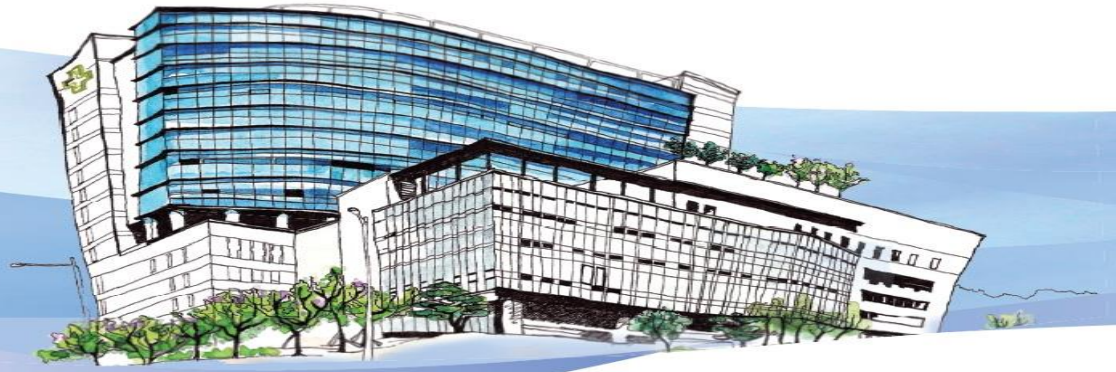


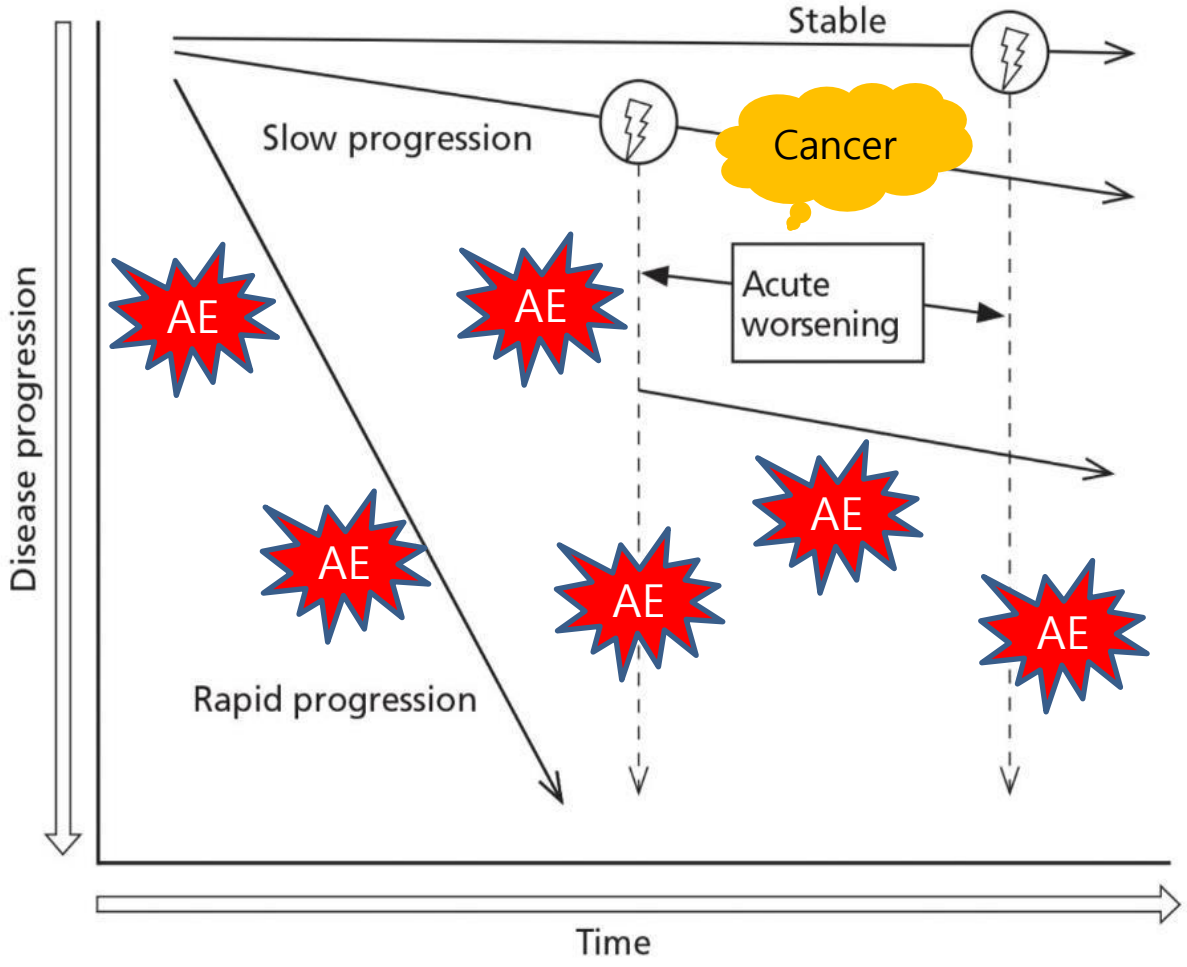
Acute Exacerbation of IPF

해운대백병원

이재하

Contents

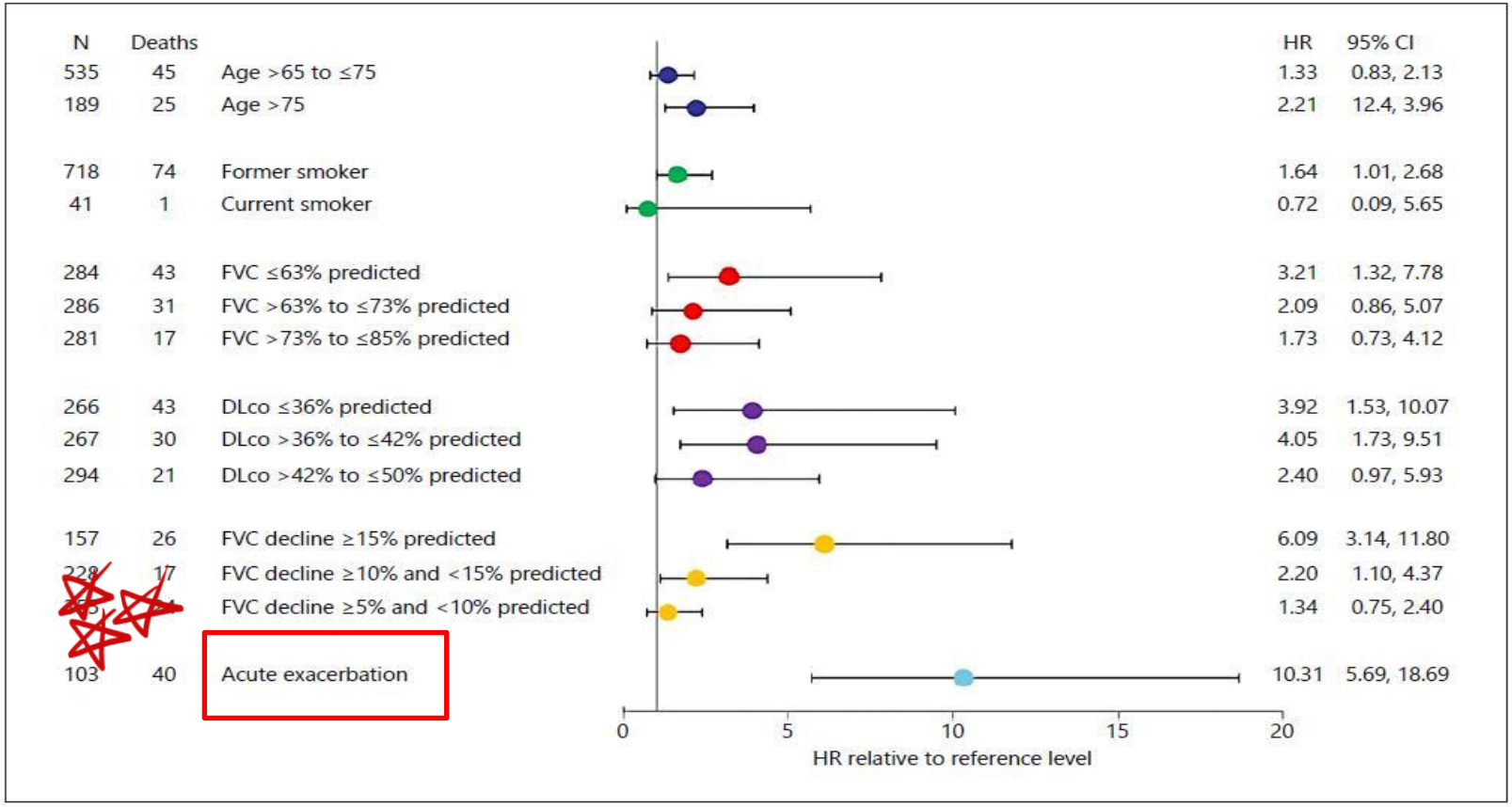
Impact of AE-IPF



- Most common cause of mortality in IPF
- In-hospital mortality: 50%
- ICU mortality:80-90%
- Median survival: 2.2 months

Importance of AE-IPF

Risk of mortality (TOMORROW, INPULSIS, CAPACITY and ASCEND trial)



Respiration 2020; 99: 73-82

Definition and Diagnosis

Revised definition

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

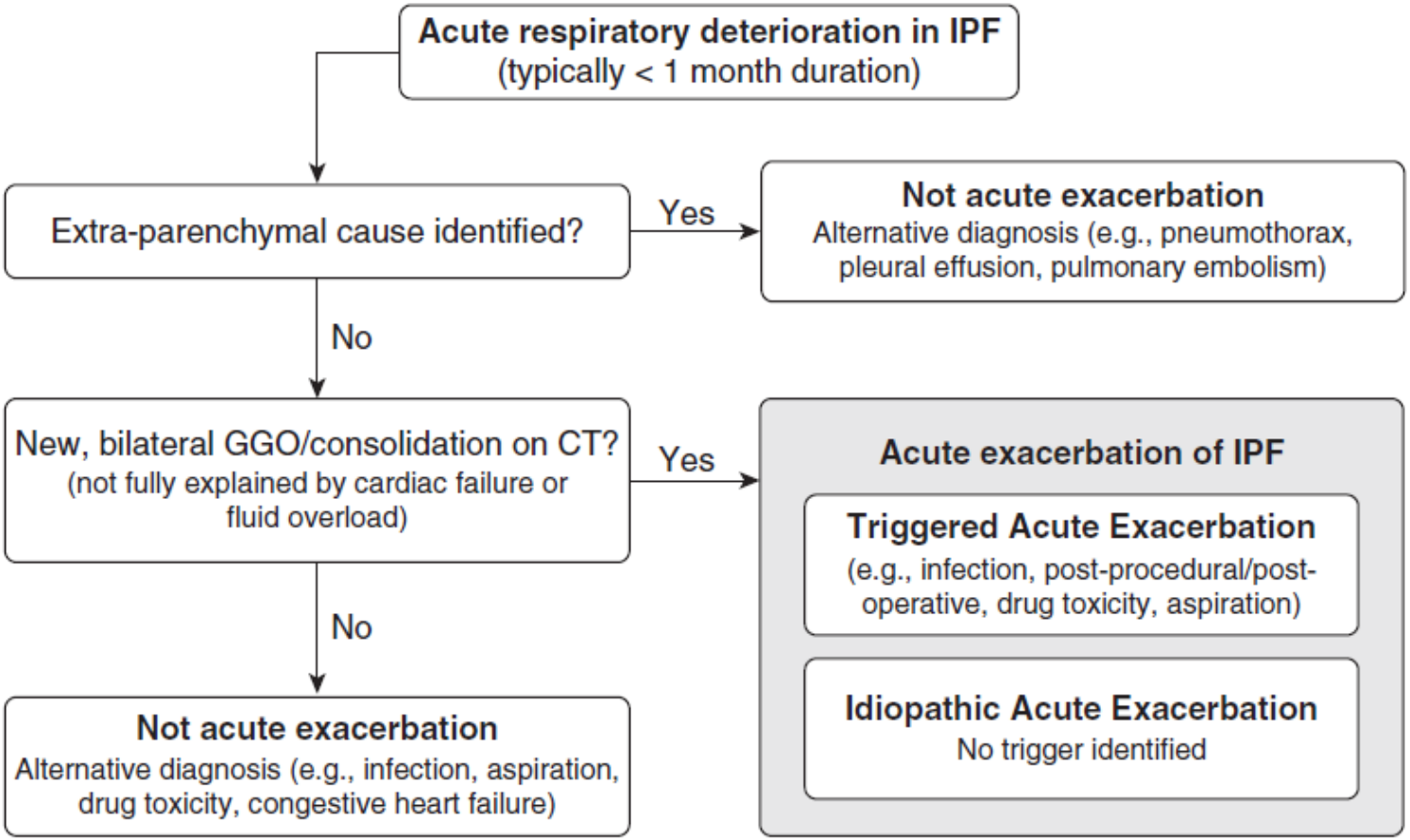
Revised diagnostic criteria

- 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

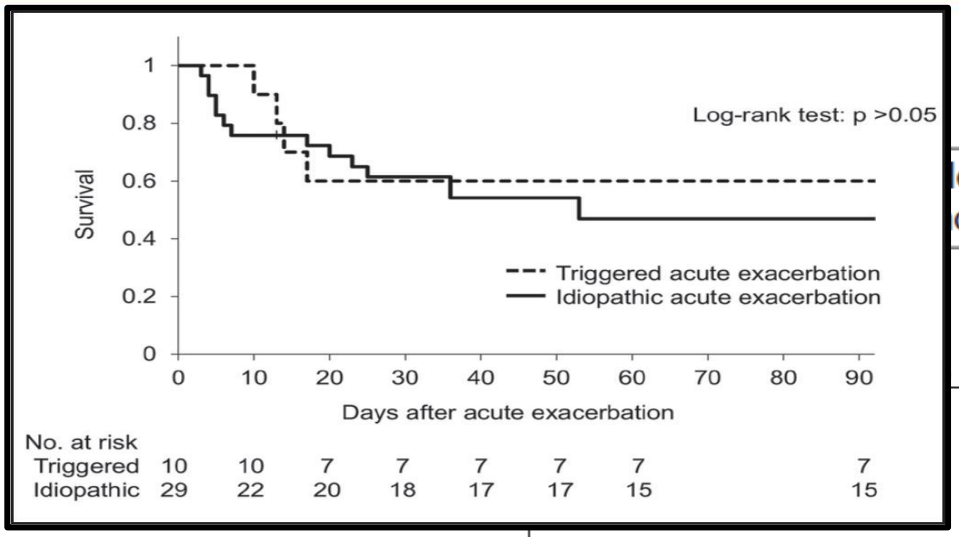
	IPF diagnosis	Course	HRCT findings	Exclusion
2007 guideline	Previous or concurrent diagnosis	Less than1 month	New bilateral GGO and/or consolidation on a background pattern of UIP pattern	Exclusion of alternative etiologies, such as infection, heart failure, and pulmonary embolism; BAL is required
2016 guideline	Previous or concurrent diagnosis	Typically less than 1 month	New bilateral GGO and/or consolidation on a background pattern of UIP pattern	Deterioration not fully explained by heart failure or fluid overload

AJRCCM2016: 194; 275

Definition and Diagnosis



Definition and Diagnosis



Retrospective single center

107 IPF / AE 39

Triggered 10 vs Idiopathic 29

The 90days survival rate

T-AE: 60% vs I-AE: 45%

CRP – only differed

New, bilateral GGO/consolidation on CT?
(not fully explained by cardiac failure or fluid overload)

Yes

No

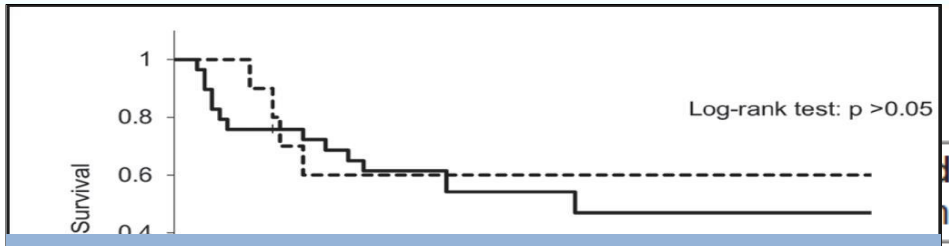
Not acute exacerbation
Alternative diagnosis (e.g., infection, aspiration, drug toxicity, congestive heart failure)

Acute exacerbation of IPF

Triggered Acute Exacerbation
(e.g., infection, post-procedural/post-operative, drug toxicity, aspiration)

Idiopathic Acute Exacerbation
No trigger identified

Definition and Diagnosis



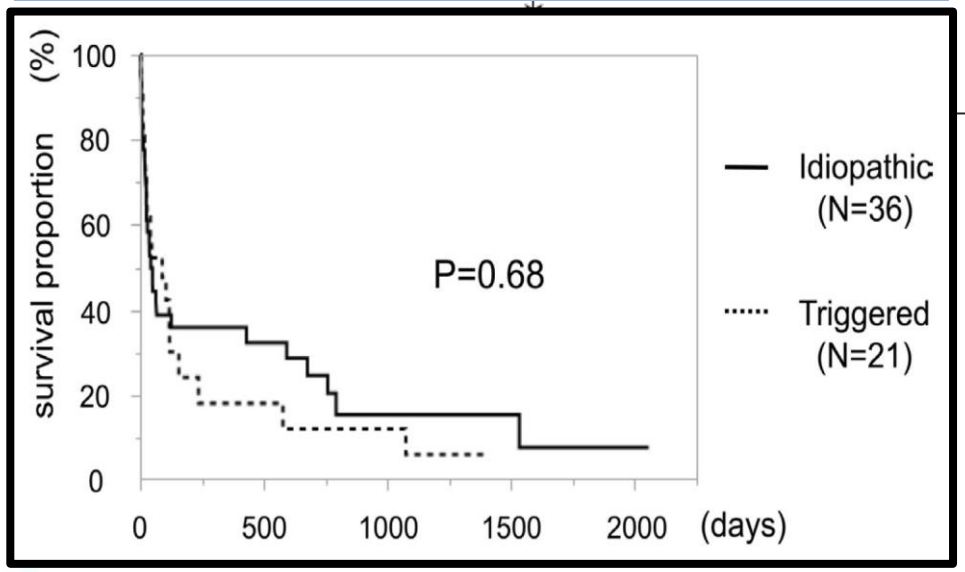
Retrospective single center

321 IPF (Biopsy proven) / AE 57

No difference in survival

Not prognosis

Find and Treat the reversible cause !

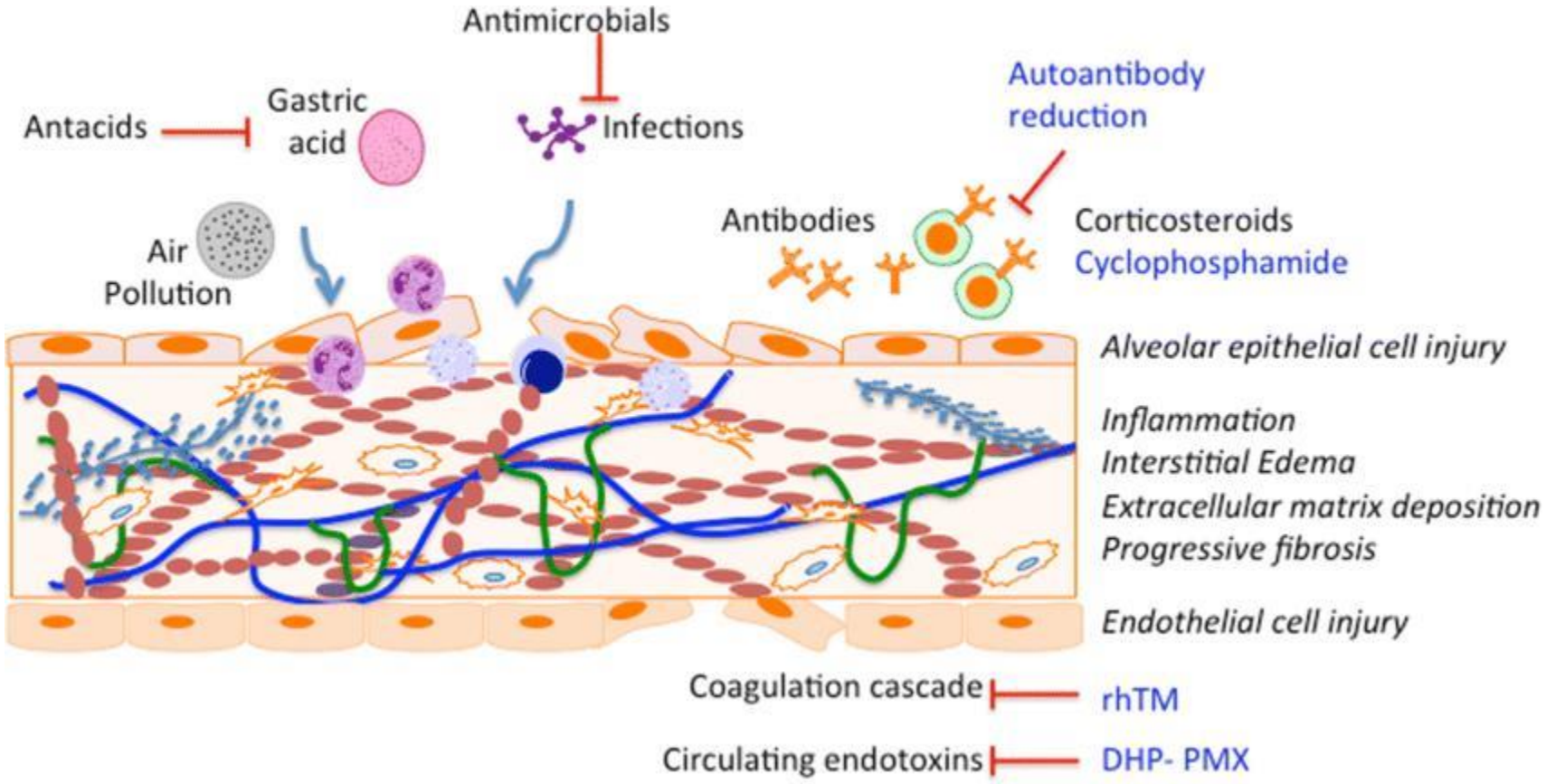


Acute exacerbation of IPF

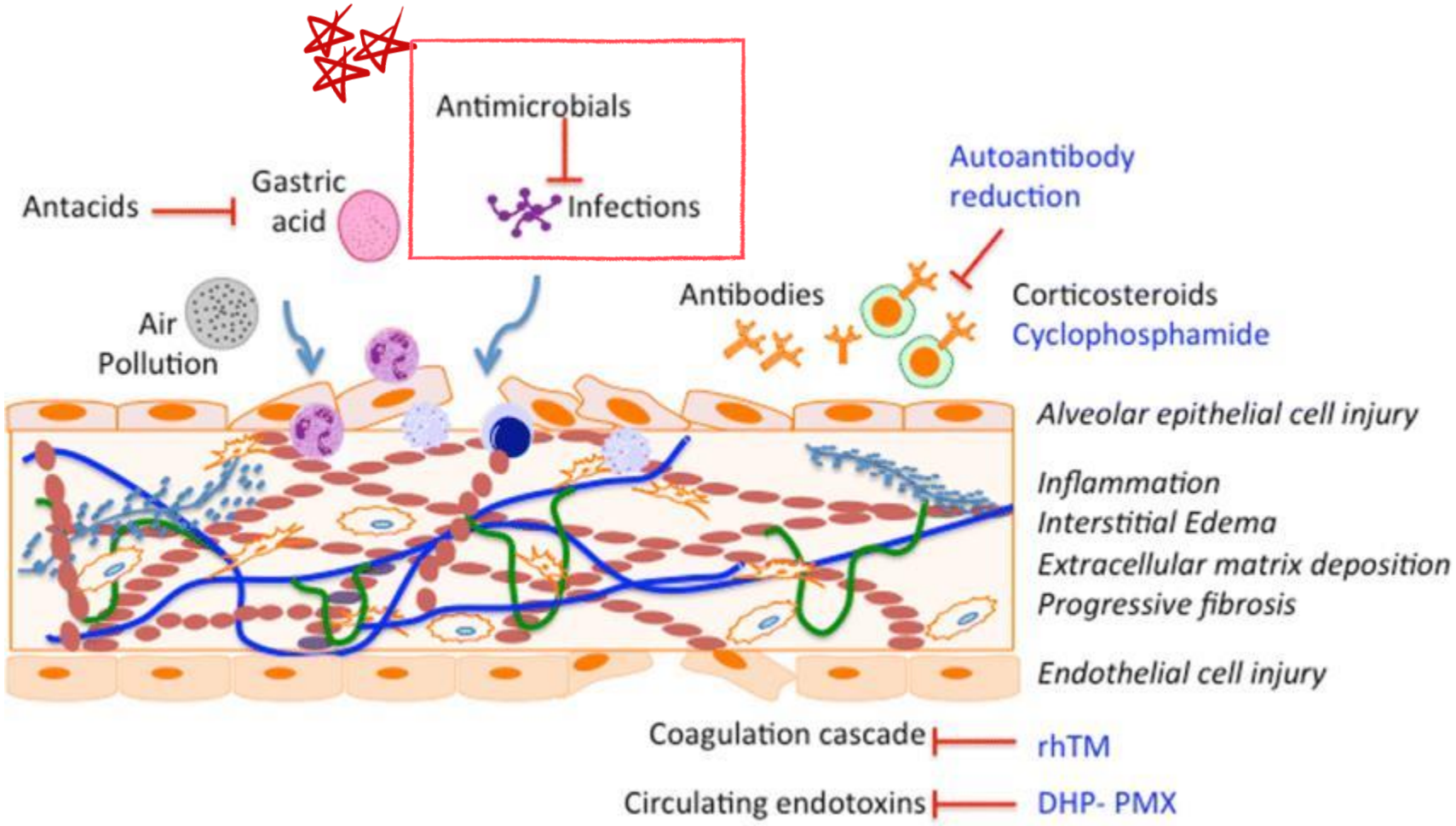
Triggered Acute Exacerbation
(e.g., infection, post-procedural/post-operative, drug toxicity, aspiration)

Idiopathic Acute Exacerbation
No trigger identified

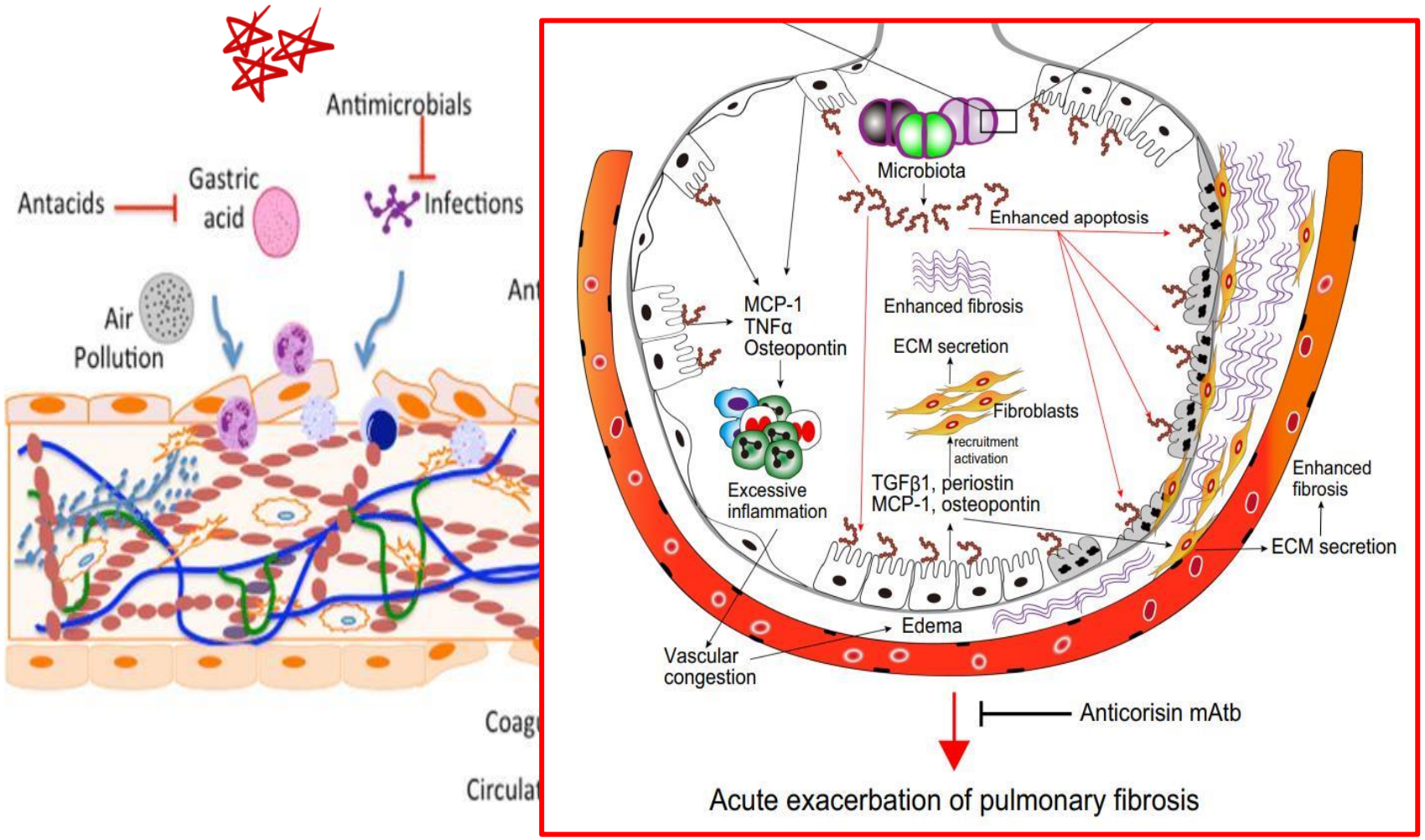
Pathogenesis



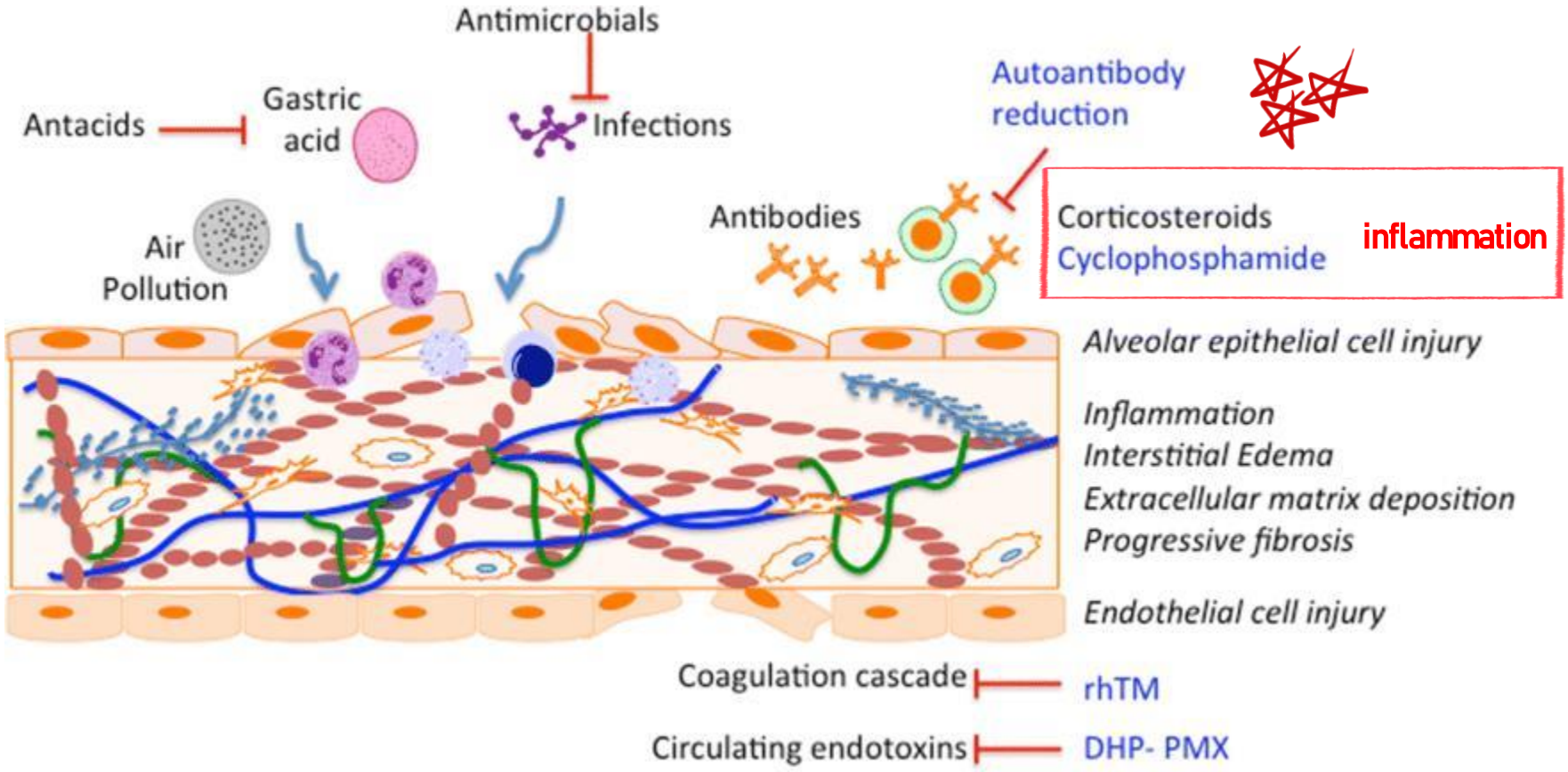
Pathogenesis



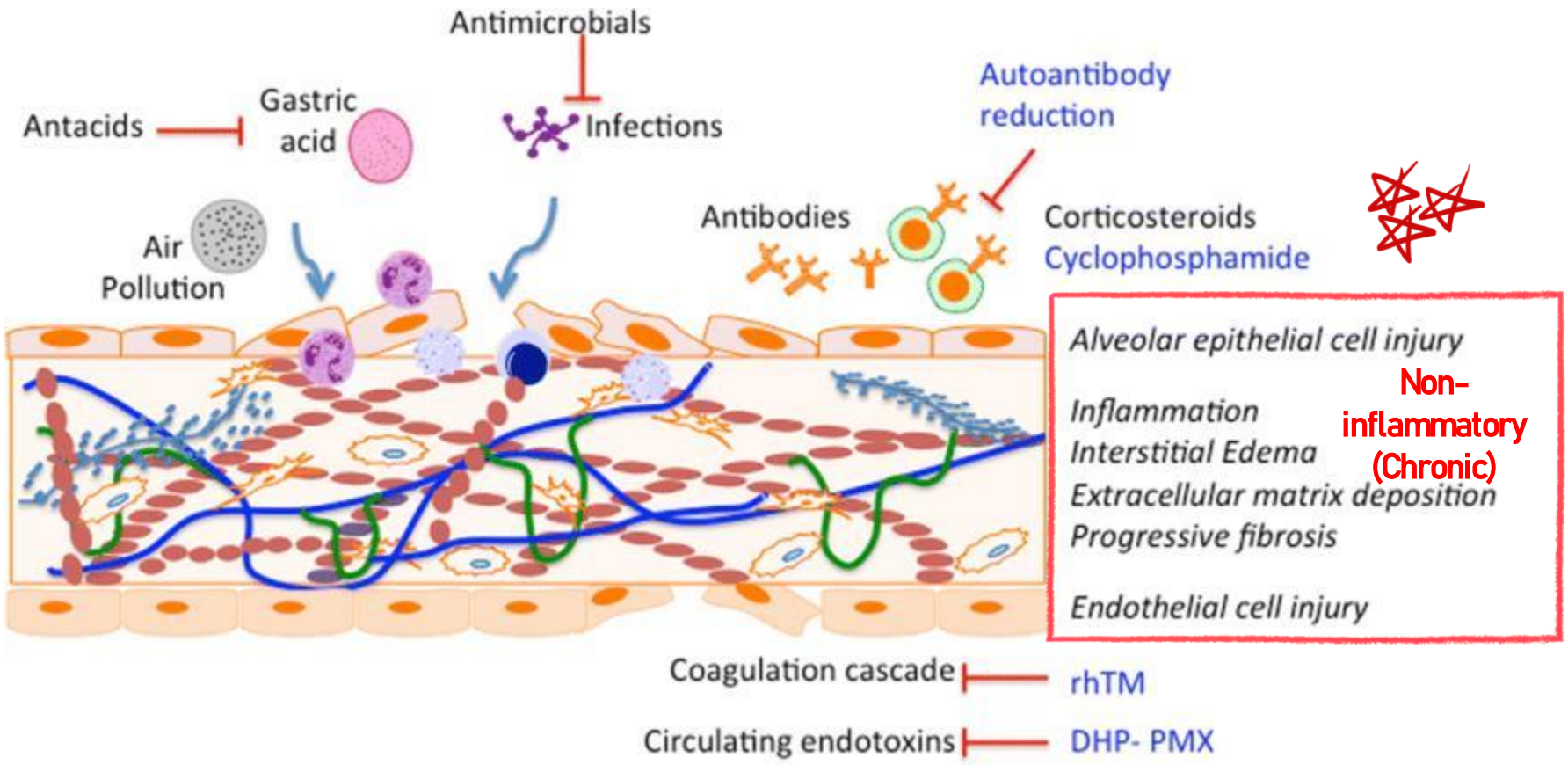
Pathogenesis



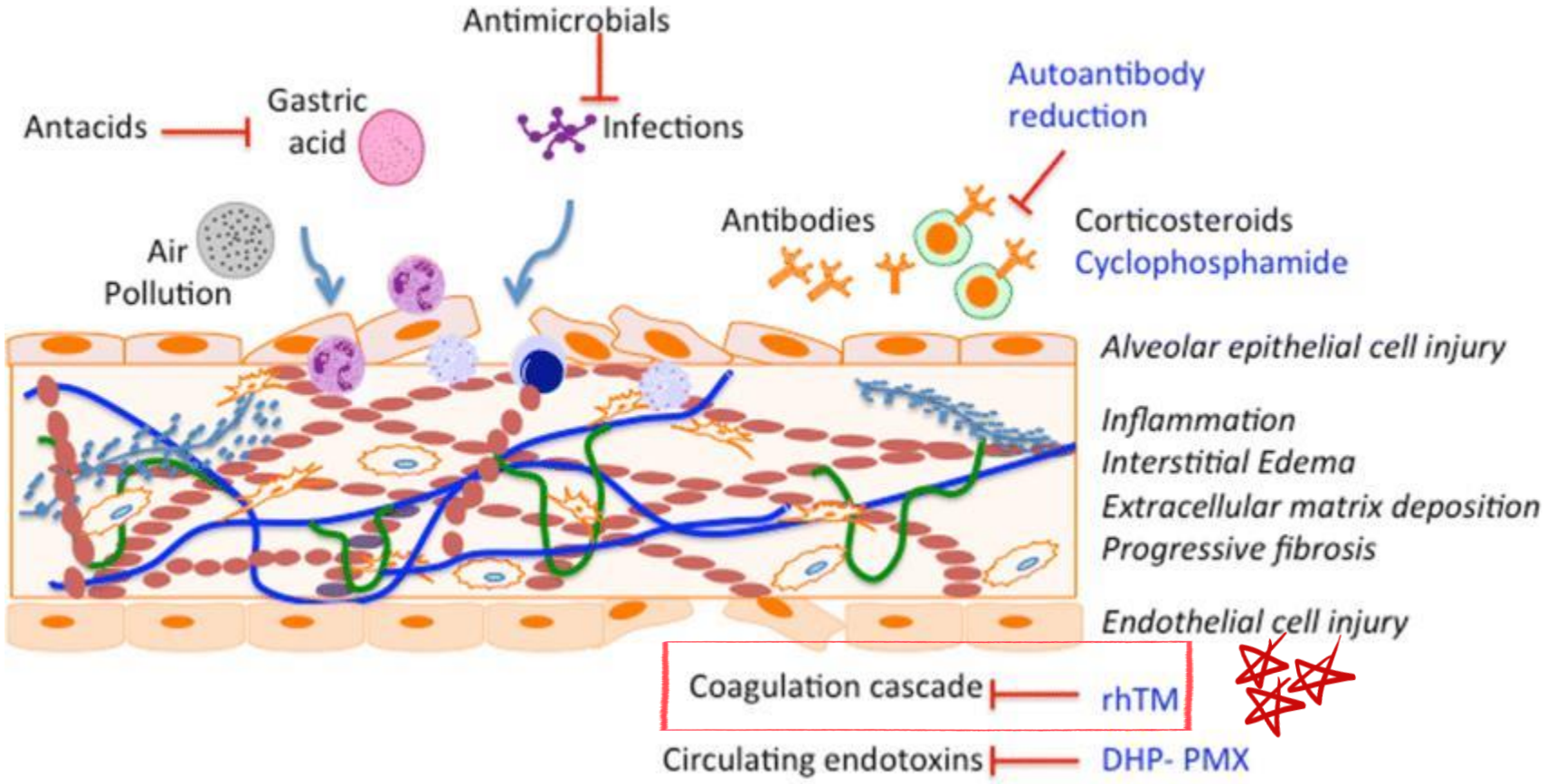
Pathogenesis



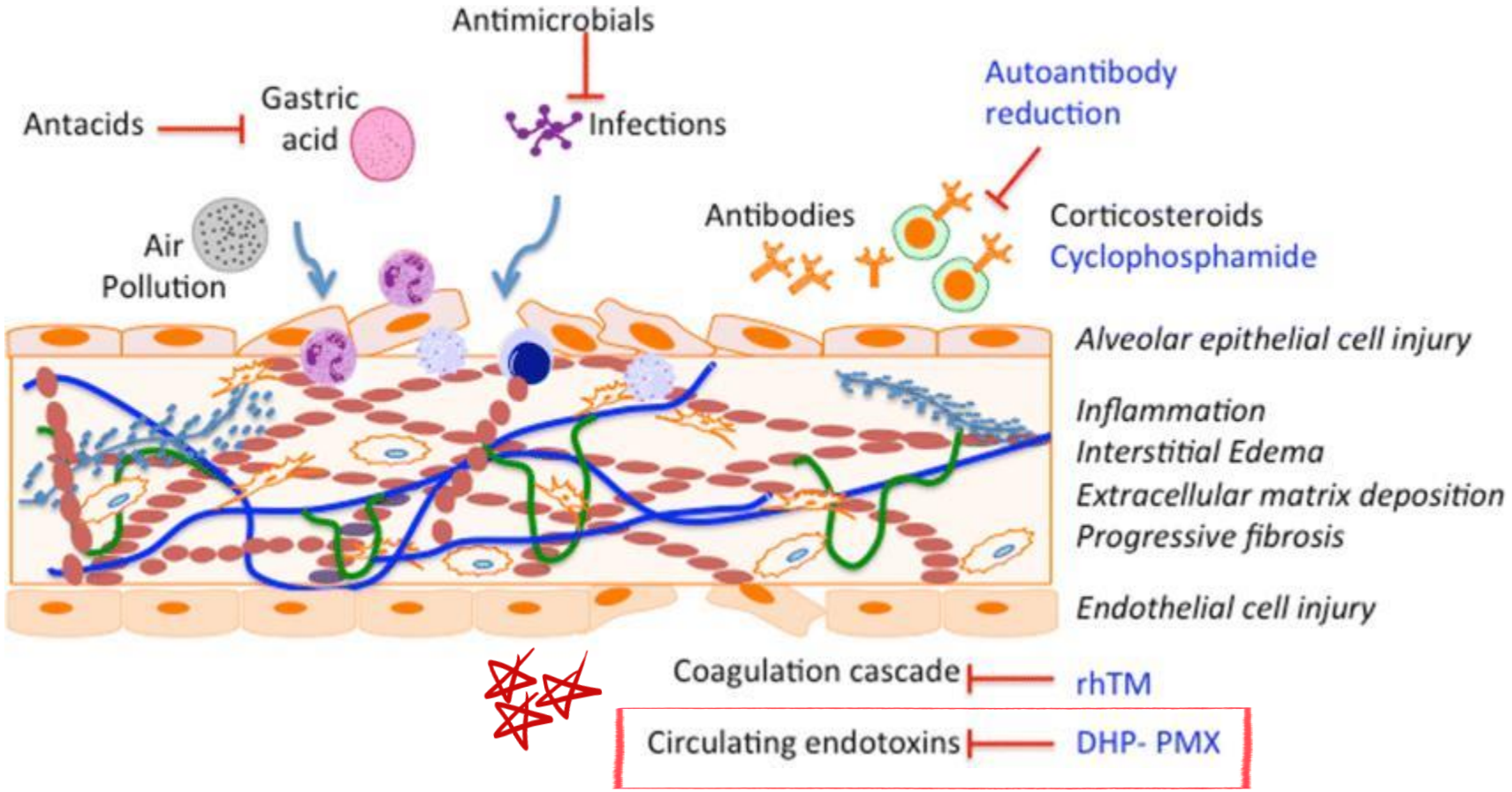
Pathogenesis



Pathogenesis



Pathogenesis



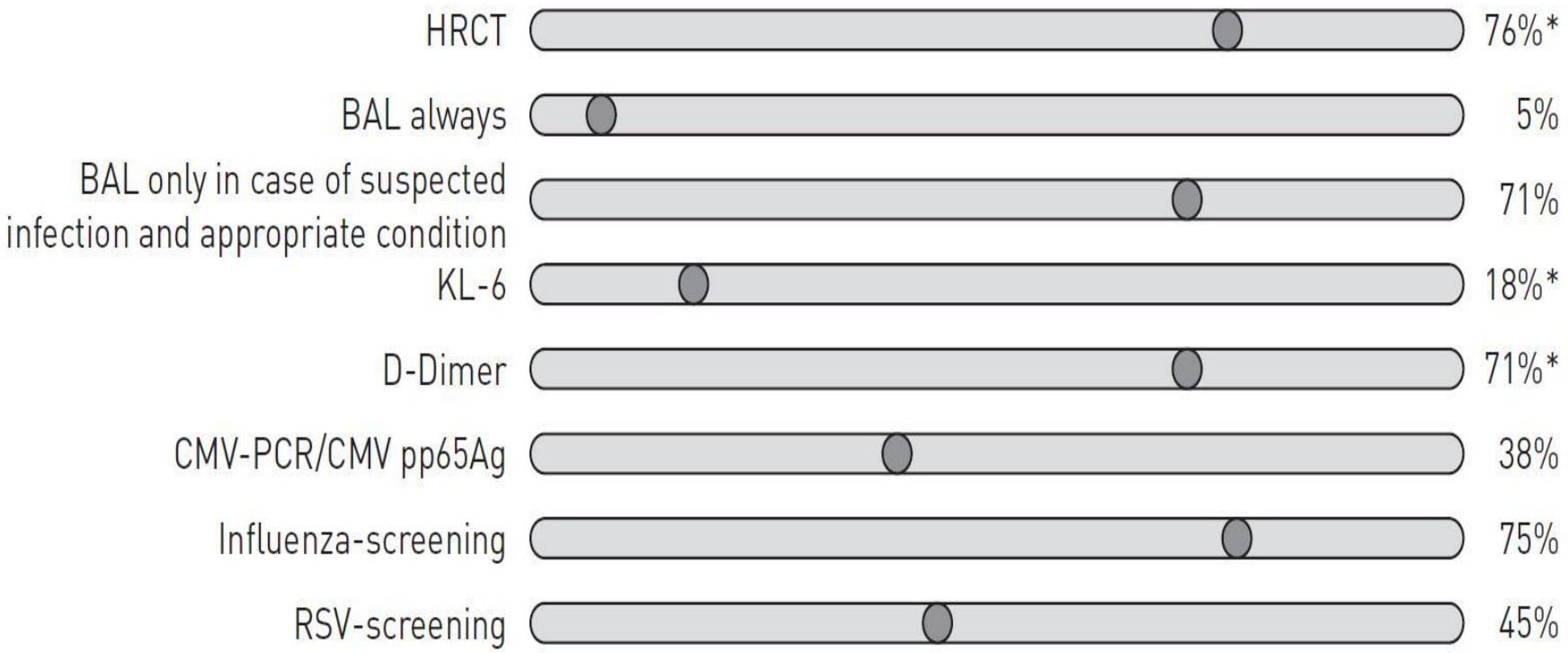
Excessive inflammatory/pro-fibrotic cytokine/chemokine

Diagnostic procedures

International Expert Survey in 2017

509 pulmonologists from 66 countries

(Europe – 42.6%, Asia – 26.7%, North America – 11.2%, Australia – 4.9%, Africa – 1%)

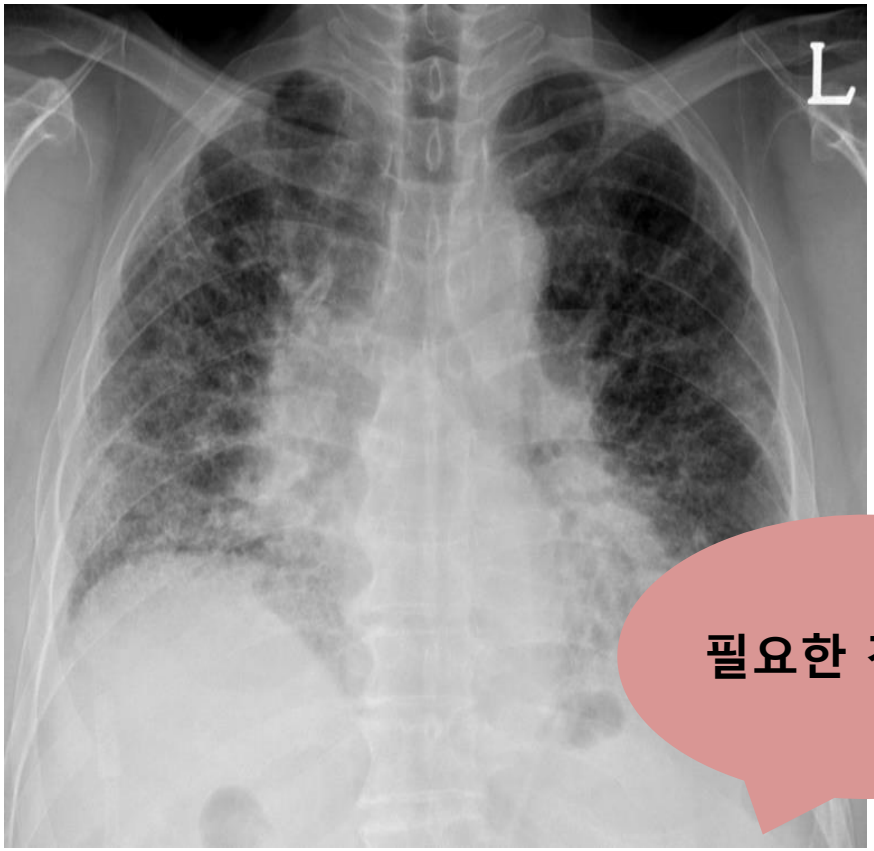


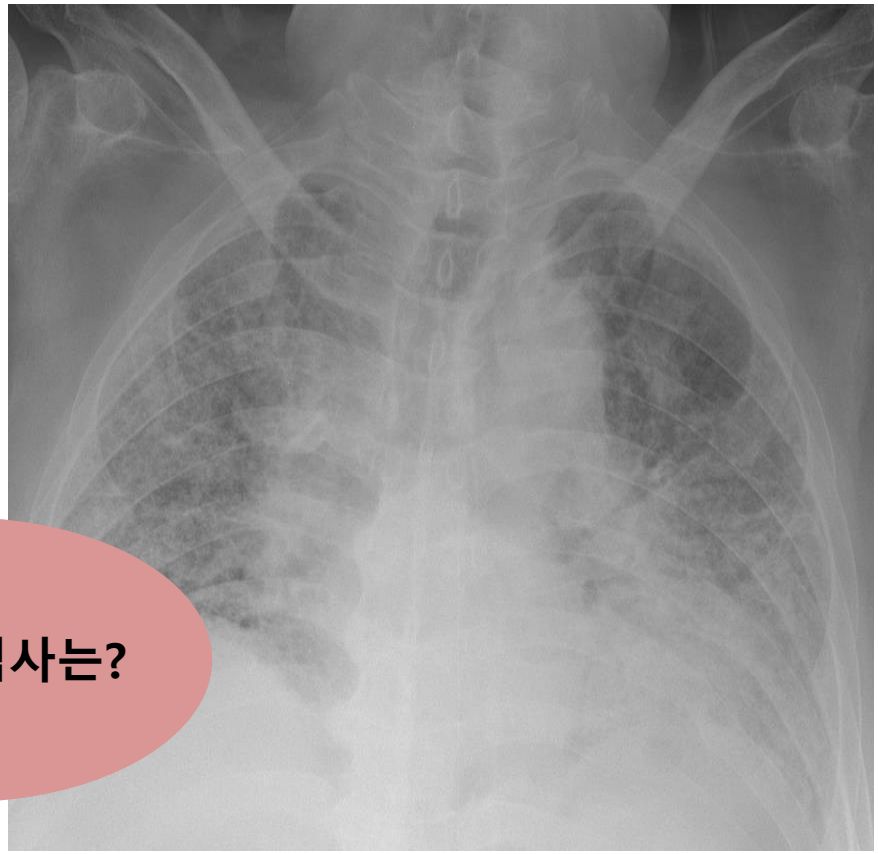
ERJ 2020; 55: 1901760

CASE

- C.C : Dyspnea
- PI : 68세 남자가 2일 전 부터 숨이 차서, 응급실로 내원하였다. 조금만 움직여도 숨이 차고, 마른 기침이 있다고 한다. 1년 6개월 전 IPF 진단 후 항섬유화제를 복용 중이다. 폐기능의 악화로 3개월 전 부터 nintedanib을 추가하여 병용 요법 중이다.
- PFT – FVC 38%, FEV1 – 46%, DLco – 38%
- GAP stage III (39.2% mortality at 1 year) on PFD 1800mg + NIN 100mg bid
- Ex-smoker (30pyrs), HTN (+), Cancer (-), Leg swelling (-)

X-ray



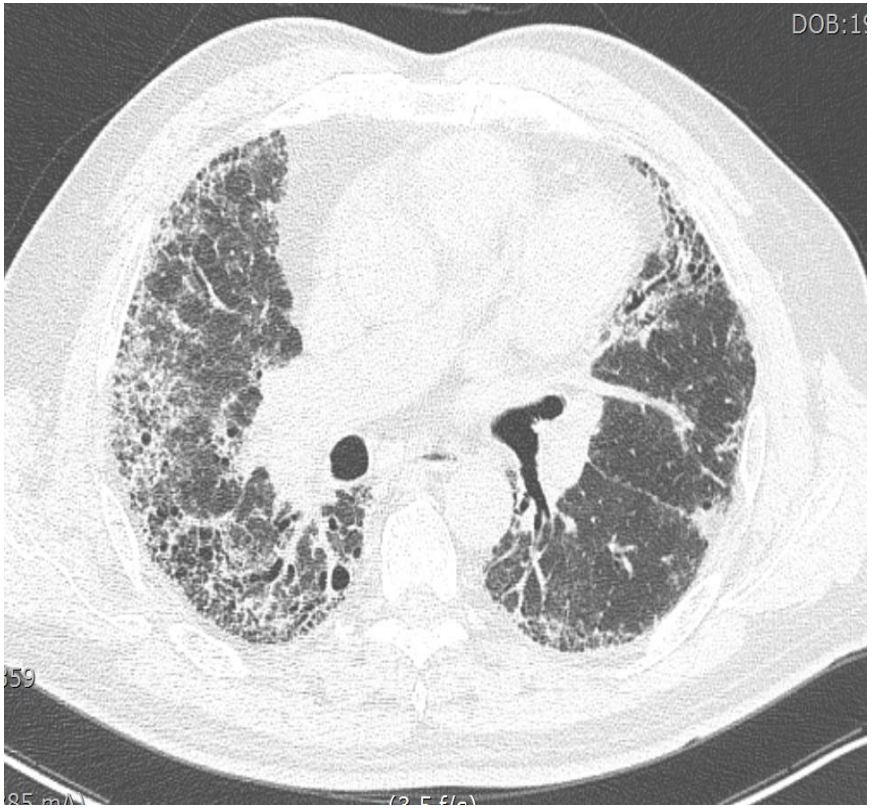


필요한 검사는?

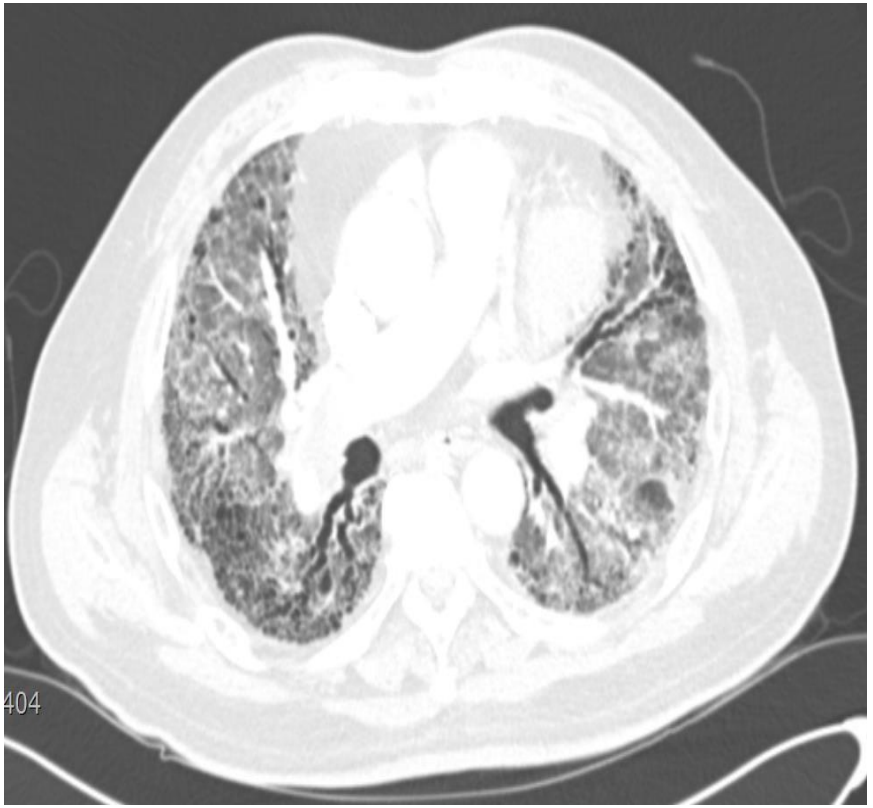
2 주전

ER

CT chest

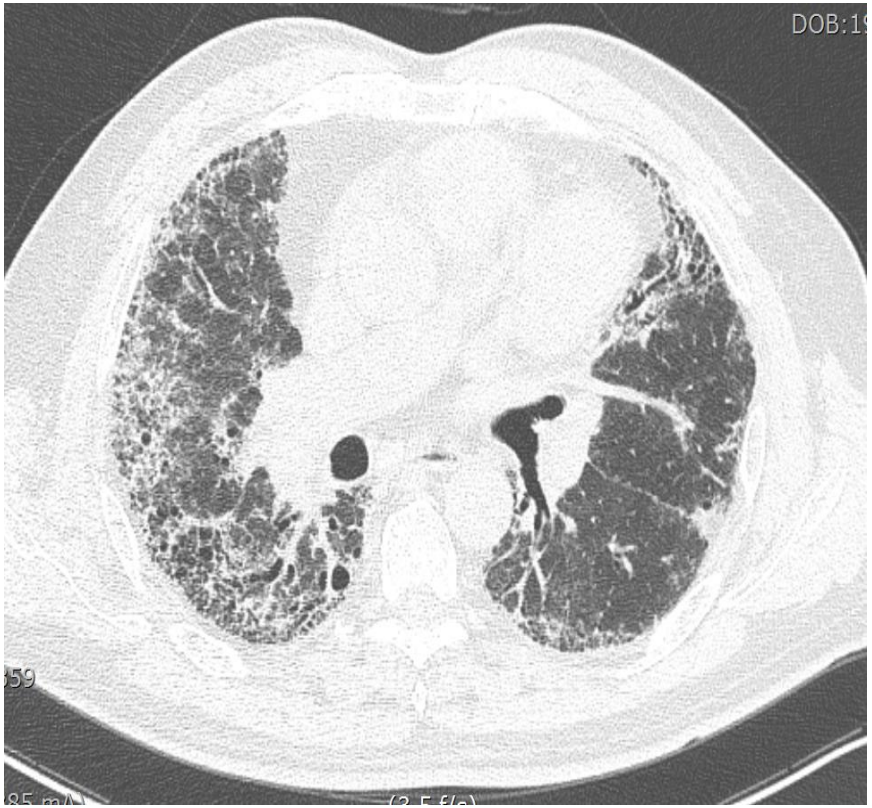


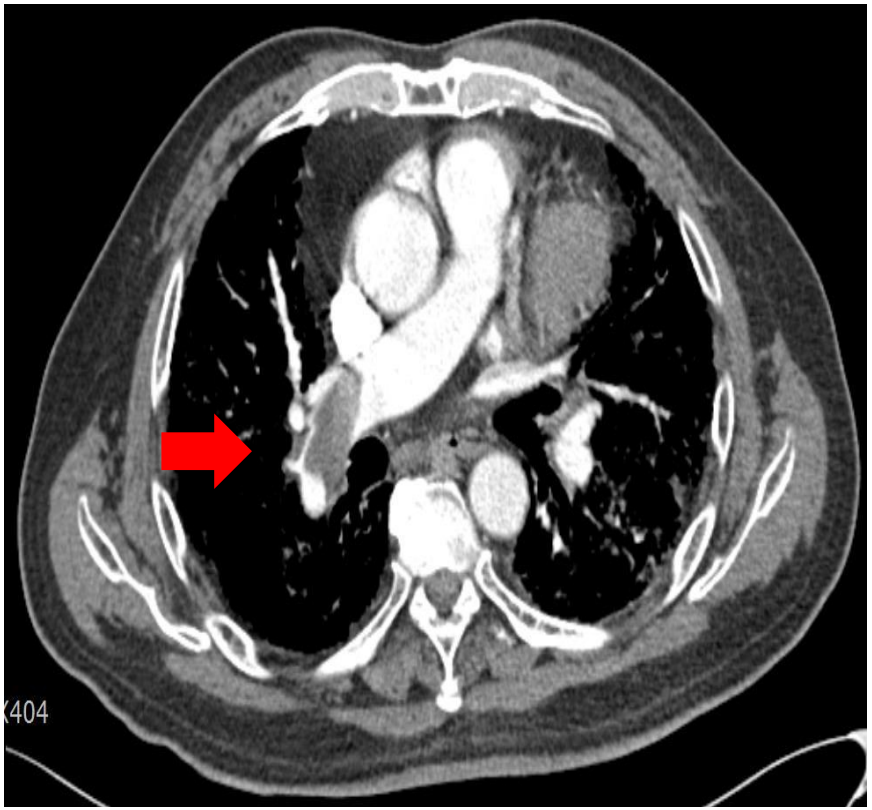
2 주전



ER

CT chest





2 주전

French (CT angiography)

ATS (HRCT)

ER

Incidence (Japan)

Retrospective study from 2008 to 2019

A Japanese claims database (9961 IPF and 2629 AE patients)

Year	Number of patients with IPF	Percentage of patients with ≥1 AE	Annual incidence of AE (%)
2008	10	10.00	10.00
2009	23	4.35	4.35
2010	183	9.84	10.93
2011	286	10.49	11.54
2012	478	11.30	11.92
2013	925	10.27	11.57
2014	1498	10.48	11.21
2015	2163	12.30	13.27
2016	3109	10.20	11.45
2017	4093	9.87	10.97
2018	4665	9.17	9.97
2019	3060	4.05	4.08

Respiratory Investigation 60 (2018) 798-805

Incidence (Japan)

Retrospective study from 2008 to 2019

A Japanese claims database (9961 IPF and 2629 AE patients)

Year after first IPF diagnosis	Observation period (patient-years)	Number of AEs	Annual incidence of AEs (per 100 patient-years)
0	5110	1433	28.04
1	2439	253	10.37
2	1162	118	10.15
3	546	50	9.16
4	246	25	10.18
5	101	11	10.88
6	37	1	2.74
7	14	1	7.35
8	6	0	0.00
9	0	0	0.00

Respiratory Investigation 60 (2018) 798-805

Incidence (KICO registry 2016-2022)

Characteristic	Overall	AE (+)	AE (-)	*P*-value
All patients	678(100.0)	165(24.3)	513(75.7)	
Male	556(82.0)	137(83.0)	419(81.7)	.694[3]
Age, year	69.37±8.23	69.40±8.02	69.37±8.30	.964[1]
BMI, Kg/m²	24.48±3.16	24.39±3.52	24.52±3.05	.333[2]
Malignancy	67(9.9)	23(13.9)	44(8.6)	.045[3]
PFT				
FVC, % predicted	85.88±17.51	79.75±17.99	87.85±16.90	<.001[2]
DLco, % predicted	61.10±20.57	50.05±17.81	64.64±20.15	<.001[2]
Six-minute walk test				
Distance, m	403.95±111.38	370.60±116.78	414.98±107.42	<.001[2]
Nadir SpO2	90.09±6.57	87.04±7.46	91.10±5.92	<.001[2]
Home oxygen				
Yes	99(16.2)	64(40.3)	35(7.7)	<.001[3]

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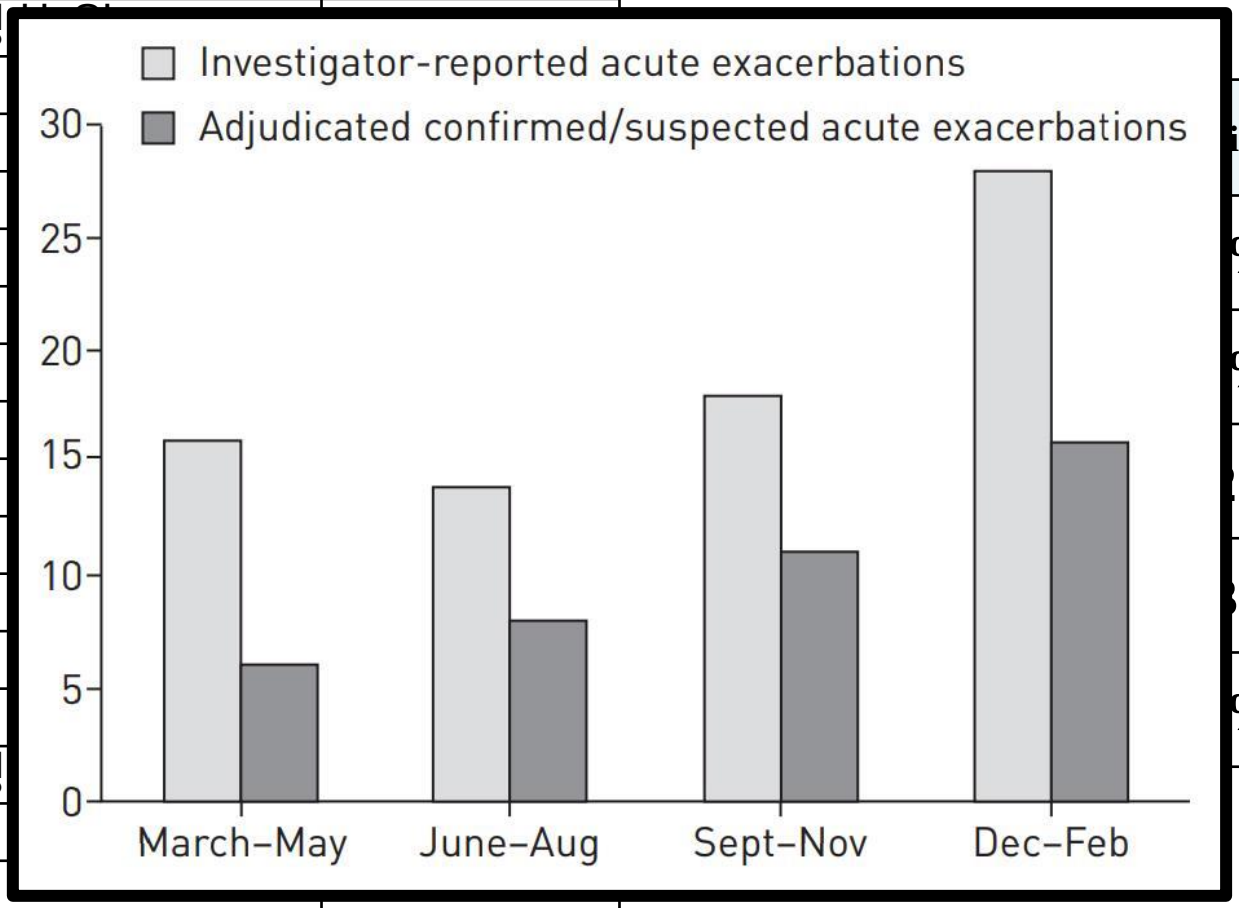
Home oxygen				
Yes	99(16.2)	64(40.3)	35(7.7)	<.001[3]

Incidence (KICO registry 2016-2022)

	급성악화
급성악화가 발생	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
급성악화가 발생	
봄	
여름	
가을	20.0 %
겨울	26.1 %



idence, %
%
%
%
%
%

Risk factors

- Advanced disease (FVC ↓, Dlco ↓ and 6MWT distance ↓)
- Pulmonary hypertension
- Poor baseline oxygenation
- Increased dyspnea
- Recent decline in FVC
- Emphysema
- Prior history of AE
- Increase level of KL-6
- Extent of GGO and fibrosis on HRCT at baseline

New risk prediction model (KICO registry)

Variable	Univariate analysis			Multivariate analysis*		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Pulmonary function test						
FVC, % predicted	0.967	0.955-0.978	<.001	0.980	0.958-1.003	.085
FEV1/FVC, % predicted	1.018	1.007-1.030	.002	0.993	0.976-1.011	.448
DLco, % predicted	0.959	0.949-0.970	<.001	0.990	0.972-1.009	.303
Six-minute walk test						
Distance, m	0.997	0.995-0.998	<.001	0.997	0.995-1.000	.045
Home oxygen	8.065	5.049-12.883	<.001	4.961	2.515-9.785	<.001

New risk prediction model (KICO registry)

Variable	Univariate analysis			Multivariate analysis*		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Pulmonary function test						
FVC, % predicted	0.967	0.955-0.978	<.001	0.980	0.958-1.003	.085
FEV1/FVC, % predicted	1.018	1.007-1.030	.002	0.993	0.976-1.011	.448
DLco, % predicted	0.959	0.949-0.970	<.001	0.990	0.972-1.009	.303
Six-minute walk test						
Distance, m	0.997	0.995-0.998	<.001	0.997	0.995-1.000	.045
Home oxygen	8.065	5.049-12.883	<.001	4.961	2.515-9.785	<.001

New risk prediction model (KICO registry)

Variable	Univariate analysis			Multivariate analysis*		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Home oxygen						
Yes	8.065	5.049-12.883	.000	6.541	3.843-11.133	.000
No	1.000					
Distance, m (6MWT)						
≥250	1.000					
<250	2.621	1.508-4.556	.001	2.091	1.038-4.214	.039
FVC, % predicted						
>75	1.000					
50-75	1.796	1.230-2.623	.002	1.828	1.151-2.904	.011
<50	5.824	2.888-11.744	.000	3.819	1.406-10.370	.009

New risk prediction model (KICO registry)

Home oxygen	FVC, % predicted	Distance, m (6MWT)	급성악화발생률, %
no	>75	≥250	13.1
no	>75	<250	24.0
no	50-75	≥250	21.6
no	50-75	<250	36.5
no	<50	≥250	36.5
no	<50	<250	54.6
yes	>75	≥250	49.6
yes	>75	<250	67.3
yes	50-75	≥250	64.3
yes	50-75	<250	79.0
yes	<50	≥250	79.0
yes	<50	<250	88.7

New risk prediction model (KICO registry)

Variable	Score	No. of patients
Home O2		
yes	3	423 (83.4)
no	0	84 (16.6)
FVC, % predicted		
>75	0	233 (46.0)
50-75	1	247 (48.7)
<50	2	27 (5.3)
Distance, m (AN)		
≥250		457 (90.1)
<250		50 (9.9)
Score		
0		200 (39.4)
1		194 (38.3)
2		23 (4.5)
3		29 (5.7)
4	4	36 (7.1)
5	5	18 (3.6)
6	6	7 (1.4)
Stage		
I	0 – 1	394 (77.7)
II	2 – 4	88 (17.4)
III	5 – 6	25 (4.9)

KICO data

중요성 !

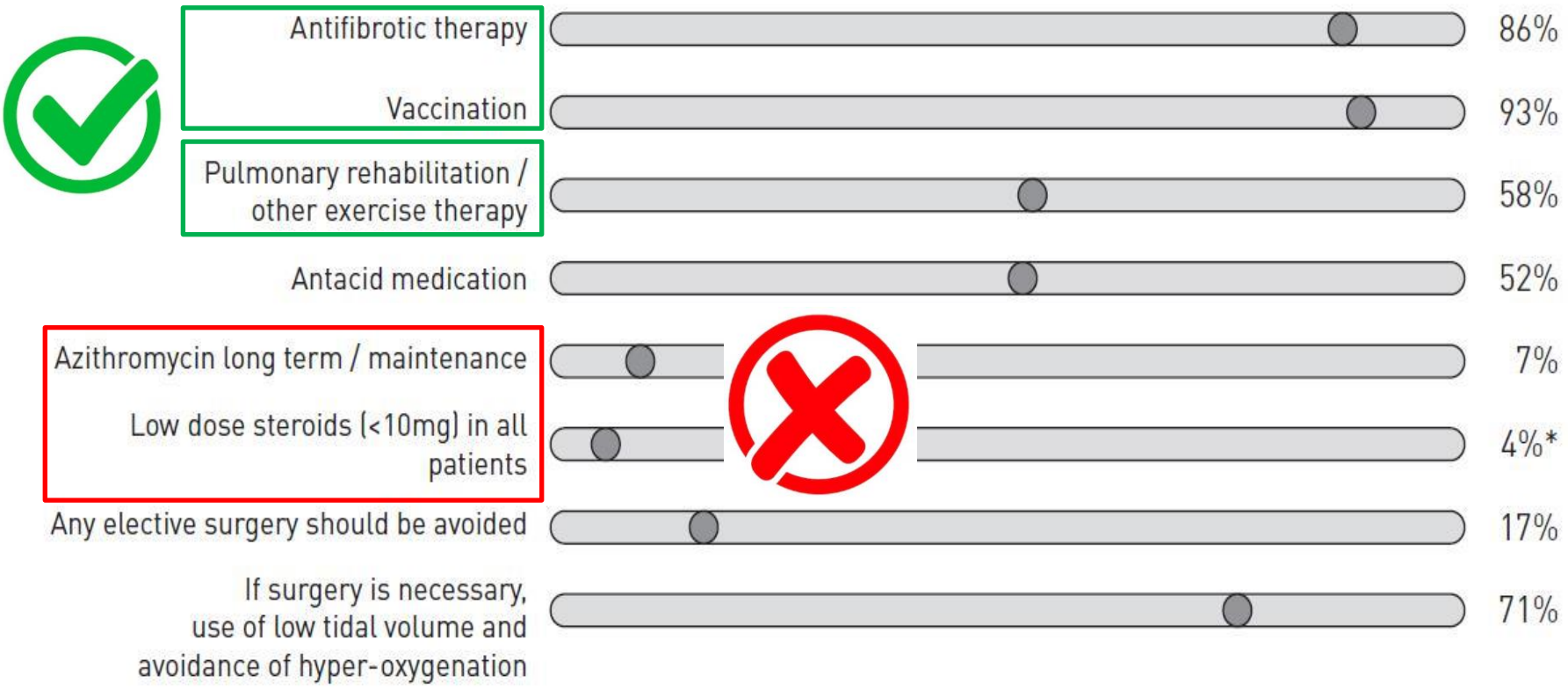
		급성악화	
Stage	**Overall**	**Yes (n=135)**	***P***
I	394(100.0)	67 (17.0 %)	<.001
II	88(100.0)	49 (55.7 %)	
III	25(100.0)	19 (76.0 %)	

Preventive strategies

International Expert Survey in 2017

509 pulmonologists from 66 countries

(Europe – 42.6%, Asia – 26.7%, North America – 11.2%, Australia – 4.9%, Africa – 1%)

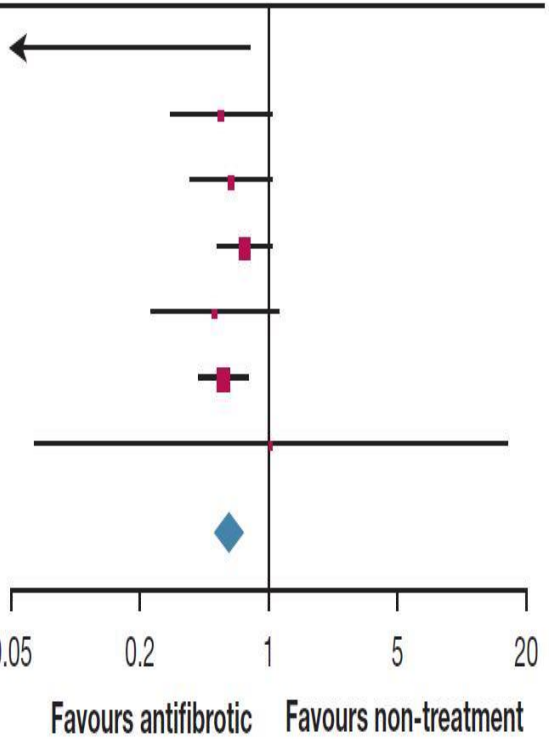


ERJ 2020; 55: 1901760

Prevention - Antifibrotics

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]**

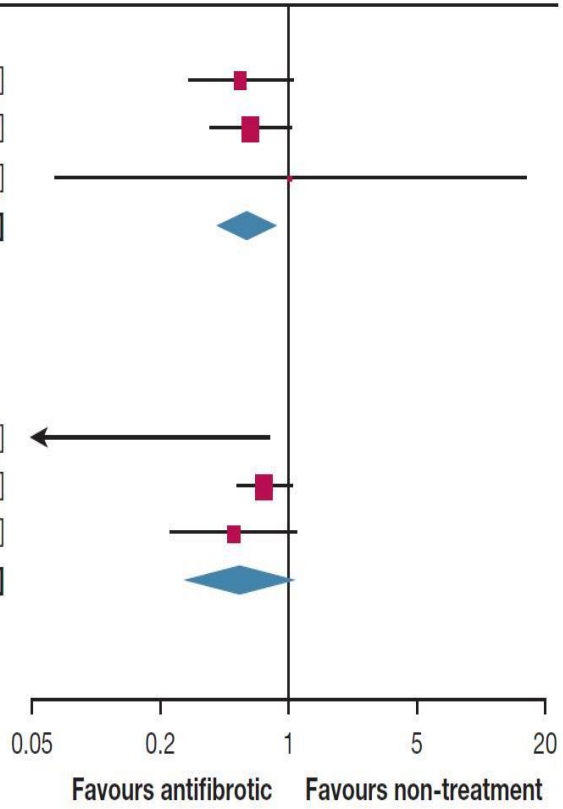
Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 5.14$, $df = 6$ ($P = .53$); $I^2 = 0\%$
Test for overall effect: $Z = 5.02$ ($P < .00001$)



CHEST 2021; 160(5): 1751-1763

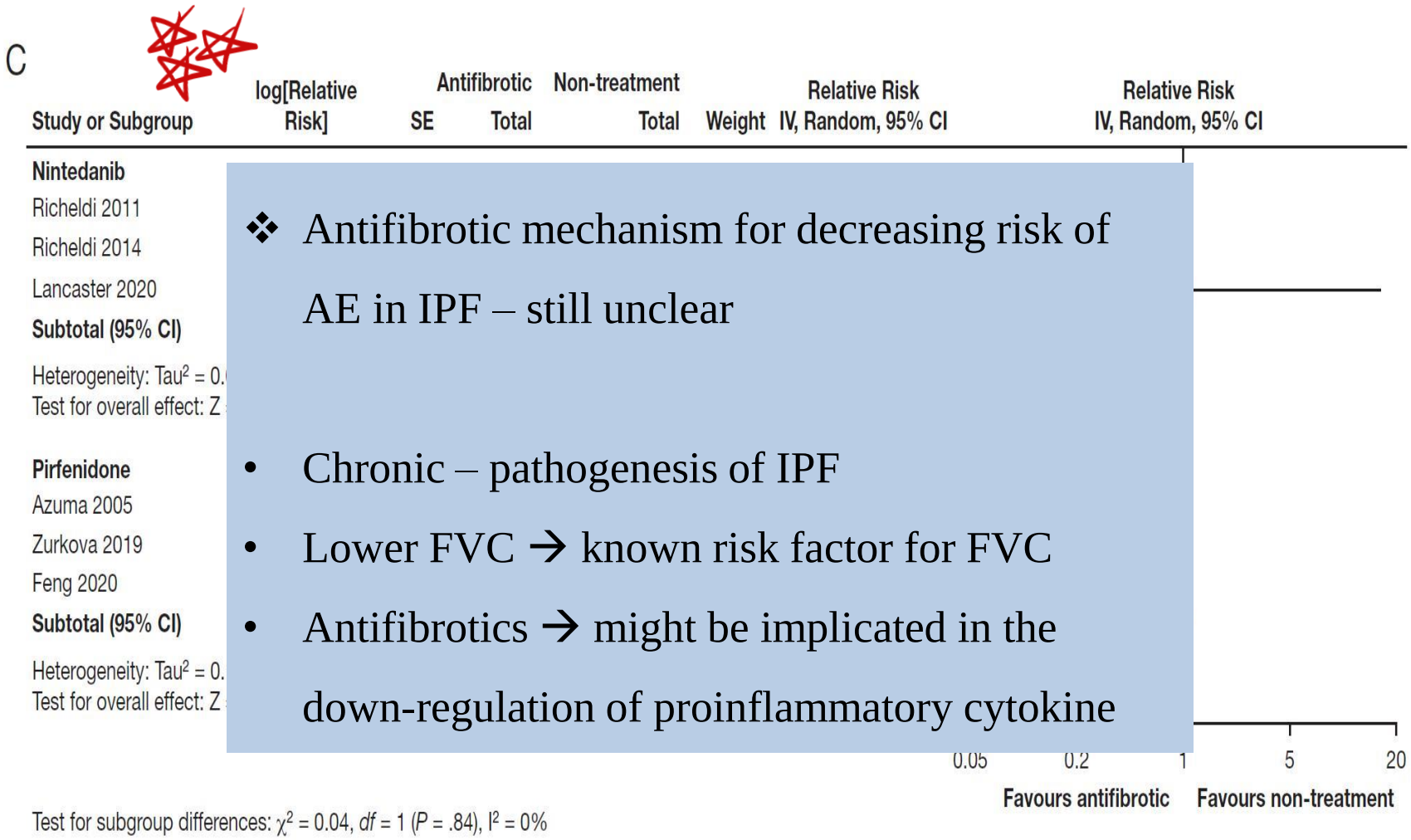
Prevention - Antifibrotics

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



CHEST 2021; 160(5): 1751-1763

Prevention - Antifibrotics



- Antifibrotic mechanism for decreasing risk of AE in IPF – still unclear

- Chronic – pathogenesis of IPF
- Lower FVC → known risk factor for FVC
- Antifibrotics → might be implicated in the down-regulation of proinflammatory cytokine

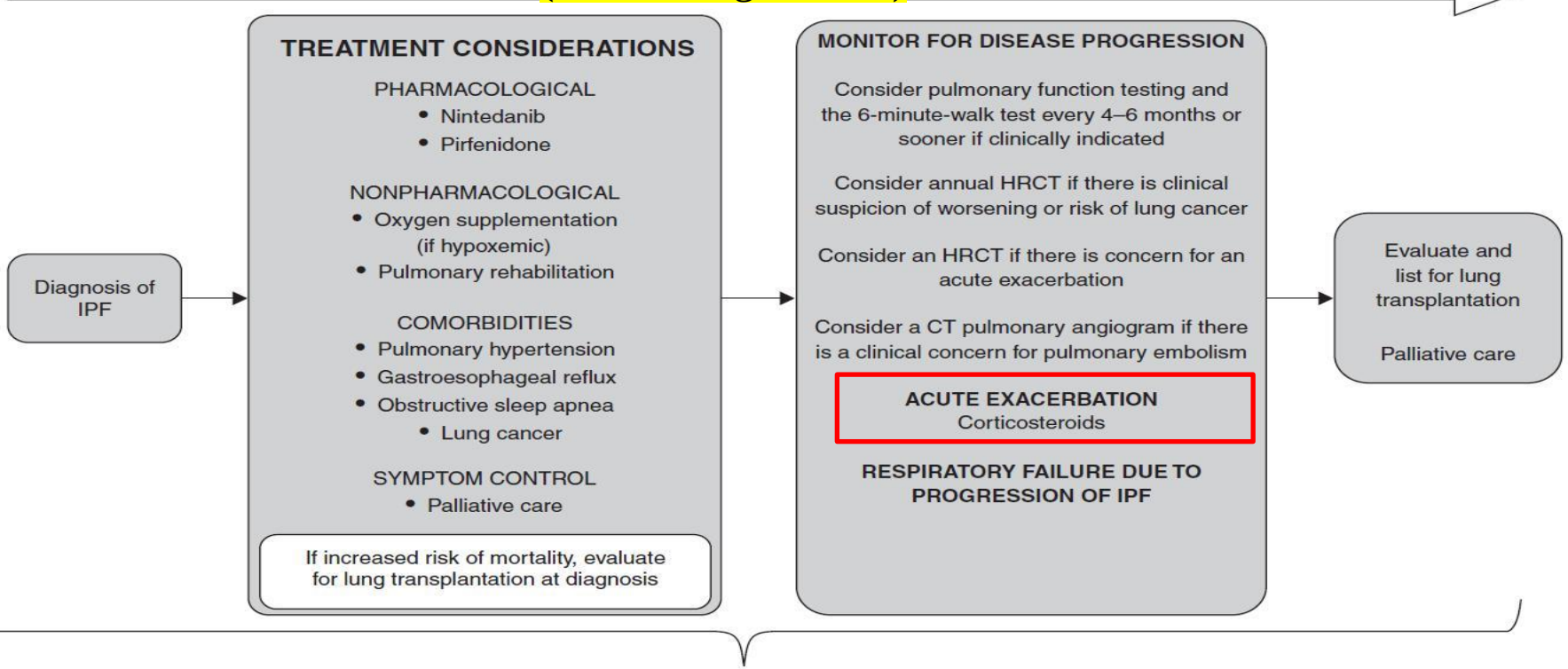
CHEST 2021; 160(5): 1751-1763

Treatment

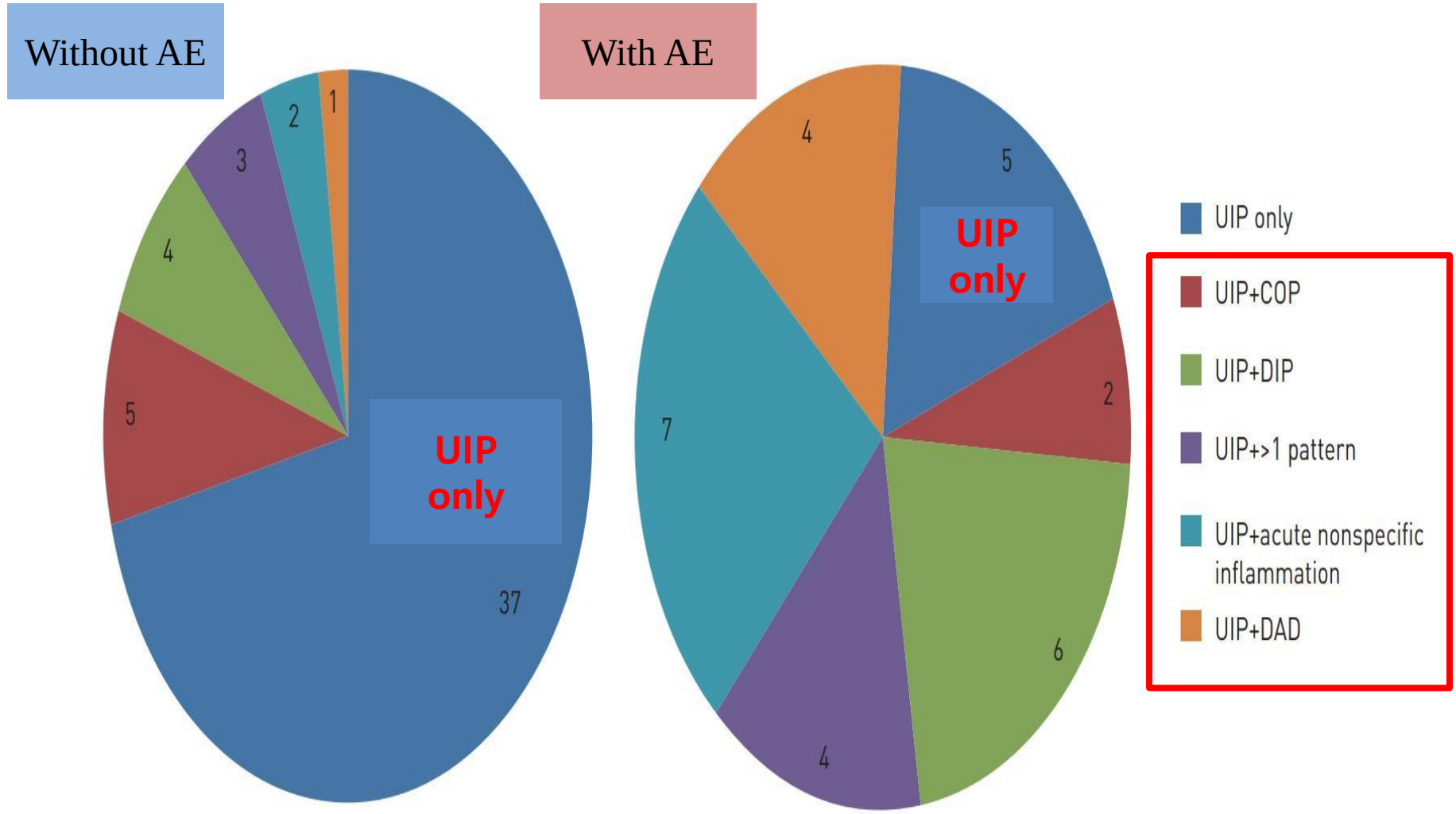
(2011 ATS guideline)

The majority of patients with AE of IPF should be treated with corticosteroids, but corticosteroids may not be reasonable in minority (weak, very low)

(2022 ATS guideline)



Role of steroid (Hypothesis)



ERJ Open Res 2020;6:00261

Immunosuppressive therapy

- Hypothesis: anti-inflammatory effect
- Cyclophosphamide (alkylating agent): 세포 및 체액면역 억제

- Double-blind, placebo-controlled trial in France from 2016 to 2018
- IV pulse of cyclophosphamide vs Placebo on mPD 10mg/kg for 3days
- 60 CYC or 59 Placebo enrolled (52% severe IPF)
- Primary endpoint – 3month all-cause mortality
- Safety profile

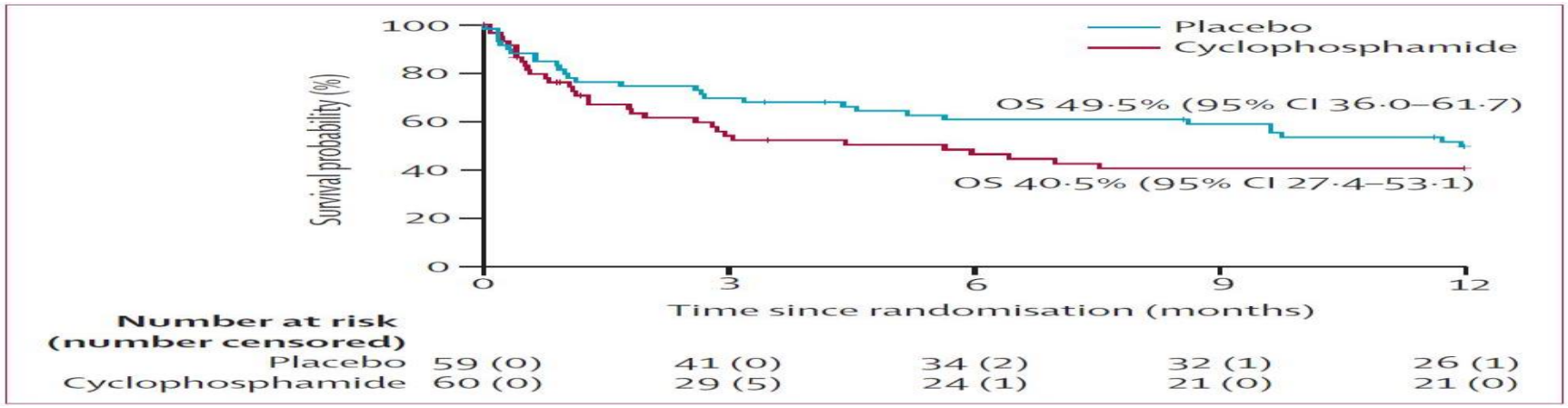
	Cyclophosphamide (n=60)	Placebo (n=59)	Difference (95% CI)	p value
Death at 3 months in the ITT population*	27/60 (45%)	18/59 (31%)	14·5 (–3·1 to 31·6)	0·10
Death at 3 months in the ITT population with available data	26/59 (44%)	18/59 (31%)	13·6 (–4·1 to 30·7)	0·13
Death at 3 months in the per-protocol 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;10:26-34

Immunosuppressive therapy



- Consistent with the result of PANTHER study
- No difference in the incidence of all infectious-related serious adverse events

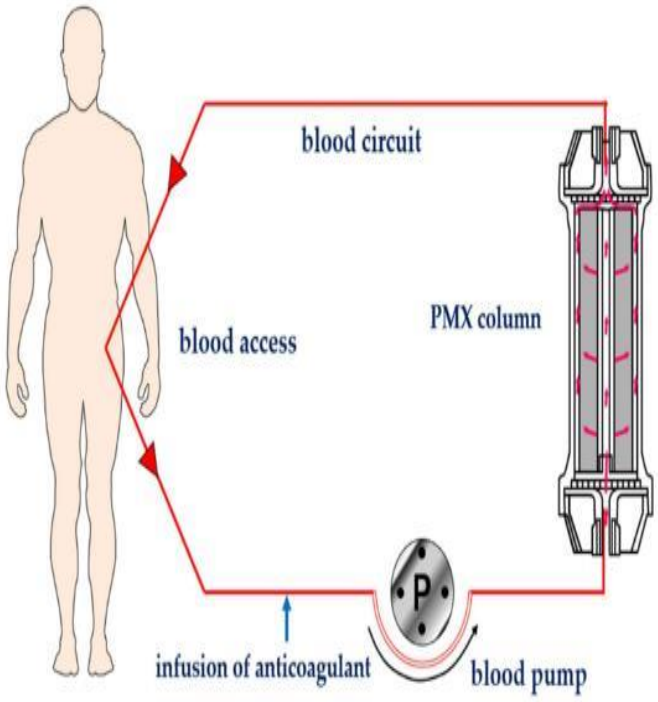
→ Cyclophosphamide might have a deleterious effect on the progression of fibrosis in IPF

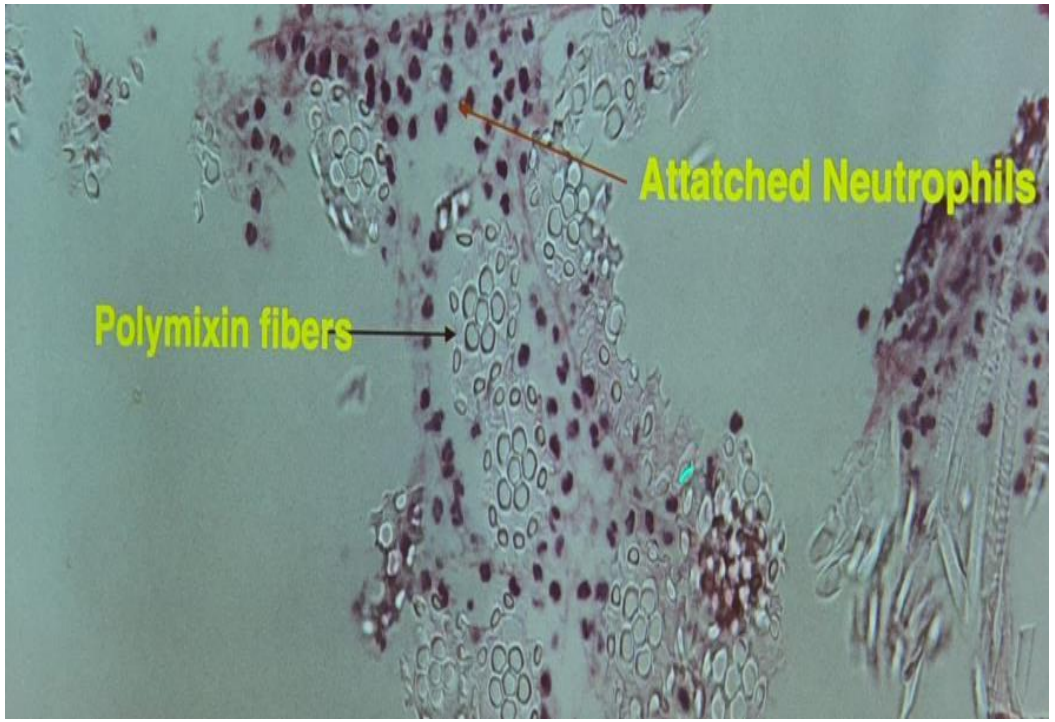
→ CYC might increase the susceptibility of the pulmonary epithelium to injury or alter the microbiome in a negative way

Lancet Respir Med 2022;10:26-34

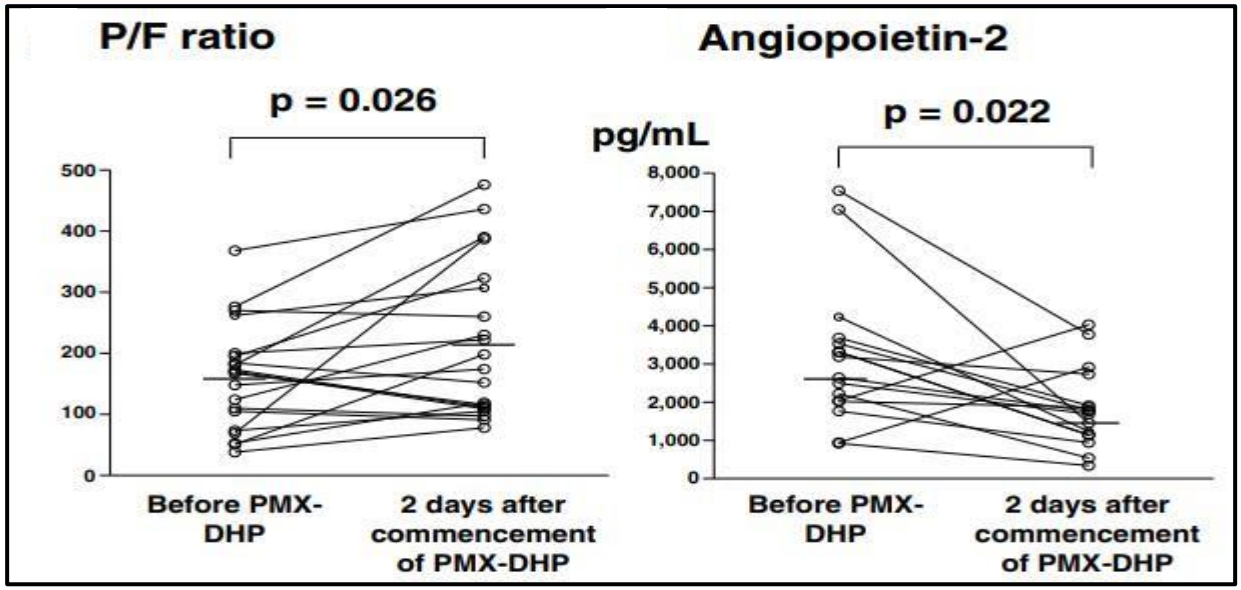
Treatment – PMX-DHP

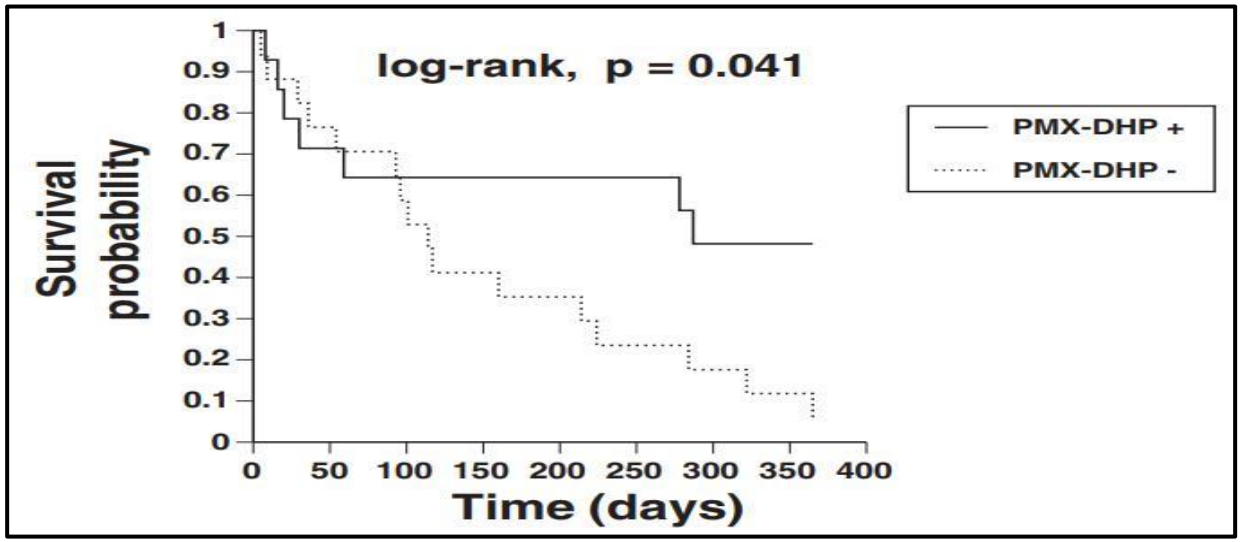
- Direct hemoperfusion with the polymixin B-immobilized fiber column
- Removal of endotoxin, decrease of vascular permeability, removal of inflammatory/profibrotic cytokine





Treatment – PMX-DHP





BMC pulmonary Medicine (2015) 15: 15

Treatment - Thrombomodulin

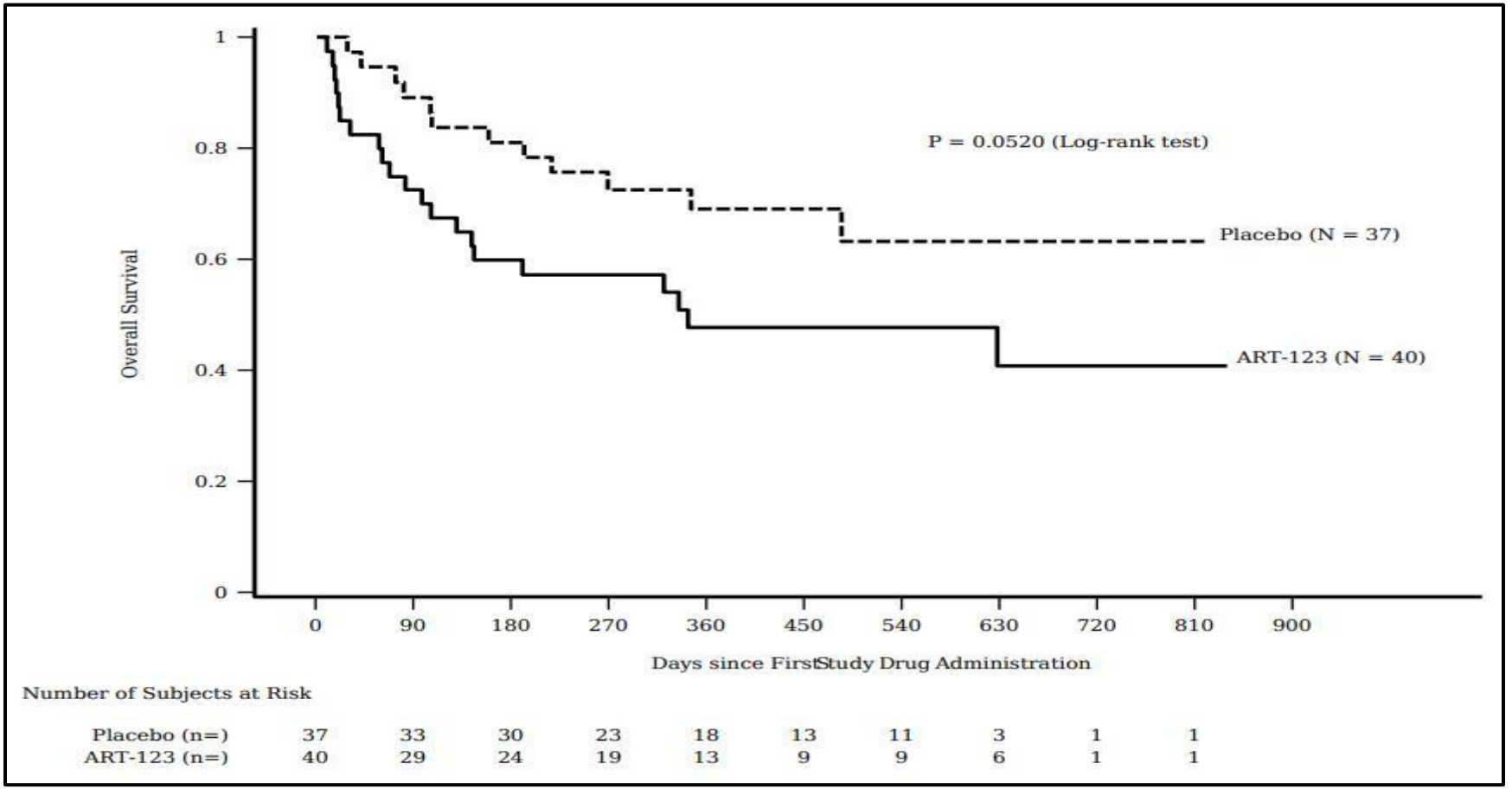
- Hypothesis: anti-coagulant effect → ameliorate pulmonary microcirculatory disorder associate with thrombus formation

- Double-blind, randomized, placebo-controlled trial in Japan from 2016 to 2018
- Thrombomodulin for 14days vs Placebo on mPD 500mg-1000mg and tapering dose
- 40 Thrombomodulin or 37 Placebo enrolled (52% severe IPF)
- Primary endpoint – survival proportion on day 90
- PF ratio / Safety profile

AJRCCM 2020;201(9) 1110: 1119

Treatment - Thrombomodulin

- Hypothesis: anti-coagulant effect → ameliorate pulmonary microcirculatory disorder associate with thrombus formation



AJRCCM 2020;201(9) 1110: 1119

Treatment - Thrombomodulin

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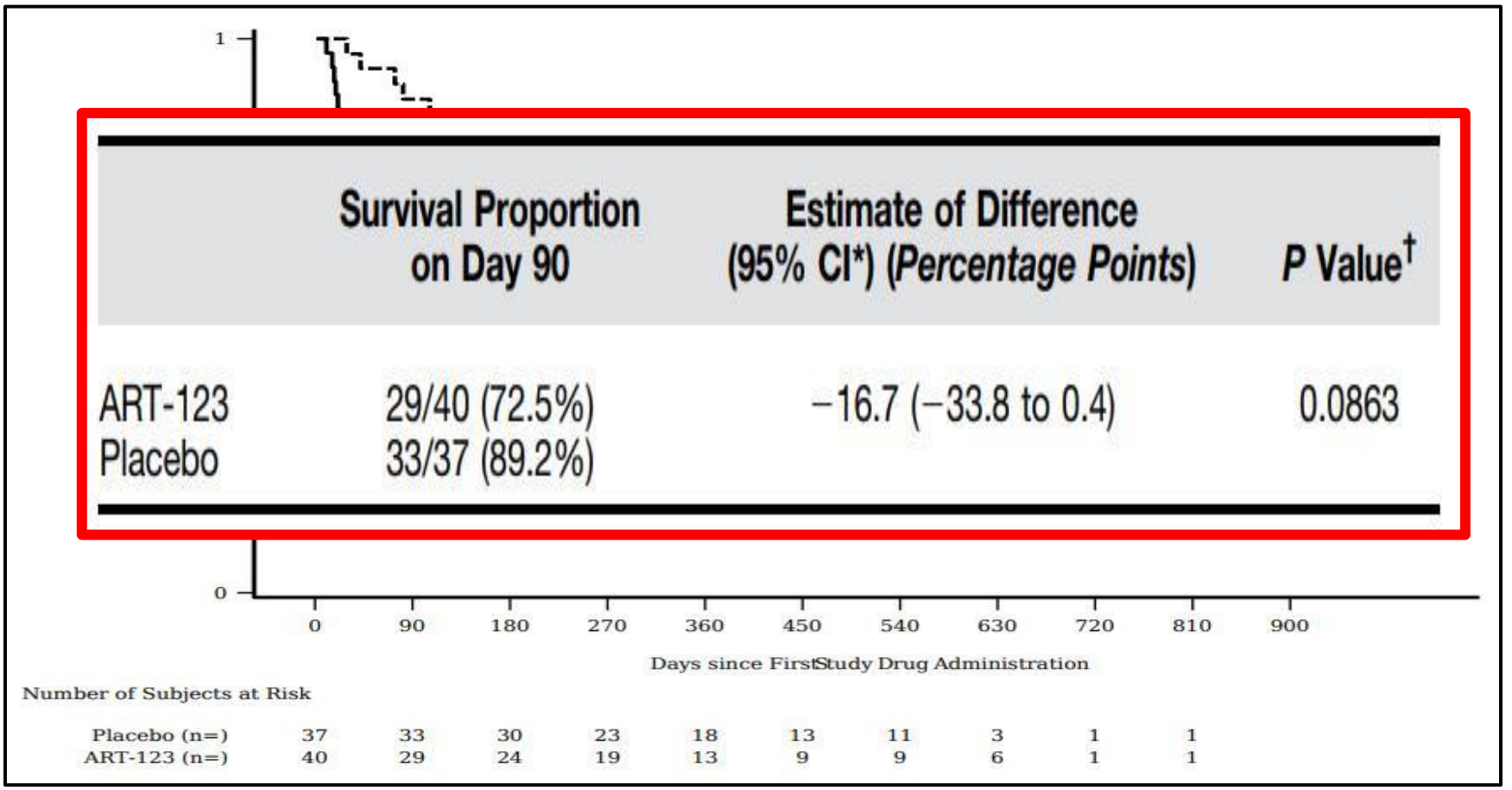
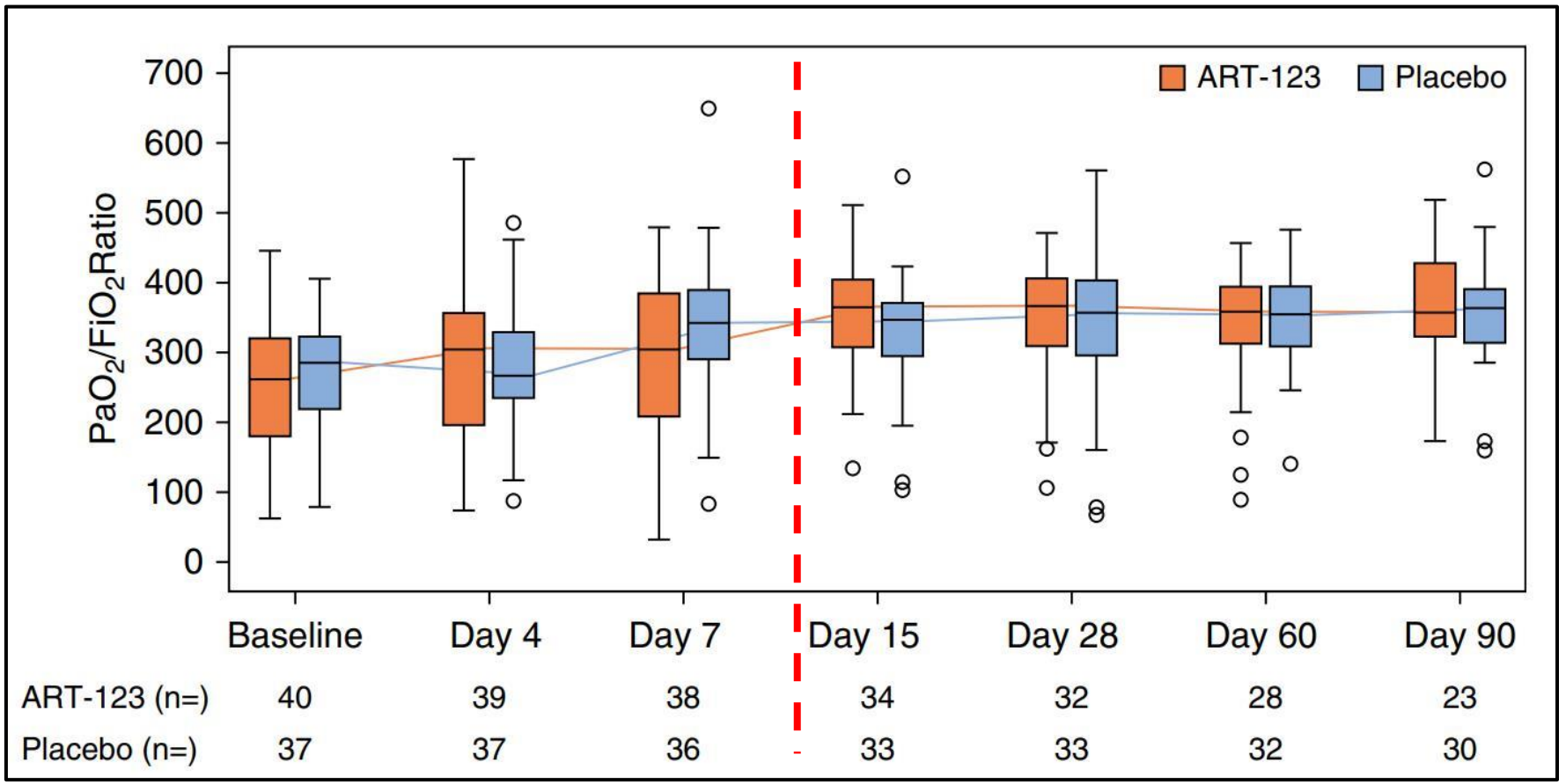


	Survival Proportion on Day 90	Estimate of Difference (95% CI*) (*Percentage Points*)	*P* Value†
ART-123	29/40 (72.5%)	−16.7 (−33.8 to 0.4)	0.0863
Placebo	33/37 (89.2%)		

AJRCCM 2020;201(9) 1110: 1119

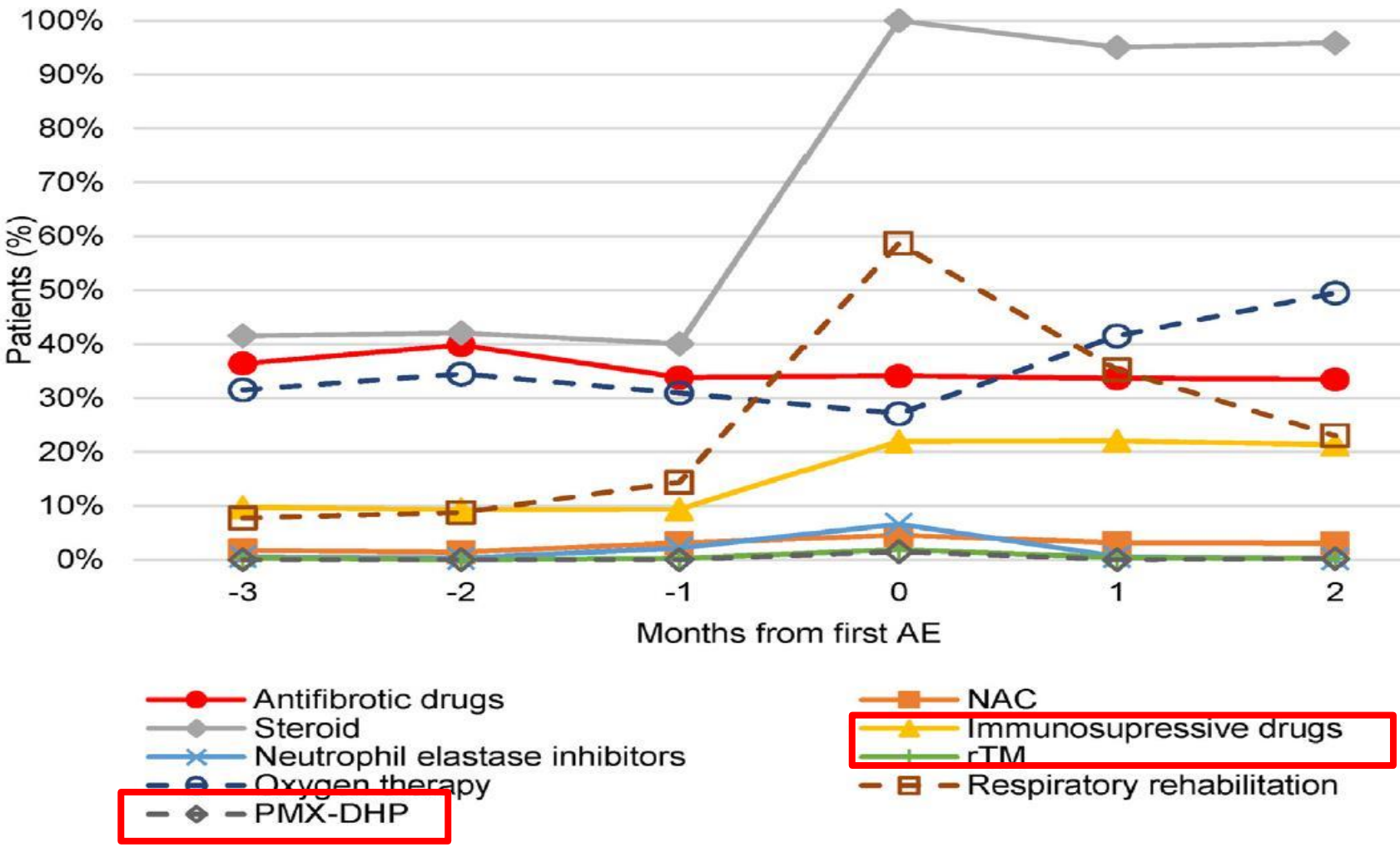
Treatment - Thrombomodulin

- Hypothesis: anti-coagulant effect → ameliorate pulmonary microcirculatory disorder associate with thrombus formation



AJRCCM 2020;201(9) 1110: 1119

Treatment – Trend (2008 – 2019 in Japan)



Respiratory Investigation 60 (2022) 798-805

Treatment – ICU care

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

(2011)

The recommendation **against mechanical ventilation** in patients with respiratory failure due to IPF is weak; that is, mechanical ventilation should not be used in the majority of patients with IPF, but may be reasonable choice in a minority.

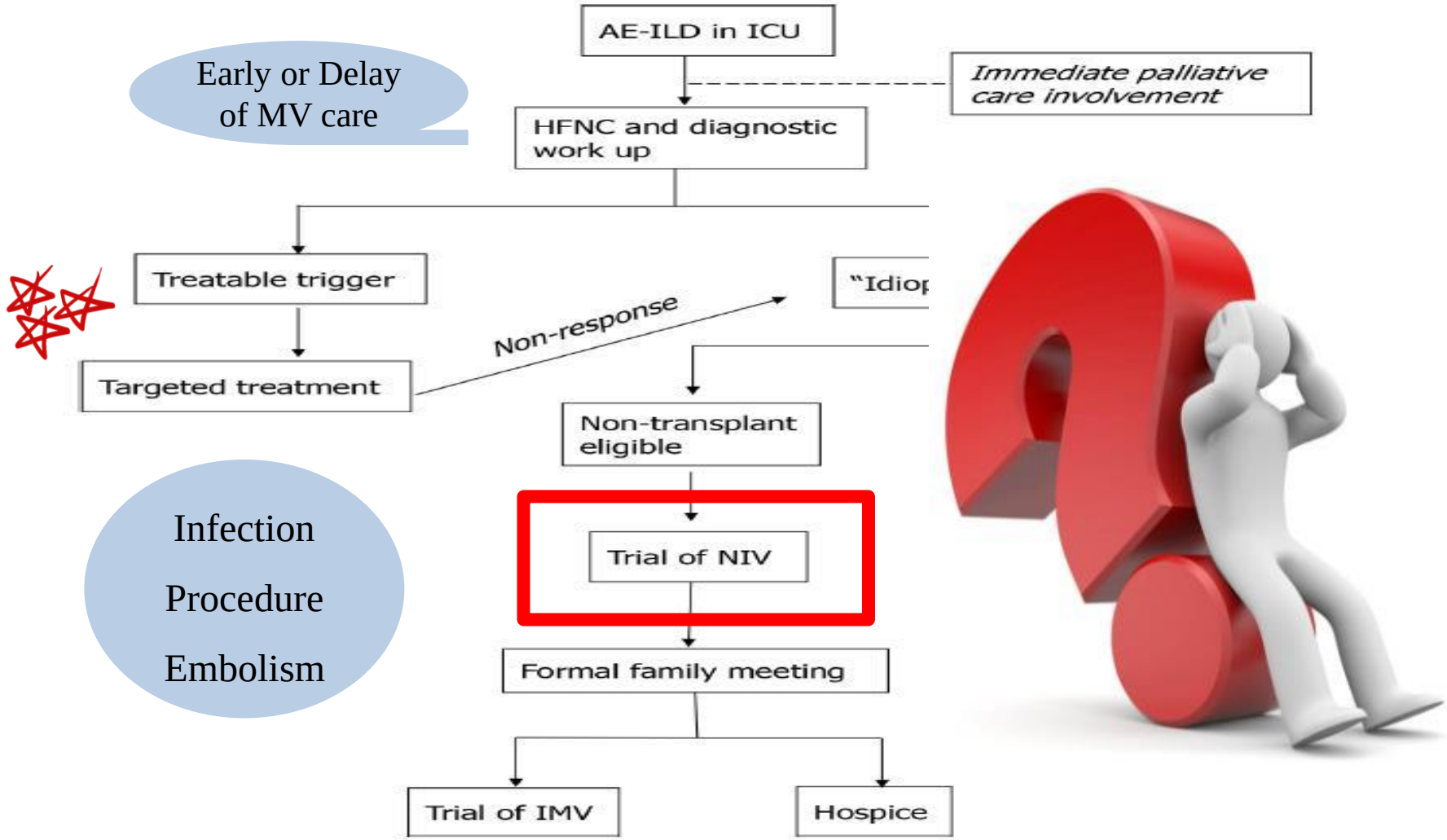
(Based on an estimated 87% in-hospital mortality)

Treatment – ICU care

- IPF AE - structural lung disease and precipitating condition causing ARF might be irreversible and progressive
- Poor prognosis
- Mechanism: de-recruitment lung → the need of high PEEP and high MV flow → high risk of ventilatory induce lung injury (volu-trauma/baro-trauma)

Apparato Respiration 2022; 203: 203-216

Treatment – ICU care



World Crit Care Med 2022 Jan 9; 11(1): 22-32

Treatment – ICU care

- Indication of MV care
  - Bridging for lung plantation (ECMO)
  - Identified and reversible cause of AE-IPF

- Information offering and discussion in patients with high risk
- Early discussion for end of life care at diagnosis of acute exacerbation

Treatment – As early as possible

Variables	Overall (n=59)		Survivors (n=27)		Non-survivors (n=32)		p value*
Age (year)	74.0	(66.0-78.0)	73.0	(65.0-78.0)	75.0	(68.0-78.5)	0.377
Sex (male)		49		24		25	0.319
Brinkman Index[a]	800	(500-1,200)	870	(660-1,200)	800	(25-1,090)	0.131
IPF Stage[b]	2	(1-4)	2	(1-3)	3	(1.25-4)	0.111
GAP Index[c]	4	(3-5)	4	(3-5)	4	(3-5)	0.421
Regular use of steroid		9		3		6	0.488
Regular use of pirfenidone		13		6		7	1.000

Intern Med 57:655-661

Treatment – As early as possible

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

Treatment – As early as possible

	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

Mortality

Retrospective, observational single-center study from 2001 to 2010

594 IPF patients, 58 (9.8%) AE during 10-year observation period

In-hospital mortality – 56.9%, 3-months mortality – 63.8%

	HR	*P* value
LDH	2.024	0.047
KL-6	2.909	0.038
P/F	2.42	0.041
Ground-glass opacity + consolidation score	2.289	0.030

Lung (2014) 192: 141-149

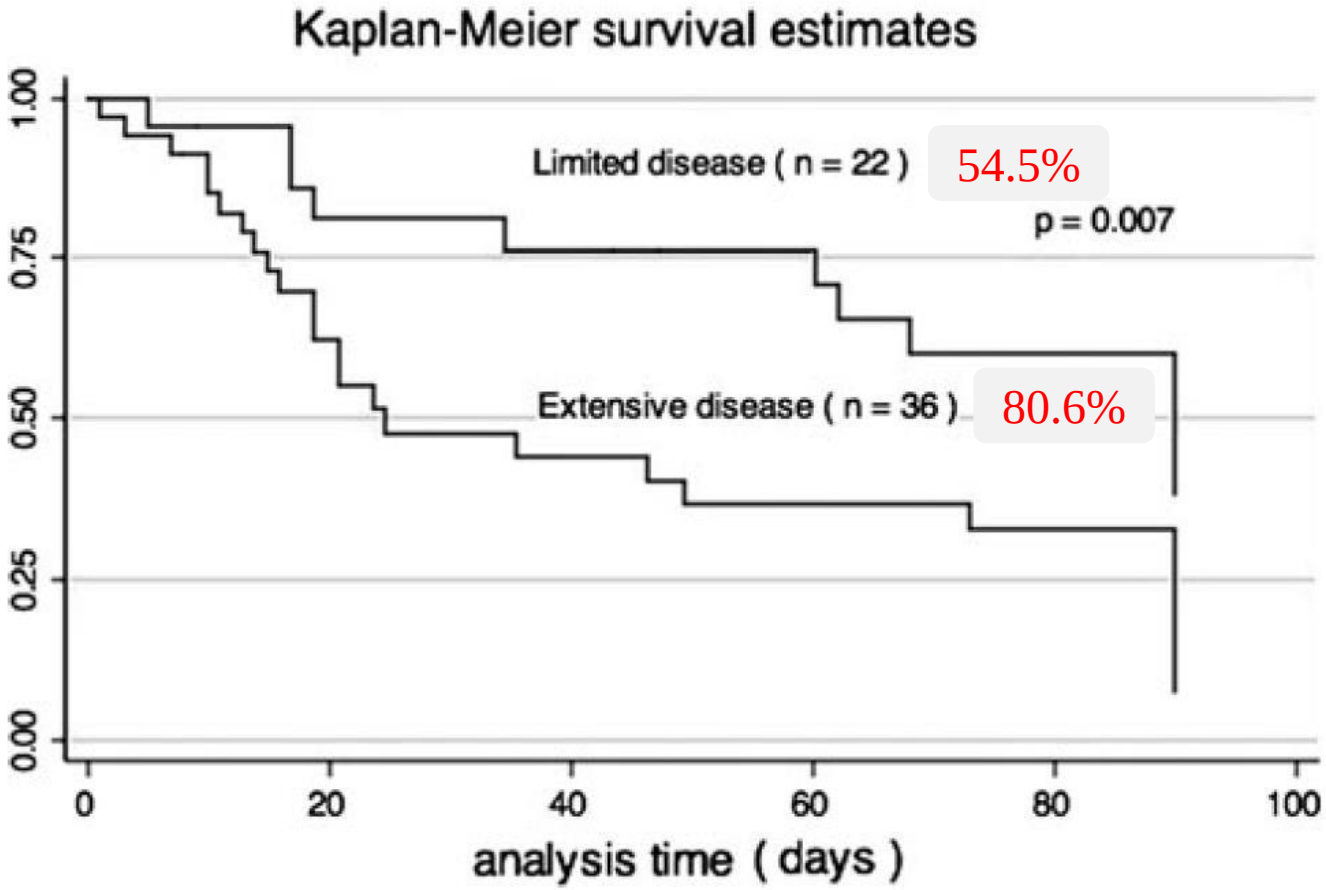
Mortality

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

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

Lung (2014) 192: 141-149

Mortality



Lung (2014) 192: 141-149

Prediction of mortality

353 consecutive patients with IPF who were admitted to Toho University Omori Medical Center during the period from January 2008 through April 2018.

A total of 106 patients who had received a first clinical diagnosis of AE-IPF according to the International Working Group Report with slight modifications* satisfied the inclusion criteria.

Two patients were excluded because data on 3 -month survival were missing.

One patient was excluded because of missing data on other variables.

- Ultimately, 103 AE -IPF patients were included in the analysis.
- During the observation period, 48 of the 103 patients (46.7%) died within 3 months. All deaths during the first 3 months were from respiratory failure caused by AE-IPF.

Scientific Reports (2022) 12: 1134

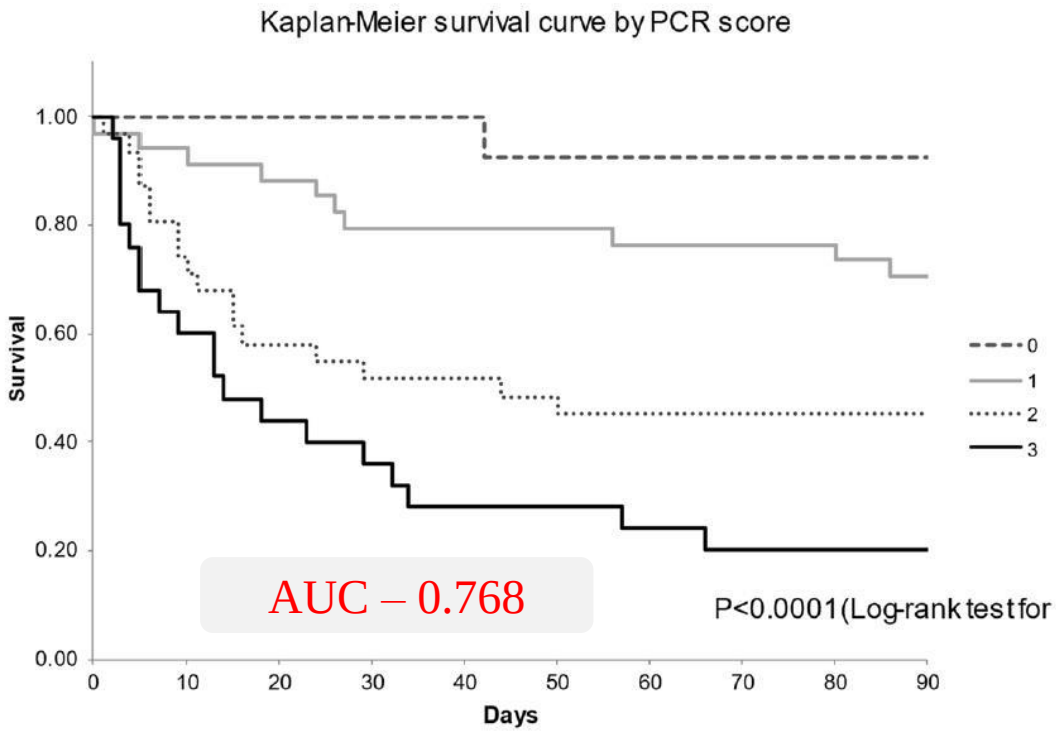
Prediction of mortality

Variables	Partial regression coefficient	95% CI of partial regression coefficient	Odds ratio	95% CI of odds ratio	*P* value	Integral weight
Diffuse HRCT pattern	1.4320	0.3677–2.4963	4.1872	1.4445–12.1378	0.0084*	1
High CRP (≥5.5)	1.0060	0.0994–1.9126	2.7347	1.1045–6.7710	0.0296*	1
Low PaO_2/FiO_2 ratio (<250)	1.1516	0.2229–2.0802	3.1632	1.2497–8.0065	0.0151*	1

Predictor	Value	Score			
PaO_2/FiO_2 ratio (P)	<250	1			
	≧250	0			
CRP (C)	≧5.5	1			
	<5.5	0			
HRCT pattern (R)	Diffuse	1			
	Non-diffuse	0			

Total score of PCR index	Measured value (n = 103)		3-Month mortality estimated by bootstrap method	95% CI	
	No. of patients	3-month mortality		Lower	Upper
Total possible points 3					
0	n = 13	0.077 (7.7%)	0.083 (8.3%)	0.072	0.081
1	n = 34	0.294 (29.4%)	0.291 (29.1%)	0.291	0.300
2	n = 31	0.548 (54.8%)	0.554 (55.4%)	0.564	0.576
3	n = 25	0.800 (80.0%)	0.803 (80.3%)	0.798	0.808

Prediction of mortality



7.7%

29.4%

54.8%

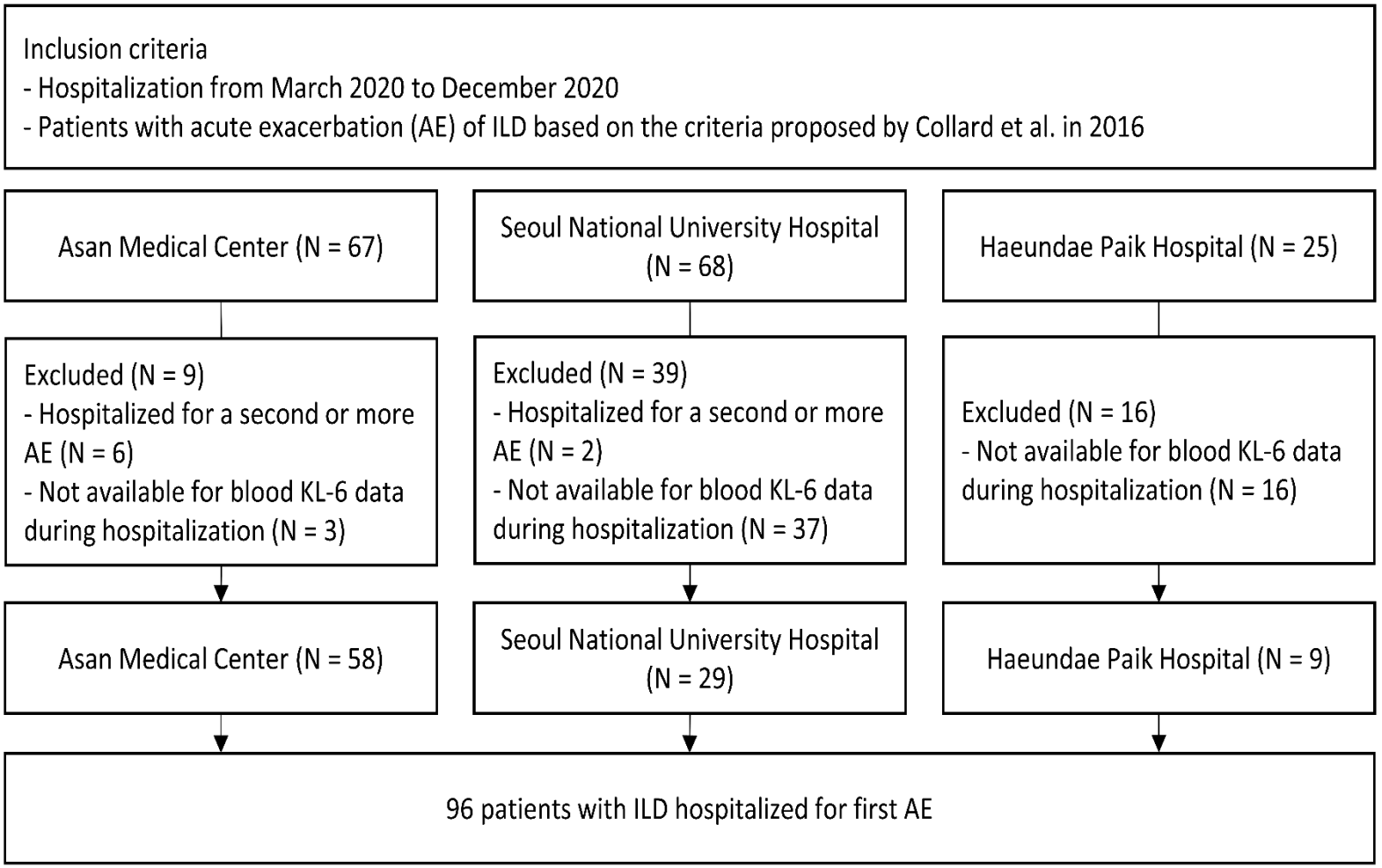
80.0%

Number at risk

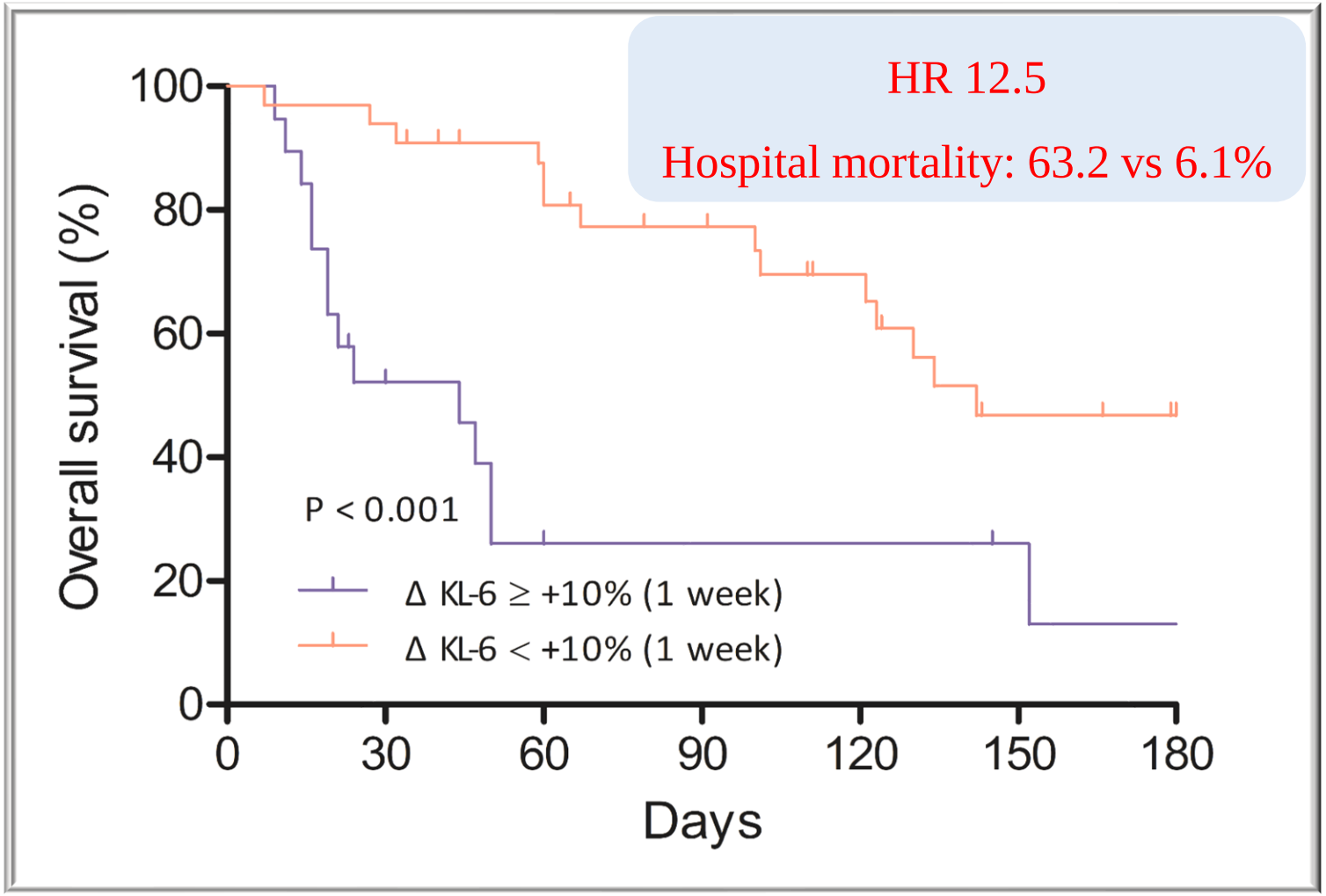
Total PCR score: 0	13	13	12	12
Total PCR score: 1	34	27	26	24
Total PCR score: 2	31	16	14	14
Total PCR score: 3	25	9	6	5

Scientific Reports (2022) 12: 1134

KL-6: Survival after AE in IPF

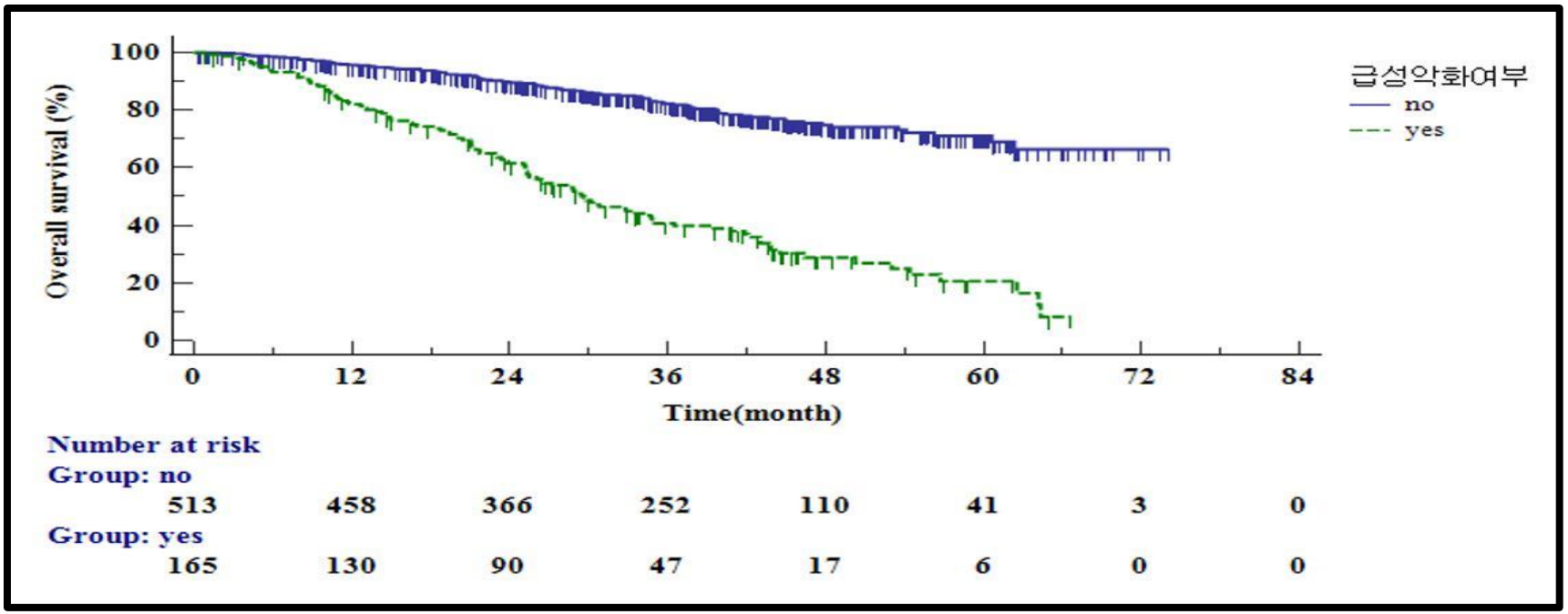


KL-6: Survival after AE in IPF



Mortality in KICO registry

- Mortality rate of AE-IPF: 36.4%
- Median survival period: 8.36 months
- Older age: independent risk factor for mortality in patients with AE-IPF



Summary

- Annual incidence – 10% (follow-up: 25%)
- Importance of AE
- Risk factors – advanced disease, hypoxemia, functional dependency, pul.HTN, history of AE…
- Prevention – vaccination, use of antifibrotics, PR
- Treatment – corticosteroid and others (if need), as early as possible
- Prevention (risk factors) >> Treatment > ICU care

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