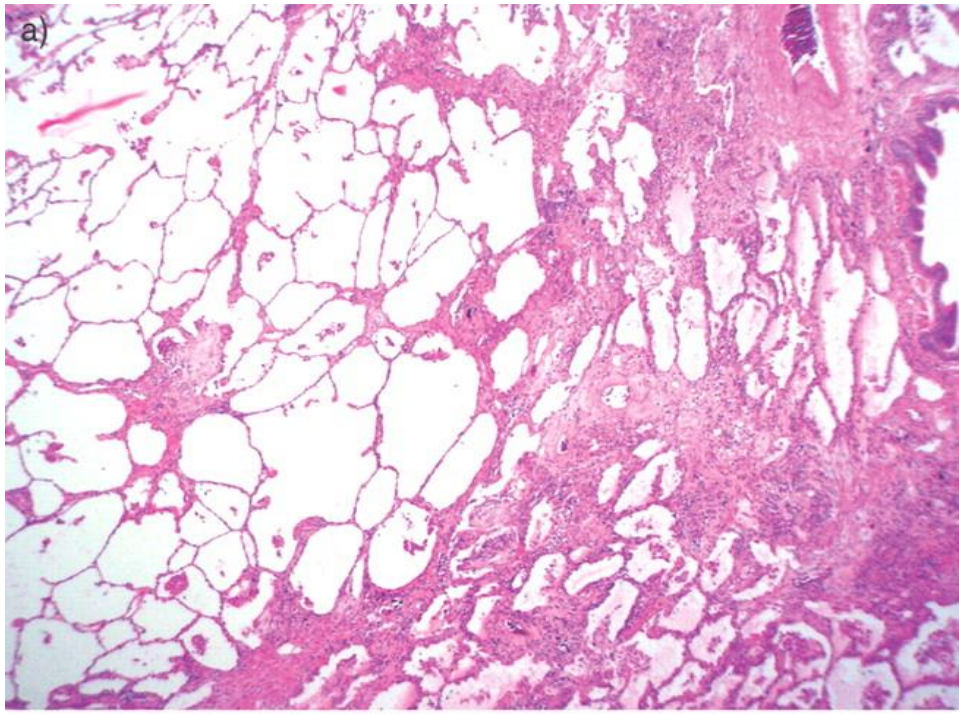
AJRCCM 2018: 198 (5), e44–e68

AMERICAN THORACIC SOCIETY DOCUMENTS

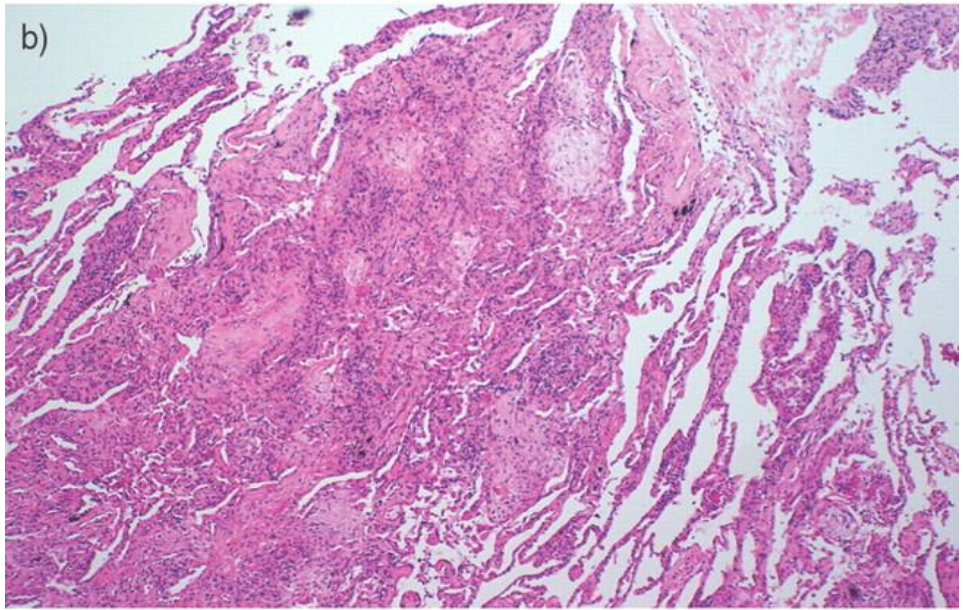
Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

- A subset of patients with previously occult IPF may present with an **acute exacerbation**, which is commonly characterized by a combination of a UIP pattern complicated by superimposed **DAD**± hyaline membranes.

AJRCCM 2018: 198 (5), e44–e68



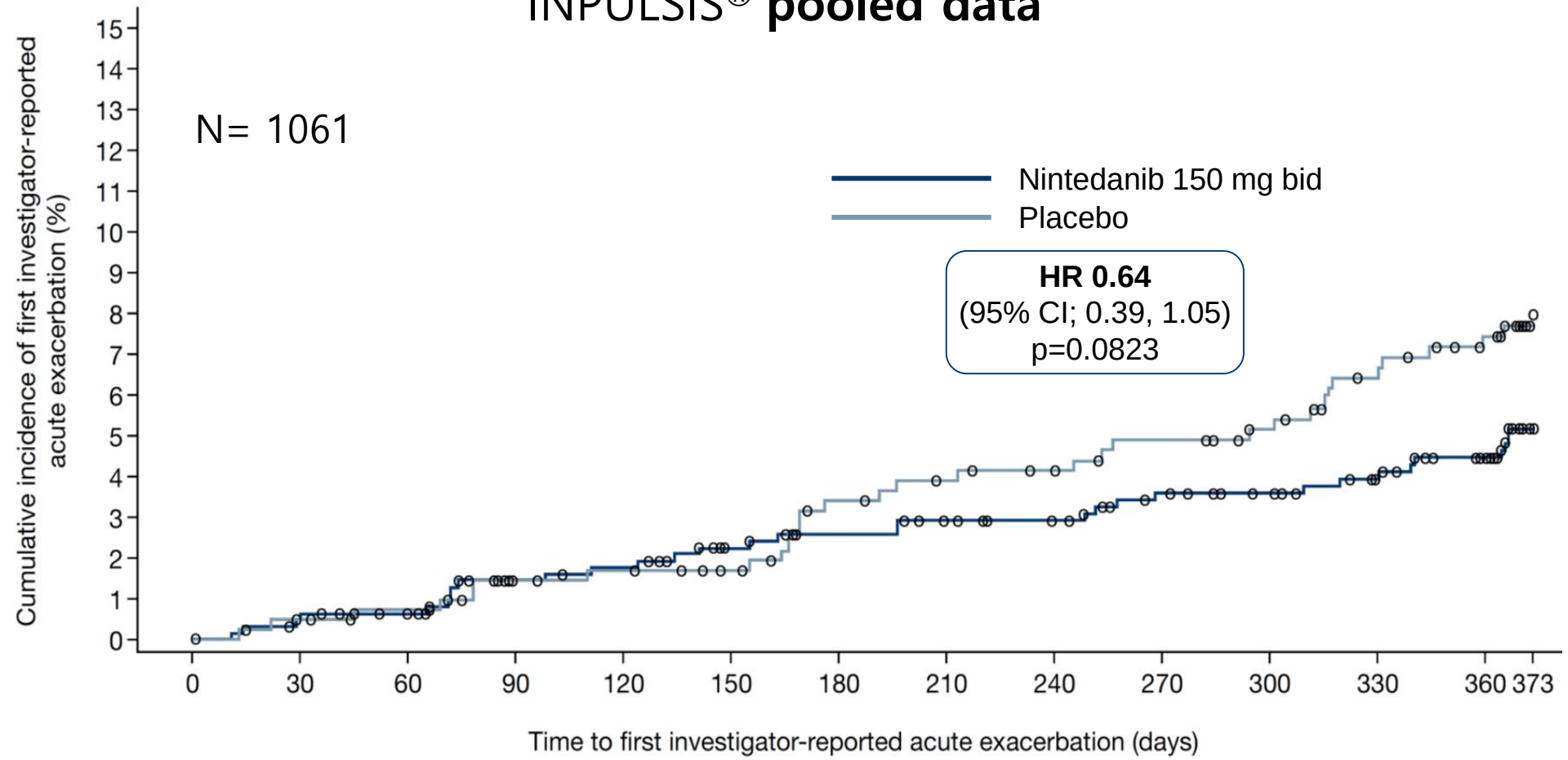
a) UIP with patchy dense fibrosis and architectural destruction (right half).



b) The AE in this case is manifested as **organising pneumonia** as seen in **COP**

Eur Respir J. 2006 Jan;27(1):143-50

Time to first investigator-reported AE: INPULSIS® **pooled data**



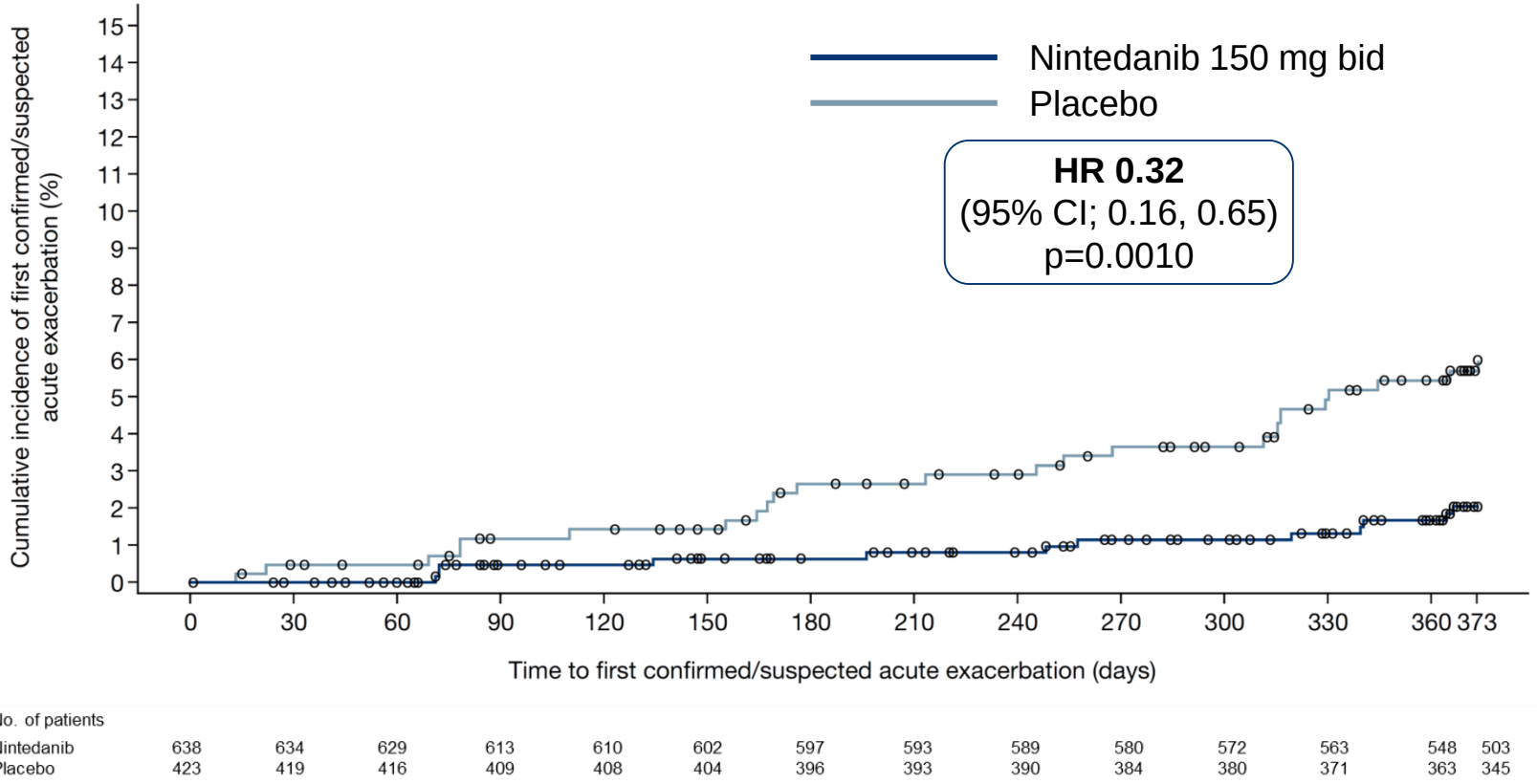
No. of patients

Nintedanib	638	632	627	609	605	595	589	584	580	570	562	553	537	492
Placebo	423	419	415	408	407	403	393	389	386	381	376	367	359	341

	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥1 acute exacerbation, n (%)	31 (4.9)	32 (7.6)

Richeldi L, et al. N Engl J Med 2014;370:2071–2082.

Time to first adjudicated confirmed or suspected AE: INPULSIS® **pooled data**



	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥1 acute exacerbation, n (%)	12 (1.9)	24 (5.7)

Richeldi L, et al. N Engl J Med 2014;370:2071–2082.