Acute Infectious Exacerbation in Interstitial Lung Disease

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Definition

Acute Exacerbation in Idiopathic Pulmonary Fibrosis*

Analysis of Clinical and Pathologic Findings in Three Cases

Yasuhiro Kondoh, M.D.; Hiroyuki Taniguchi, M.D.; Yoshinori Kawabata, M.D.; Toyoharu Yokoi, M.D.; Kiyoshi Suzuki, M.D.; and Kenzo Takagi, M.D., F.C.C.P.

- Initially flu-like symptoms
- Exacerbation of dyspnea, hypoxemia; newly developed diffuse pulmonary infiltrates
- Negative microbiological test including BAL
- Surgical biopsy showing ALI pattern on UIP
- Improvement after steroid therapy (1000mg x 3 days, then tapering)

Chest. 1993 Jun;103(6):1808-12.

2007 definition of AE-IPF

- Previous or concurrent diagnosis of IPF
- Unexplained worsening or development of dyspnea within 30 days
- HRCT with new bilateral GGO and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with UIP pattern
- No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage
- Exclusion of alternative causes, including the left heart failure, pulmonary embolism, or identifiable cause of acute lung injury

Am J Respir Crit Care Med. 2007 Oct 1;176(7):636-43.

Exacerbation of other lung diseases

- **Bronchiectasis**
- Antibiotics targeting the causative or presumptive pathogen (with *Haemophilus influenzae* and *P. aeruginosa* isolated commonly) should be administered in acute exacerbations

- **COPD**
- A variety of stimuli may result in the final common pathway of airway inflammation
- Viral respiratory infections had been thought to be a less common cause of COPD exacerbations than bacterial infection
- Other inciting factors include air pollution, allergens

Harrison's Principles of Internal Medicine, 22nd edition

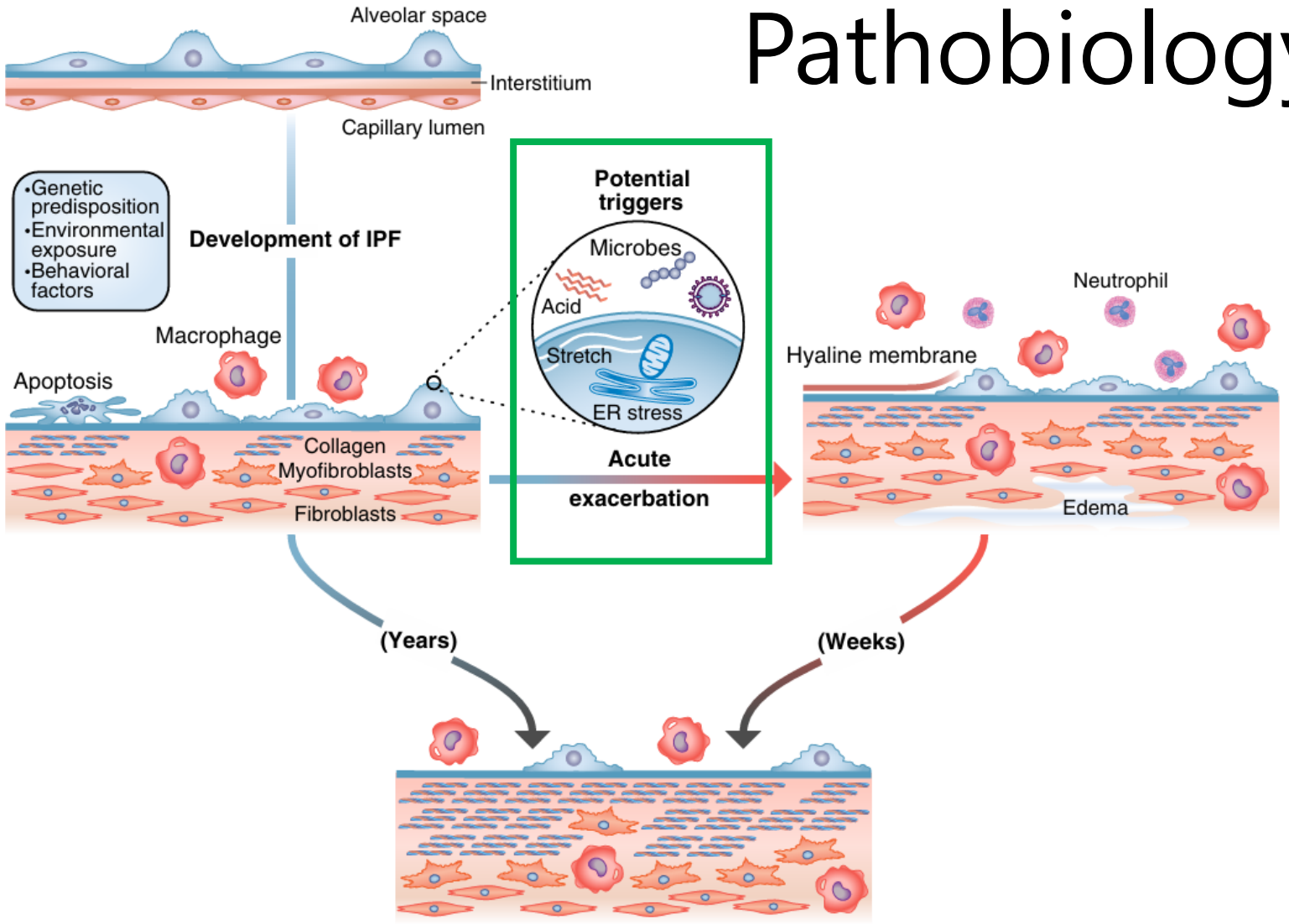
Idiopathic exacerbation?

- **No evidence of pulmonary infection** by endotracheal aspirate or bronchoalveolar lavage
- → Evaluation of samples should include studies for routine bacterial organisms, opportunistic pathogens, and common viral pathogens

- **Exclusion** of alternative causes, including the left heart failure, pulmonary embolism, or **identifiable cause of acute lung injury**
- → Causes of acute lung injury: sepsis, aspiration, trauma, reperfusion pulmonary edema, pulmonary contusion, fat embolization, inhalational injury, cardiopulmonary bypass, drug toxicity, acute pancreatitis, transfusion of blood products, and stem cell transplantation

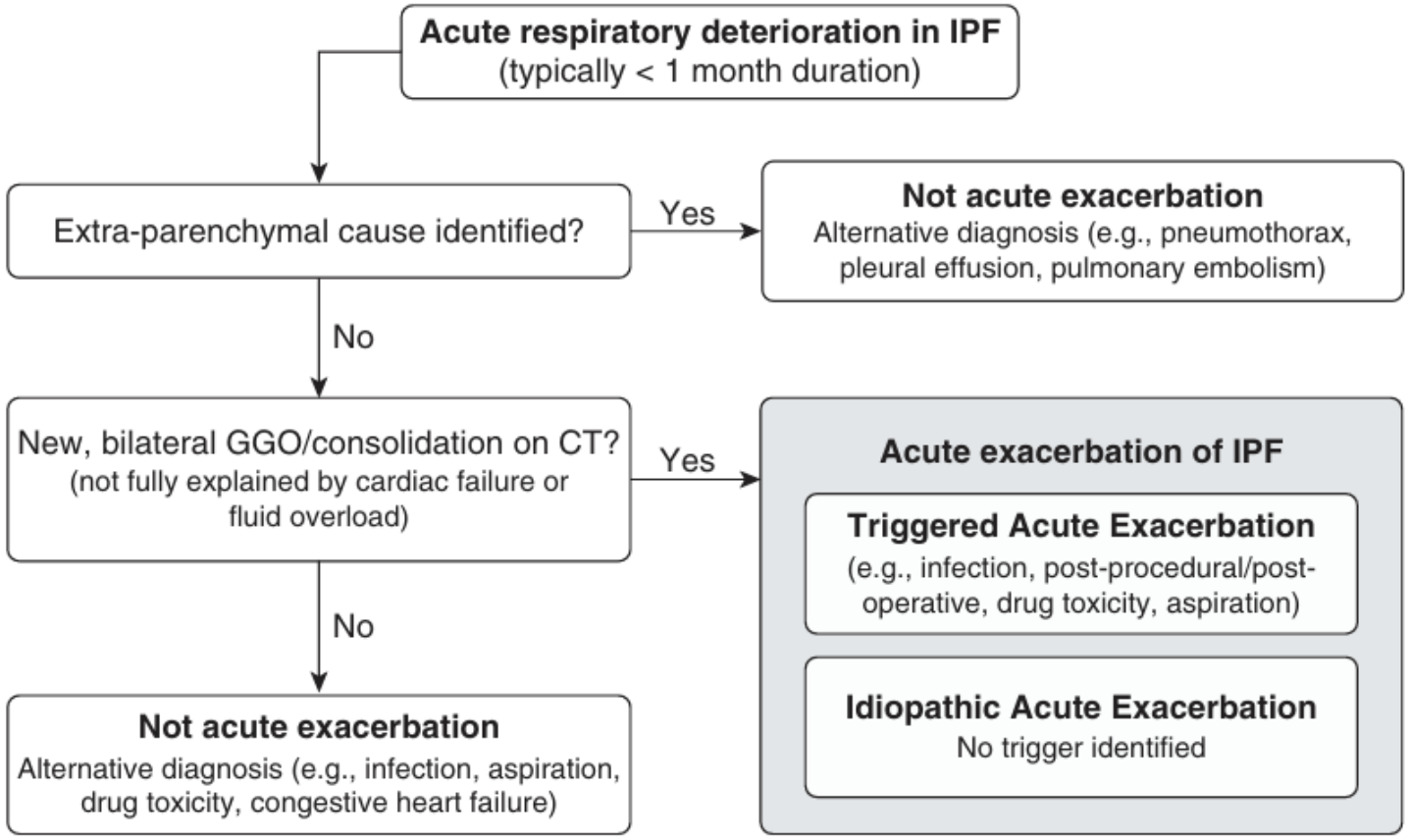
Am J Respir Crit Care Med. 2007 Oct 1;176(7):636-43.

Pathobiology of AE-IPF



Am J Respir Crit Care Med. 2016 Aug 1;194(3):265-75.

Revised definition in 2016



Am J Respir Crit Care Med. 2016 Aug 1;194(3):265-75.

Revised definition in 2016

Table 3. Proposed Revised Definition and Diagnostic Criteria for Acute Exacerbation of Idiopathic Pulmonary Fibrosis

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

Am J Respir Crit Care Med. 2016 Aug 1;194(3):265-75.

Exacerbation of ILD other than IPF

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

In line with the categorization of acute exacerbations of IPF in the latest international working group report,[25] we defined acute exacerbations of interstitial lung disease as acute, clinically significant respiratory deteriorations characterized by evidence of new, widespread alveolar abnormality meeting all the following criteria: acute worsening or development of dyspnea (typically of <1 month duration), CT with new bilateral ground-glass opacity or consolidation superimposed on a background pattern consistent with fibrosing interstitial lung disease, and deterioration not fully explained by cardiac failure or fluid overload. Infection was not an exclusion criterion for an acute exacerbation. Safety was assessed by clinical and laboratory evaluation and the recording of adverse events, as coded with the use of the *Medical Dictionary for Regulatory Activities*, version 22.0.

N Engl J Med. 2019 Oct 31;381(18):1718-1727.

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.

Nat Rev Rheumatol. 2022 Feb;18(2):85-96.

Similarity with ARDS

Table 1. Diagnostic Criteria for the New Global Definition of ARDS

Conceptual model: ARDS is an acute, diffuse, inflammatory lung injury precipitated by a predisposing risk factor, such as pneumonia, nonpulmonary infection, trauma, transfusion, burn, aspiration, or shock. The resulting injury leads to increased pulmonary vascular and epithelial permeability, lung edema, and gravity-dependent atelectasis, all of which contribute to loss of aerated lung tissue. The clinical hallmarks are arterial hypoxemia and diffuse radiographic opacities associated with increased shunting, increased alveolar dead space, and decreased lung compliance. The clinical presentation is influenced by medical management (position, sedation, paralysis, positive end-expiratory airway pressure, and fluid balance). Histological findings vary and may include intraalveolar edema, inflammation, hyaline membrane formation, and alveolar hemorrhage.

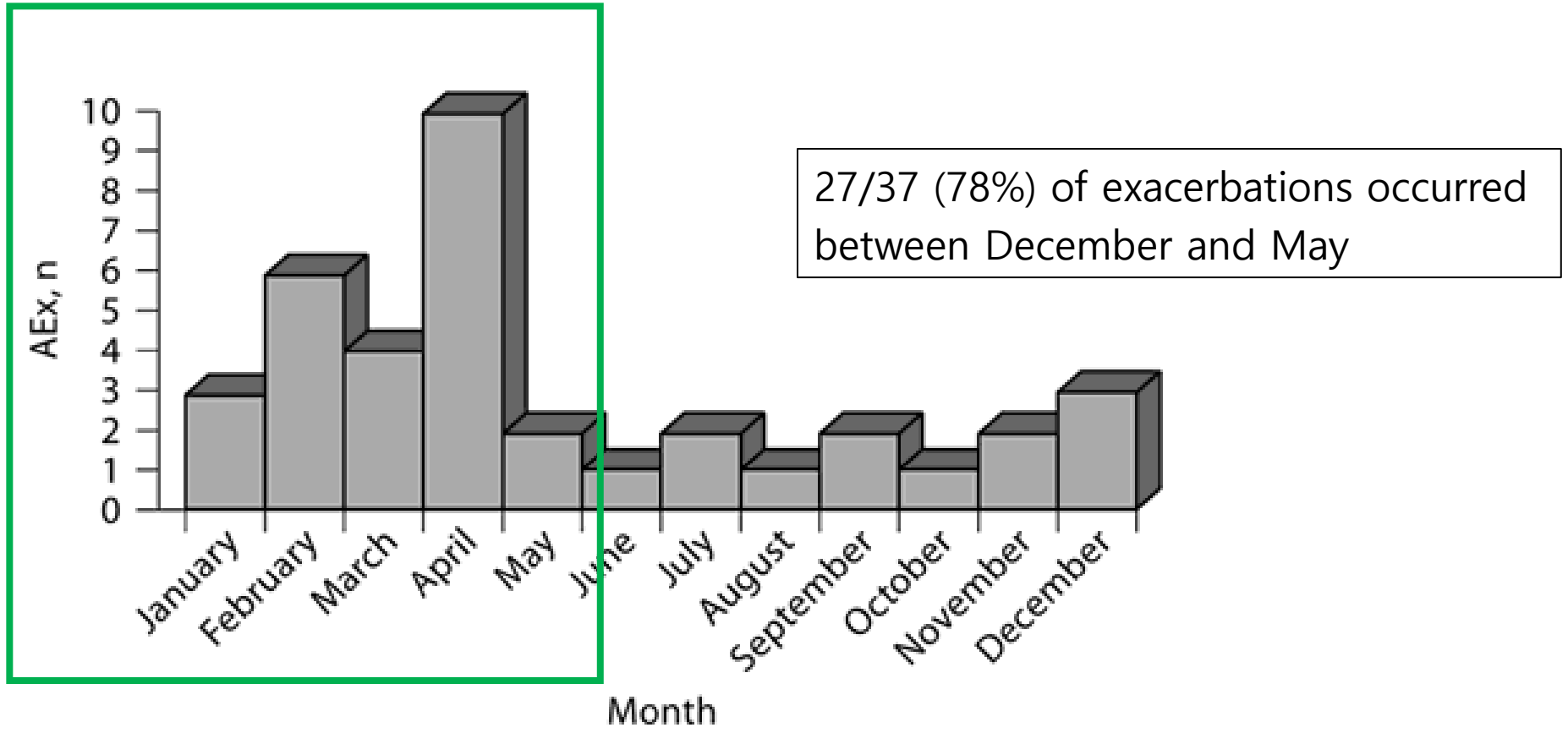
	Criteria That Apply to All ARDS Categories
Risk factors and origin of edema	Precipitated by an acute predisposing risk factor, such as pneumonia, nonpulmonary infection, trauma, transfusion, aspiration, or shock. Pulmonary edema is not *exclusively or primarily* attributable to cardiogenic pulmonary edema/fluid overload, and hypoxemia/gas exchange abnormalities are not primarily attributable to atelectasis. However, ARDS can be diagnosed in the presence of these conditions if a predisposing risk factor for ARDS is also present.
Timing	Acute onset or worsening of hypoxemic respiratory failure within 1 week of the estimated onset of the predisposing risk factor or new or worsening respiratory symptoms.
Chest imaging	Bilateral opacities on chest radiography and computed tomography or bilateral B lines and/or consolidations on ultrasound* not fully explained by effusions, atelectasis, or nodules/masses.

	Criteria That Apply to Specific ARDS Categories		
	Nonintubated ARDS†	**Intubated ARDS**	**Modified Definition for Resource-Limited Settings‡**

Am J Respir Crit Care Med. 2024 Jan 1;209(1):37-47.

Infection and Exacerbation

Seasonal variation



27/37 (78%) of exacerbations occurred between December and May

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

Immunosuppressant use

Table 2. Safety End Points.*

End Point	Combination Therapy (N=77)	Placebo (N=78)	Hazard Ratio	P Value
Death — no. (%)				
From any cause	8 (10)	1 (1)		0.01
From respiratory causes	7 (9)	1 (1)		0.02
Hospitalization for any cause — no. (%)	23 (30)	7 (9)		<0.001
Acute exacerbation — no. (%)	5 (6)	0		0.03
Serious adverse event — no. (%)	24 (31)	8 (10)		0.001

Table 3. Adverse Events.

Adverse Event	Combination Therapy (N=77)	Placebo (N=78)	P Value
	no. of patients (%)		
Serious adverse event			
Any	24 (31)	8 (10)	0.001
Respiratory system	12 (16)	4 (5)	0.03
Infectious	5 (6)	1 (1)	0.12

Prednisone + Azathioprine + NAC
- More acute exacerbation
- More serious respiratory adverse event

N Engl J Med. 2012 May 24;366(21):1968-77.

Autopsy study

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)

15 deaths were attributed to bronchopneumonia
In 3 cases, infectious lesions were not diagnosed until autopsy

Respir Res. 2014 Sep 1;15(1):109.

Role of virus

TABLE 2. RESPIRATORY VIRAL DETECTION IN ACUTE EXACERBATION AND STABLE IDIOPATHIC PULMONARY FIBROSIS

Virus	Acute Exacerbation ($n = 43$)	Stable ($n = 40$)	*P* Value
Any respiratory virus (%)	4 (9)	0 (0)	0.12
Rhinovirus (%)	2 (5)	0 (0)	0.49
Coronavirus (%)	1 (2)	0 (0)	1
Parainfluenza (%)	1 (2)	0 (0)	1
Adenovirus (%)	0 (0)	0 (0)	–
Enterovirus (%)	0 (0)	0 (0)	–
Influenza (%)	0 (0)	0 (0)	–
Metapneumovirus (%)	0 (0)	0 (0)	–
Respiratory syncytial virus (%)	0 (0)	0 (0)	–

TABLE 3. ARRAY-BASED VIRAL DETECTION IN ACUTE EXACERBATION AND STABLE IDIOPATHIC PULMONARY FIBROSIS

Virus	Acute Exacerbation ($n = 43$)	Stable ($n = 40$)	Acute lung injury ($n = 29$)	*P* Value*
Torque teno virus (%)	12 (28)	0 (0)	7 (24)	0.0003
Epstein-Barr virus (%)	2 (5)	0 (0)	NA	0.49
Herpes simplex virus (%)	1 (2)	0 (0)	NA	1
Cytomegalovirus (%)	0 (0)	0 (0)	NA	–

Numerically higher virus detection rates in AE-IPF patients than stable IPF

Similar detection of TTV in AE-IPD and ALI

Am J Respir Crit Care Med. 2011 Jun 15;183(12):1698-702.

Role of virus

Table 1. Clinical data of patients with idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, acute interstitial pneumonia, and bronchiolitis obliterans organizing pneumonia.

Underlying disease	Age (years)/ gender	Clinical data			Pathological pattern	NCE	CVI	Virus IHC
		Dyspnea	Fever	Tobacco history				
IPF	34/F	+	–	+	UIP	+	–	none
IPF	52/F	+	+	+	UIP	+	–	none
IPF	76/F	+	–	+	UIP	+	–	none
IPF	69/F	+	–	–	UIP	+	–	none
IPF	79/F	+	–	–	UIP	+	–	none
IPF	74/F	+	+	+	UIP plus DAD	+	–	MV
IPF	72/M	+	+	+	UIP plus DAD	+	–	none
IPF	70/M	+	+	+	UIP plus DAD	+	–	CMV
IPF	66/M	+	+	–	UIP plus DAD	+	–	none
IPF	66/M	+	+	–	UIP plus DAD	+	–	MV
IPF	66/M	+	–	+	UIP	+	–	none
IPF	71/M	+	–	–	UIP	+	–	none
IPF	66/M	+	–	–	UIP	+	–	none
NSIP	76/F	+	–	–	NSIP	+	–	none
NSIP	65/F	+	–	+	NSIP	+	–	none
NSIP	67/F	+	–	+	NSIP	+	–	none
NSIP	47/F	+	+	–	NSIP plus DAD	+	–	CMV
NSIP	65/F	+	+	–	NSIP plus DAD	+	–	none
NSIP	65/M	+	+	–	NSIP plus DAD	+	–	none
NSIP	65/M	+	–	–	NSIP	+	–	none
NSIP	69/M	+	–	–	NSIP	+	–	none
AIP	40/M	+	+	+	DAD	+	–	CMV
AIP	42/M	+	+	–	DAD	+	–	CMV
AIP	52/M	+	+	–	DAD	+	–	MV
AIP	85/F	+	+	–	DAD	+	–	MV
AIP	50/F	+	+	–	DAD	+	–	MV
AIP	46/F	+	+	–	DAD	+	–	none
AIP	40/F	+	+	+	DAD	+	–	none
AIP	35/F	+	+	+	DAD	+	–	none
AIP	49/F	+	+	–	DAD	+	–	none
AIP	49/M	+	+	–	DAD	+	–	none
AIP	57/M	+	+	–	DAD	+	–	none
AIP	49/M	+	+	+	DAD	+	–	none
BOOP	75/F	+	+	+	OP	+	–	CMV
BOOP	72/F	+	+	+	OP	+	–	none
BOOP	70/M	+	+	–	OP	+	–	none
BOOP	72/M	+	+	–	OP	+	–	none

Virus detected in 3 of 5 AE-IPF pts
Virus detected in 1 of 3 AE-NSIP pts

Braz J Med Biol Res. 2013 Nov 18;46(11):985–992.

Role of virus

Table 2
Distribution of the detected pathogens.

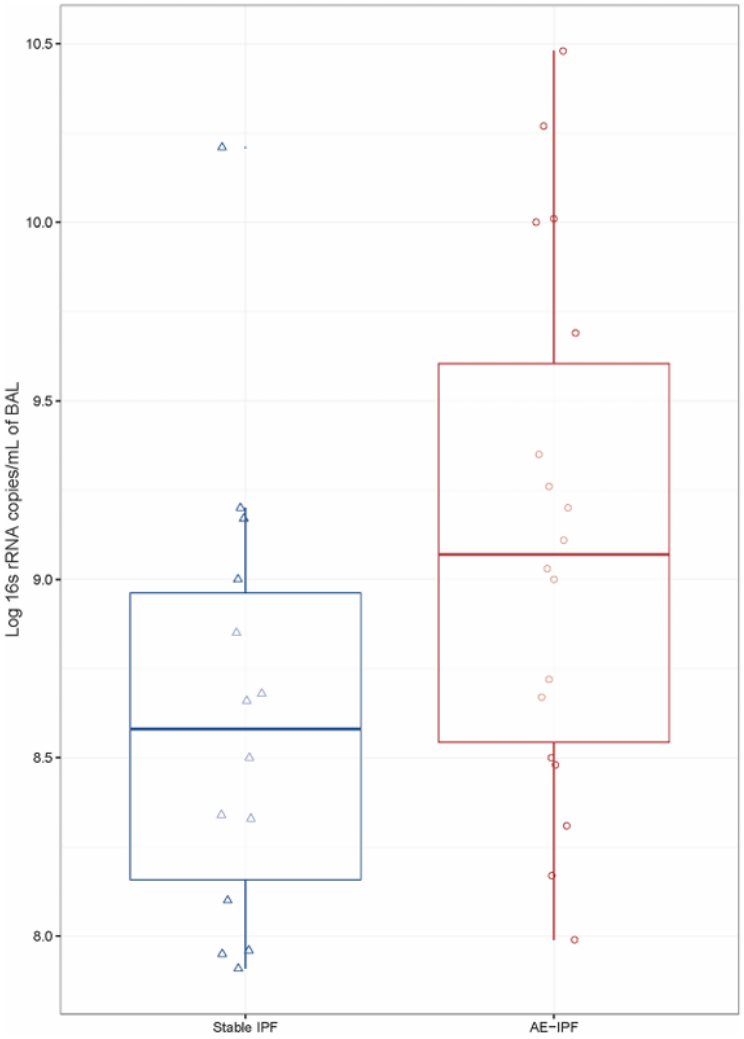
	All patients (N = 78)	IPF (N = 27)	Non-IPF ILDs (N = 51)	p value
Any respiratory virus (%)	15 (19.2)	5 (18.5)	10 (19.6)	0.762
HHV7 (%)	4 (5.1)	2 (7.4)	2 (3.9)	
CMV/HHV7 (%)	3 (3.8)	1 (3.7)	2 (3.9)	
Influenza virus alone (%)	3 (3.8)	0	3 (5.9)	
AH3	2 (2.6)	0	2 (3.9)	
H1N1	1 (1.3)	0	1 (2.0)	
HPIV (%)	2 (2.6)	1 (3.7)	1 (2.0)	
Influenza virus AH3/HHV7	1 (1.2)	0 (0)	1 (2.0)	
CMV (%)	1 (1.3)	1 (3.7)	0 (0)	
HMPV (%)	1 (1.3)	0 (0)	1 (2.0)	
HRV (%)	0 (0)	0 (0)	0 (0)	
Adenovirus (%)	0 (0)	0 (0)	0 (0)	
Enterovirus (%)	0 (0)	0 (0)	0 (0)	
Coronavirus (%)	0 (0)	0 (0)		
Parbovirus B19 (%)	0 (0)	0 (0)	0 (0)	
Bocavirus (%)	0 (0)	0 (0)	0 (0)	
Varicella zoster virus (%)	0 (0)	0 (0)	0 (0)	

CMV, cytomegalovirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; HRV, human rhinovirus; RSV, respiratory syncytial virus.

Detection of any virus in 20% of patients with AE-ILD
Mostly, CMV and HHV7

Respir Med. 2018 Mar:136:88-92.

Role of bacteria



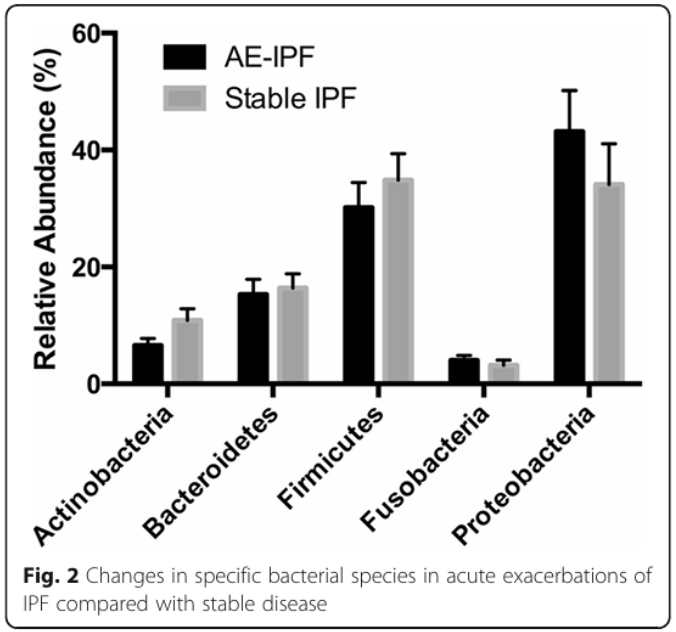


Fig. 2 Changes in specific bacterial species in acute exacerbations of IPF compared with stable disease

BAL fluid sample from AE-IPF vs stable IPF
No clinical infection of virus and bacteria
Higher bacterial burden in AE-IPF group
Difference in microbiota

Respir Res. 2017 Feb 1;18(1):29.

Role of bacteria

Table 3 Comparison of disease status, survival time and death occurrence between non-infected, bacterial-, viral- and co-infected IPF patients, respectively

Characteristics	Non-infected *Group 1* (n = 8)	Bacterial Infection *Group 2* (n = 7)	Viral Infection *Group 3* (n = 12)	Coinfection *Group 4* (n = 40)	p^*	p^+	$p^\$$
Disease status$^-$ (acute vs. stable)	0	1 (14.3)	1(8.3)	22 (55)	0.675	0.930	**< 0.001**
Death status$^-$ (death vs. survive)	0	2 (28.5)	0	15 (37.5)	0.40	0.622	**0.043**
Survival time$^+$ (months-to-death)	42.5 ± 6.55	38.5 ± 7.02	34.4 ± 2.83	32.9 ± 9.12	0.426	0.193	**0.026**

Disease- and death-status are indicated as "n" (%). Survival time is indicated as median ± IQR

IPF uninfected patients are considered as the reference group (Group 1). Bold values indicated as statistically significant at $p < 0.05$ level. Follow up period is 60 months

* Comparison between group 2 versus group 1

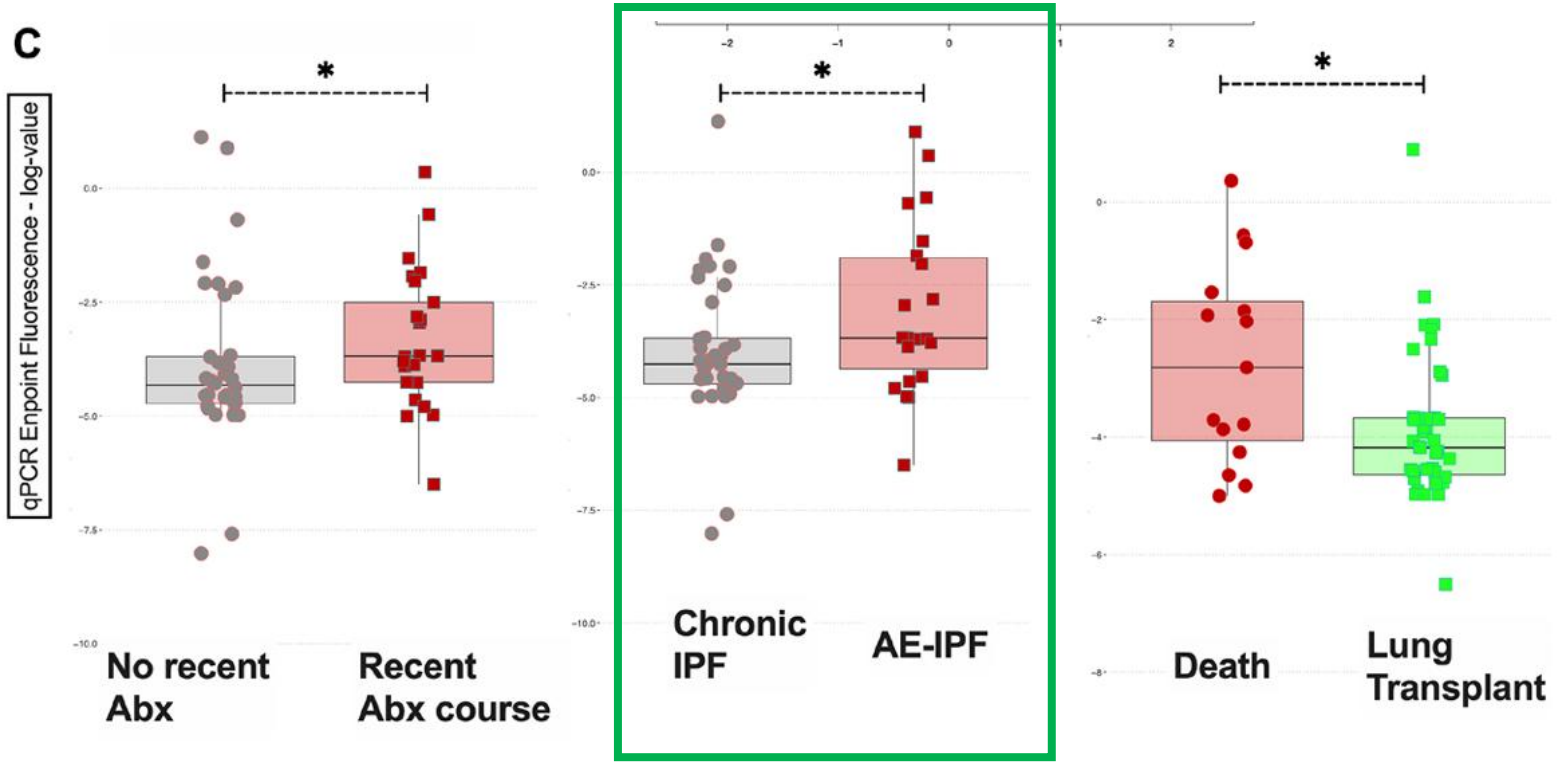
+ Comparison between group 3 versus group 1

$ Comparison between group 4 versus group 1

Nasopharyngeal and BAL sample
DNA array and PCR for virus and bacteria detection
Higher rate of AE-IPF in coinfection group

BMC Pulm Med. 2022 Feb 11;22(1):60.

Role of bacteria

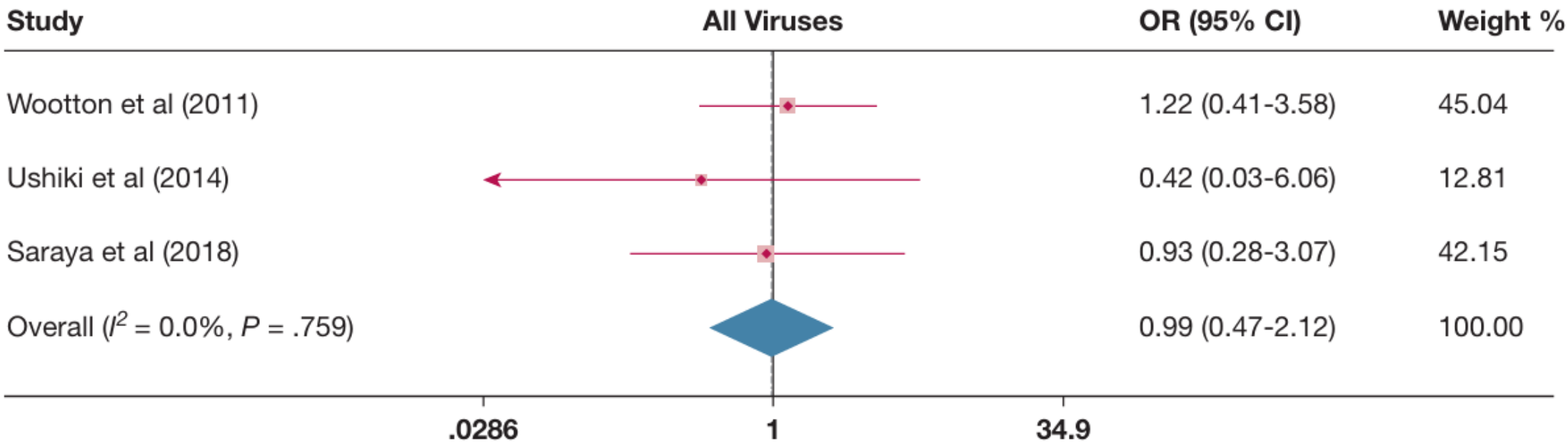


Increased bacterial burden in AE-IPF compared to chronic IPF

Thorax. 2021 Mar;76(3):239-247.

Role of virus - con

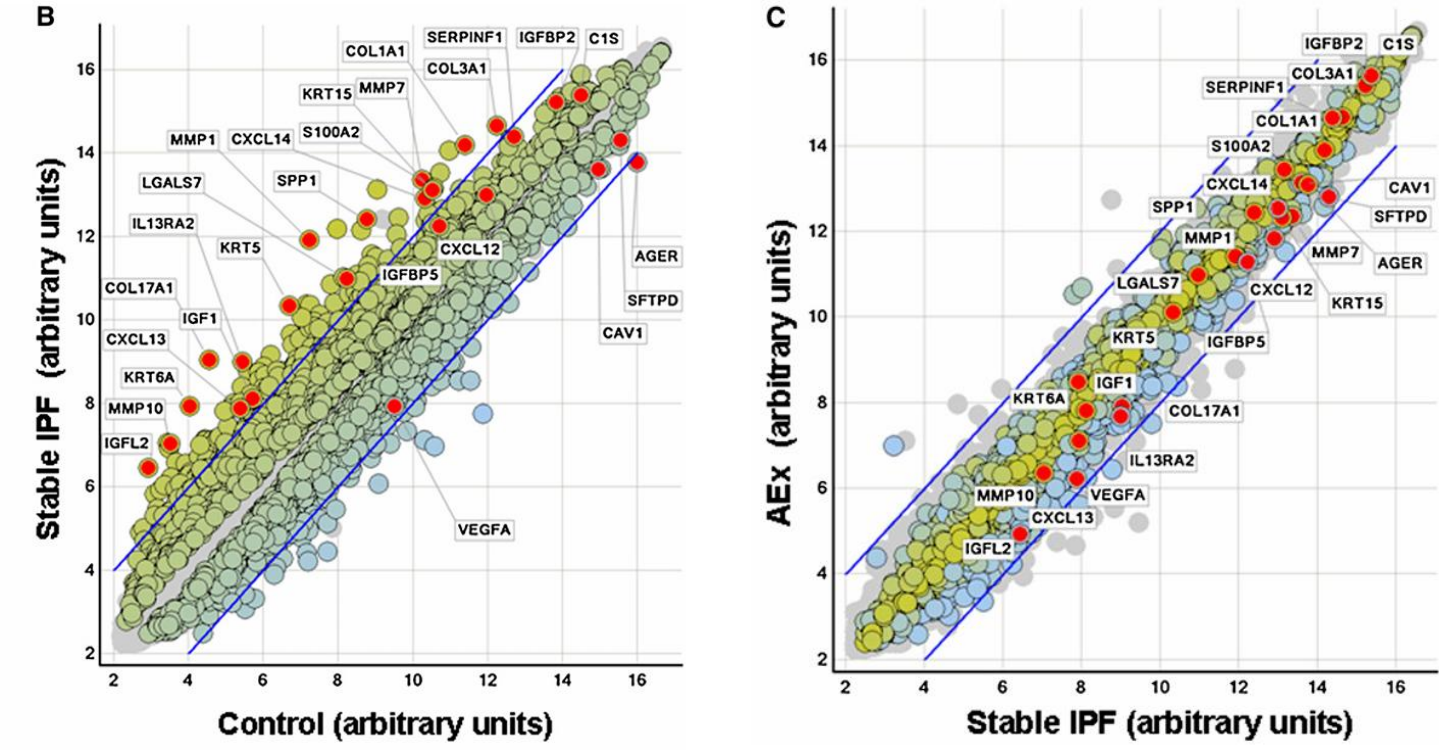
B



Viral infection was not associated with AE-IPF (OR, 0.99; 95% CI, 0.47-2.12; P = 0.988)

Chest. 2020 May;157(5):1175-1187.

Acceleration of intrinsic process

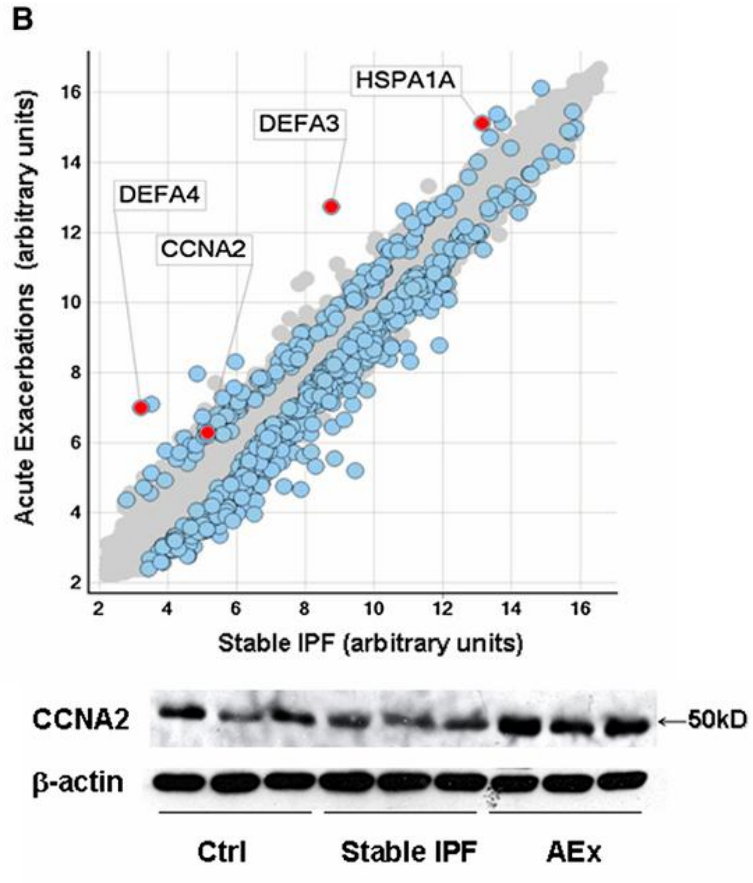


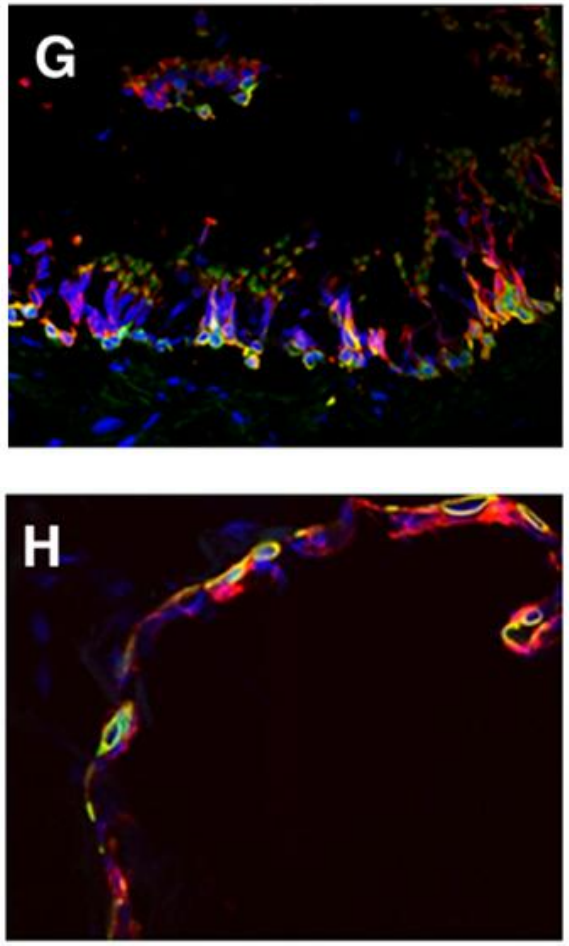
Two-fold increase of fibrosis related gene in stable IPF vs control

Similar gene expression between stable IPF and AE-IPF

Am J Respir Crit Care Med. 2009 Jul 15;180(2):167-75.

Acceleration of intrinsic process





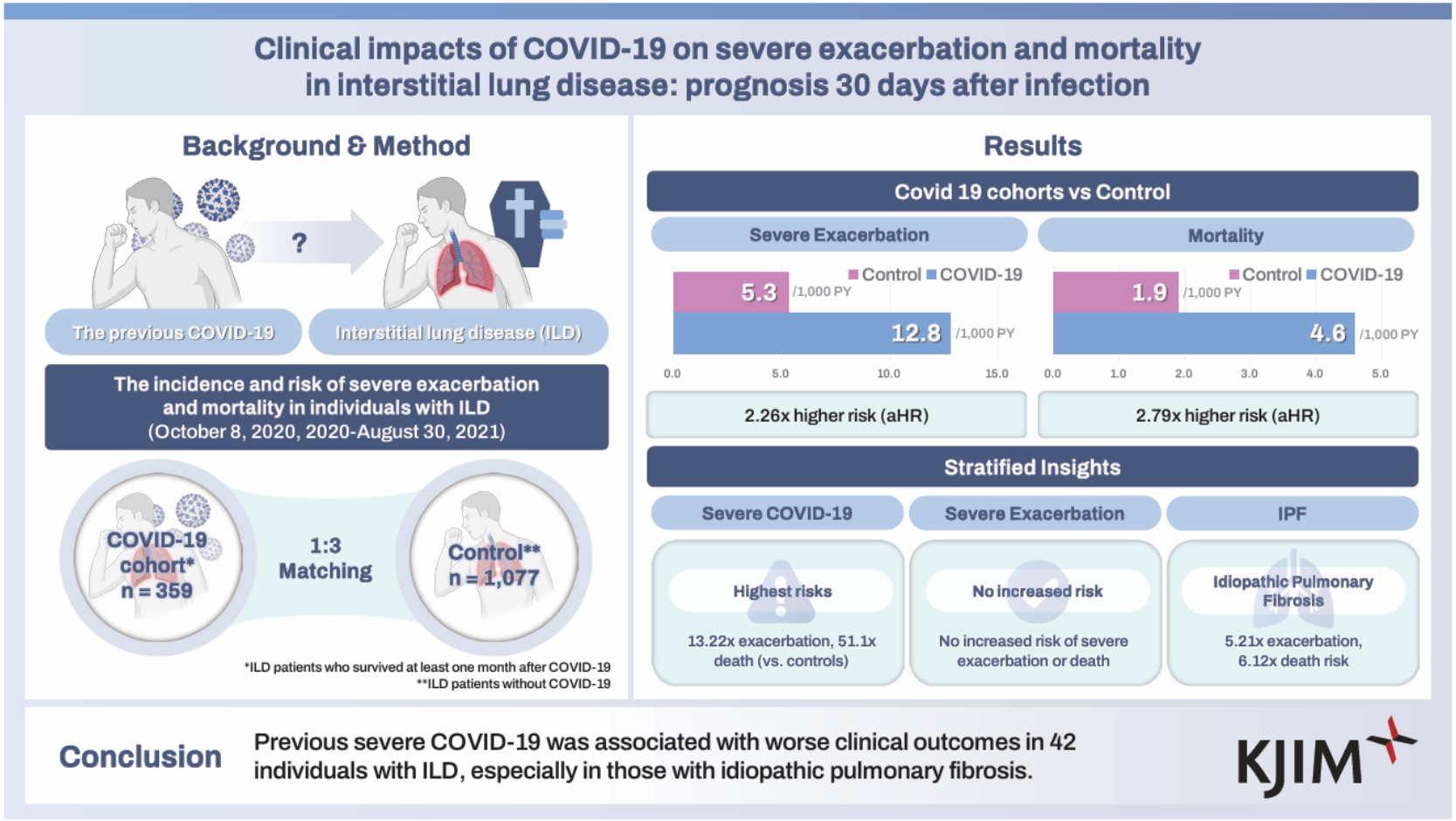
Increased expression of CCNA2 gene
Increased production of CCNA2
Localization of CCNA2 in pulmonary epithelium
*CCNA2: cell cycle regulation

No changes in inflammation related genes between AE-IPF and stable IPF

✓ AE-IPF as a result of enhanced epithelial injury and proliferation

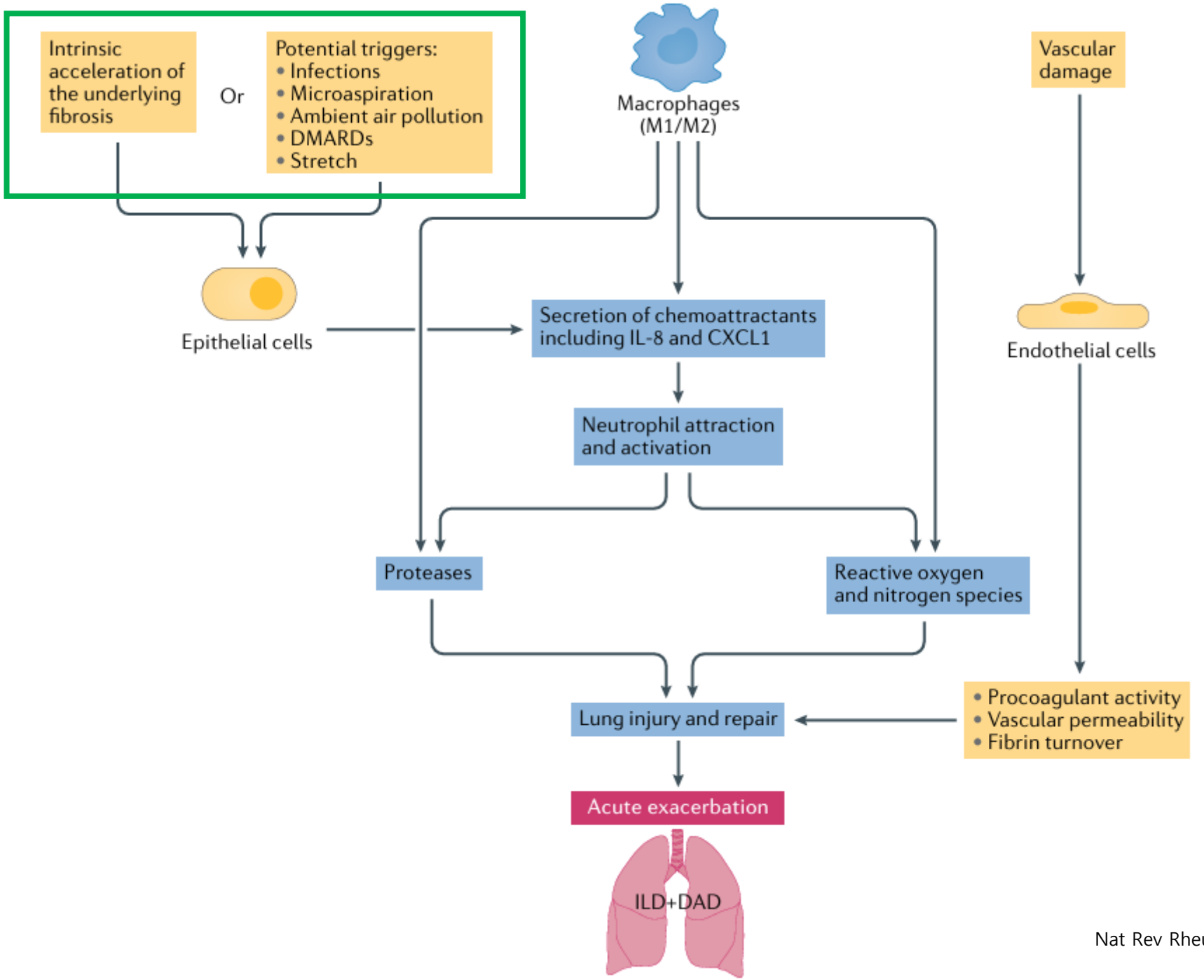
Am J Respir Crit Care Med. 2009 Jul 15;180(2):167-75.

Role of infection in AE-IPF



Increased risk of AE-ILD 30-days after COVID-19 infection

Korean J Intern Med. 2025 Jul;40(4):634-644.



Nat Rev Rheumatol. 2022 Feb;18(2):85-96.

Diagnosis

Expert consensus for AE-IPF

509 pulmonologists from 66 countries

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).

Eur Respir J. 2020 Apr 3;55(4):1901760.

Expert consensus for AE-IPF

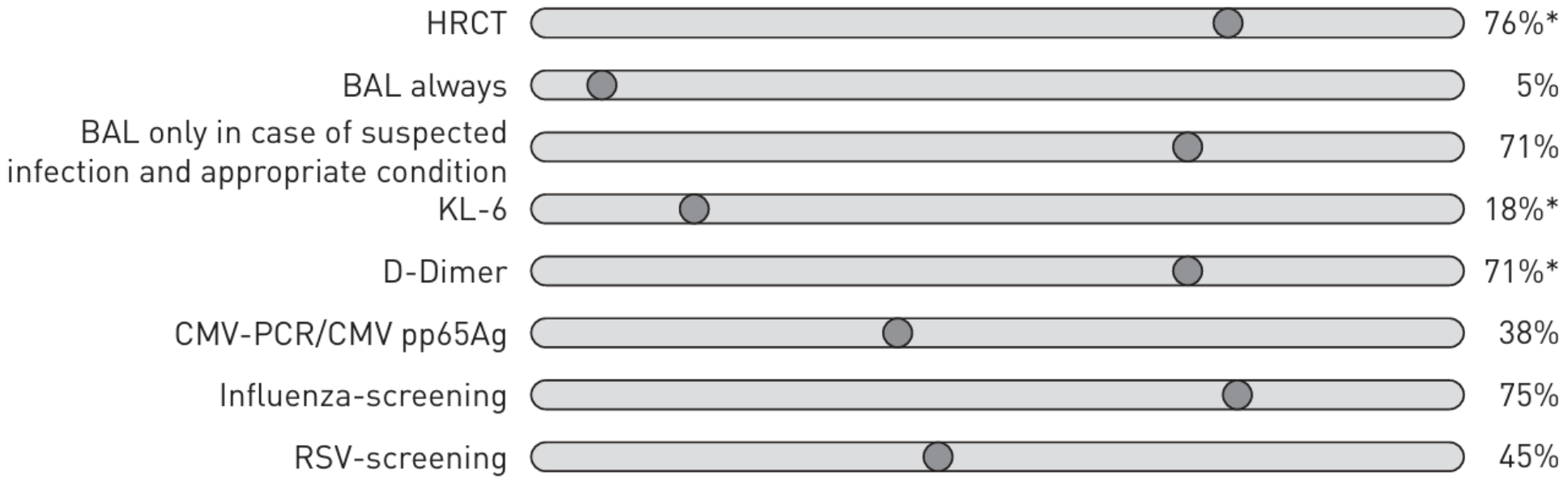


FIGURE 2 Main diagnostic procedures. *: p⩽0.0001.

Echocardiography in 66%
N-terminal pro-BNP in 72%
Screening for atypical bacteria 61%
Screening for Pneumocystis 58%

Eur Respir J. 2020 Apr 3;55(4):1901760.

Bronchoscopy is necessary?

Table 4 Management and outcomes in patients with positive bronchoscopy findings (n = 16)

Age at admission	Gender	ILD type	Infection/ haemorrhage	Days in hospital	Change in initial management	Abx†	Steroid†	Outcome
74	Male	CTD-ILD	Haemorrhage	5	No	Yes	Yes	DC
73	Male	MPA-vasculitis	Haemorrhage	62	No	Yes	Yes	Died‡
76	Male	IPF	Haemorrhage	6	Yes (added i.v. steroids)	Yes	No	Died
66	Male	IPF	Haemorrhage	14	No	Yes	Yes	DC
77	Male	Asbestosis	Infection (*Escherichia coli*)	24	No	Yes	No	Died
74	Male	IPF	Infection (PJP)	36	Yes (added Bactrim)	Yes	No	DC
75	Male	IPF	Infection (EBV)	8	No (considered colonizer)	Yes	Yes	Died
68	Female	CTD-ILD	Infection (*Mycobacterium*)	7	No (considered contaminant)	Yes	Yes	Died
62	Male	CTD-ILD	Infection (Influenza A)	9	Yes (added oseltamavir)	Yes	No	Died
84	Female	iNSIP	Infection (PJP)	9	No (started on coverage before bronchoscopy results)	Yes	No	Died
63	Female	IPF	Infection (*Staphylococcus aureus*)	8	No	Yes	No	DC
46	Female	CTD-ILD	Infection (PJP)	13	Yes (added Bactrim)	Yes	No	DC
42	Male	iNSIP	Infection (CMV)	55	No (considered colonizer)	Yes	Yes	DC
66	Female	IPF	Infection (PJP)	15	No (started on coverage before bronchoscopy results)	Yes	Yes	Died
55	Female	CTD-ILD	Infection (CMV)	5	No	Yes	No	DC
65	Male	IPF	Infection (*S. aureus*)	24	No	Yes	No	Died

119 Bronchoscopy done
Positive findings in 16 pts
Management change in 4 pts
: 2 died, 2 survived

Respirology. 2017 Feb;22(2):352-359.

Bronchoscopy is necessary?

Bronchoscopy performed, *n* = 119	
Time from admission to bronchoscopy (days, mean and range)	2.25 (0.3–19)
Bronchoscopy on general floor, *n* = 55 (47%)	
Total patients transferred to the ICU within 12 h of bronchoscopy, *n* (%)	14 (25)
Transfer to ICU after bronchoscopy intubated, *n* (%)	10 (71)
Bronchoscopy in ICU, *n* = 64 (53%)	
Bronchoscopy performed in patients already intubated and ventilated, *n* (%)	45 (70)
Patients not intubated during bronchoscopy, no related complication, *n* (%)	2 (3)
Patients intubated to safely perform bronchoscopy, *n* (%)	17 (27)
Patients not extubatable at the end of the procedure, *n* (%)	10 (59)
Patients experienced reintubation for RF within 12 h, *n* (%)	2 (11)
Patients extubated safely without related complication, *n* (%)	5 (29)

Respirology. 2017 Feb;22(2):352-359.

Bronchoscopy is necessary?

Table 1 Table represents final diagnosis in IPF patients admitted with acute respiratory failure. Two most common final diagnosis were AEX-IPF and pulmonary infection

Final diagnosis	
AEX-IPF	47
Pulmonary infection	14
IPF progression	5
Acute CHF	2
NSIP flare	
Hypoglycemia and respiratory failu	
COPD exacerbation	
Pulmonary embolism	
Transtracheal oxygen catheter rela	
Pneumomediastinum	
Ischemic heart disease	
Bronchogenic carcinoma	
Total number of cases	

29 BAL performed in 77 pts
23 received antibiotics before BAL

6 of 14 pts with infection underwent BAL
Infection identified in one patient: PJP and CMV

Table 5 Multivariable association between final diagnosis of pulmonary infection and patient risk factors

Effect	Odds ratio	95 % CI		*P*-value
Steroids on admission: Yes vs No	7.817	1.31	46.64	0.024*
Cytotoxic agents on admission: No vs Yes	2.407	0.196	29.524	0.49
Antibiotics on admission: Yes vs No	2.051	0.308	13.65	0.46
Sputum culture positive: Yes vs No	2.427	0.148	39.718	0.53
Elevated WBC on admission: Yes vs No	1.474	0.268	8.094	0.66
Fever on admission: Yes vs No	1.651	0.109	25.021	0.72
Tachycardia on admission: No vs Yes	1.552	0.201	11.956	0.67
Tachypnea on admission: Yes vs No	1.088	0.142	8.362	0.94

*Patients who were on steroids on admission were more likely diagnosed with pulmonary infection then patients who were not on steroids ($p = 0.024$)

BMC Pulm Med. 2015 Jul 10:15:70.

Opportunistic infection

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 a wors alve or co
Diagnostic criteria			
Disease	Previous or concurrent diagnosis of IPF	Previous or concurrent diagnosis of IPF	Rheu conc
Symptoms	Unexplained worsening or development of dyspnoea <1 month duration	Acute worsening or development of dyspnoea typically <1 month duration	Acut typic
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	HRC and/ back
Infection	No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage	Not considered as an exclusion criterion for acute exacerbation	Not acut
Triggers	Infections*, gastroesophageal reflux, microaspiration, surgery, bronchoscopy, air pollution	Infections*, gastroesophageal reflux, microaspiration, surgery, bronchoscopy, air pollution	Infect ns, opportunistic infections, DMARDs, gastro ophageal reflux, microaspiration, surge , 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	Deteri ion not fully explained by cardiac failure, fl 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.

Infections, opportunistic infections, DMARDs, gastroesophageal reflux, microaspiration, surgery, bronchoscopy, air pollution

Deterioration not fully explained by cardiac failure, fluid overload or DMARD use

Nat Rev Rheumatol. 2022 Feb;18(2):85-96.

Table 1 The EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases

Overarching principles	LoE	GoR	LoA mean (SD)
(A) The risk of chronic and opportunistic infections should be considered and discussed with all patients with AIIRD prior to treatment with csDMARDs, tsDMARDs, bDMARDs, immunosuppressants and/or glucocorticoids and reassessed periodically.	NA	NA	9.5 (1.0)
(B) Collaboration between rheumatologists and other specialists including but not limited to infectious disease doctors, gastroenterologists, hepatologists and pulmonologists is important.	NA	NA	9.6 (0.8)
(C) Individual risk factors should be considered in the decision for screening and prophylaxis of chronic and opportunistic infections and reassessed periodically.	NA	NA	9.8 (0.7)
(D) National guidelines and recommendations, among other country/region-level factors pertaining to endemic infectious diseases, should be considered.	NA	NA	9.7 (0.8)
Recommendations			
(1) Screening for latent tuberculosis is recommended in patients prior to starting bDMARDs or tsDMARDs*. Screening should also be considered in patients with increased risk for latent tuberculosis prior to starting csDMARDs, immunosuppressants* and/or glucocorticoids (according to dose and duration).	2b 5*	B D*	9.5 (0.9)
(2) Screening for latent tuberculosis should follow national and/or international guidelines and would typically include a chest X-ray* and Interferon-gamma release assay over tuberculin skin test where available.	2b 5*	B D*	9.5 (0.8)
(3) Choice and timing of latent tuberculosis therapy should be guided by national and/or international guidelines. Special attention should be given to interactions with drugs commonly used to treat AIIRD.	5	D	9.3 (1.4)
(4) All patients being considered for treatment with csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants* and glucocorticoids (according to dose and duration) should be screened for HBV.	2a 2b*	C C*	9.1 (1.3)
(5) Screening for chronic hepatitis C should be considered in patients prior to starting csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants and glucocorticoids* (according to dose and duration). Screening is recommended for patients with elevated alanine aminotransferase or those with known risk factors.	2b 5*	C D*	9.0 (1.3)
(6) Screening for HIV is recommended prior to treatment with bDMARDs and should be considered prior to treatment with csDMARDs, tsDMARDs, immunosuppressants and glucocorticoids (according to dose and duration).	5	D	8.9 (1.6)
(7) All patients commencing csDMARDs, bDMARDs, tsDMARDs, immunosuppressants and/or glucocorticoids (according to dose and duration) who are non-immune to VZV should be informed about post-exposure prophylaxis following contact with VZV.	5	D	8.9 (1.5)
(8) Prophylaxis against PCP should be considered in patients with AIIRD in whom high doses of glucocorticoids are used, especially in combination with immunosuppressants* and depending on the risk–benefit ratio.	2b 5*	B D*	9.2 (1.1)

Ann Rheum Dis. 2023 Jun;82(6):742-753.

Opportunistic infection

Table 2
Summary of potential risk factors for IFIs in patients with CTD.

Predictor	Pooled ORs [95% CI]	Numbers of studies	Certainty of evidence (GRADE)
Comorbidity			
Diabetes	**1.62 [1.00; 2.64]**	13	Very low
Pulmonary disease	**3.43 [2.49; 4.73]**	19	Moderate
ILD	**4.06 [2.22; 7.41]**	10	Moderate

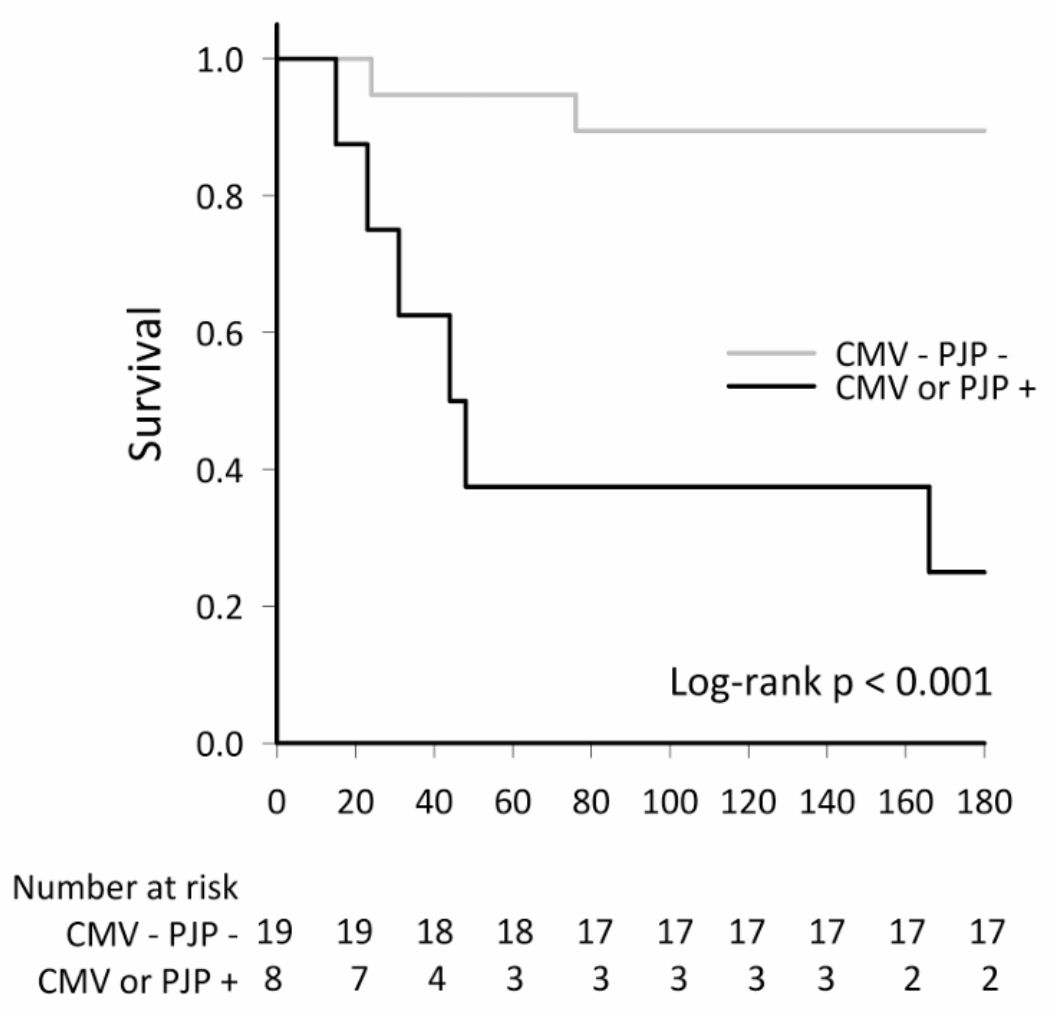
Increased risk of IFI (PJP) in CTD pts with ILD and immunosuppressant

Table 3
Summary of potential risk factors for PJP in patients with CTD.

Predictor	Pooled ORs (95% CI)	Numbers of studies	I^2, %
Comorbidity			
Diabetes	1.64 [0.88; 3.04]	10	61
Pulmonary disease	**3.11 [2.23; 4.36]**	15	22
ILD	**2.72 [1.81; 4.09]**	8	13
Renal disease	5.71 [0.66; 49.30]	3	99
Immunosuppression			
GC	**4.72 [2.98; 7.48]**	7	0
AZA	1.39 [0.89; 2.18]	5	12
CNI	**3.15 [1.85; 5.36]**	7	18
CYC	**3.79 [2.66; 5.39]**	8	22
HCQ	**0.65 [0.51; 0.84]**	4	21
MMF	**3.68 [1.46; 9.24]**	7	60
MTX	**2.31 [1.10; 4.85]**	10	55
Biologics	**3.32 [2.26; 4.89]**	5	38
Leucopenia	1.43 [0.49; 4.20]	2	0
Lymphopenia	**3.41 [1.30; 8.99]**	3	0

Semin Arthritis Rheum. 2023 Dec:63:152257.

Opportunistic infection



BAL performed in 27 pts SLE-DAH
CMV or PJP detected in 8 pts (30%)
Higher mortality in CMV/PJP (+) pts

J Rheumatol. 2019 Mar;46(3):251-258.

Opportunistic infection

Microbiology, *n*	Total (n = 131)	IPF (n = 74)	Non-IPF ILD (n = 57)
Negative results, %	81 (61.8)	46 (62.2)	35 (61.4)
Bacterial infection, %	28 (21.4)	18 (24.3)	10 (17.5)
Pseudomonas aeruginosa	7 (5.3)	5 (6.8)	2 (3.5)
Mycoplasma	6 (4.6)	5 (6.8)	1 (1.8)
Legionella	6 (4.6)	4 (5.4)	2 (3.5)
Klebsiella pneumoniae	5 (3.8)	2 (2.7)	3 (5.4)
Stenotrophomonas maltophilia	1 (0.7)	1 (1.4)	0 (0)
Streptococcus pneumoniae	1 (0.7)	1 (1.4)	0 (0)
Acinetobacter baumannii	1 (0.7)	0 (0)	1 (1.8)
Serratia marcescens	1 (0.7)	0 (0)	1 (1.8)
Viral infection[a], %	10 (7.0)	7 (9.5)	3 (5.4)
Fungal infection, %	12 (9.2)	3 (4.2)	9 (15.8)
Pneumocystis jiroveci	11 (8.4)	2 (2.7)	9 (15.8)
Aspergillus	1 (0.7)	1 (1.4)	0 (0)

Table 3. Microbiologic results in the triggered AE-ILD group. *AE-ILD* acute exa disease. [a]Metapneumovirus, Influenza virus, Coronavirus, Rhinovirus, and RSV.

Bacteria is the most common cause of trigger in both IPF and non-IPF ILD

PJP is the second most common cause of trigger in non-IPF ILD

Sci Rep. 2021 Mar 11;11(1):5762.

Treatment

Expert consensus for AE-IPF

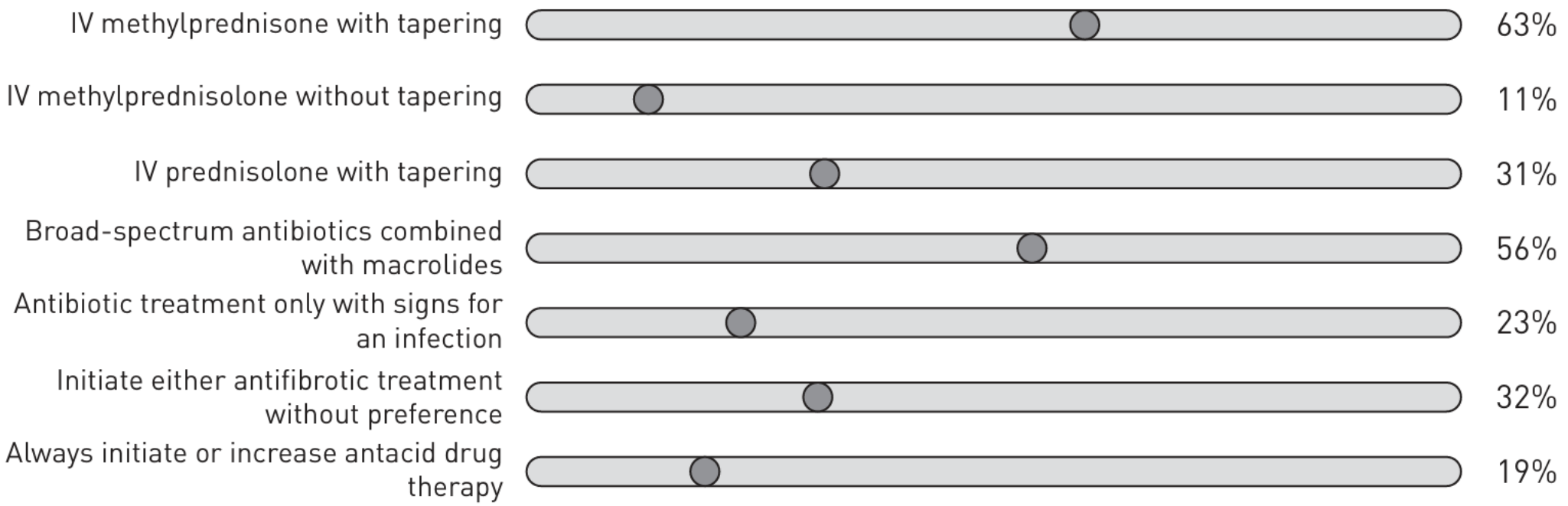


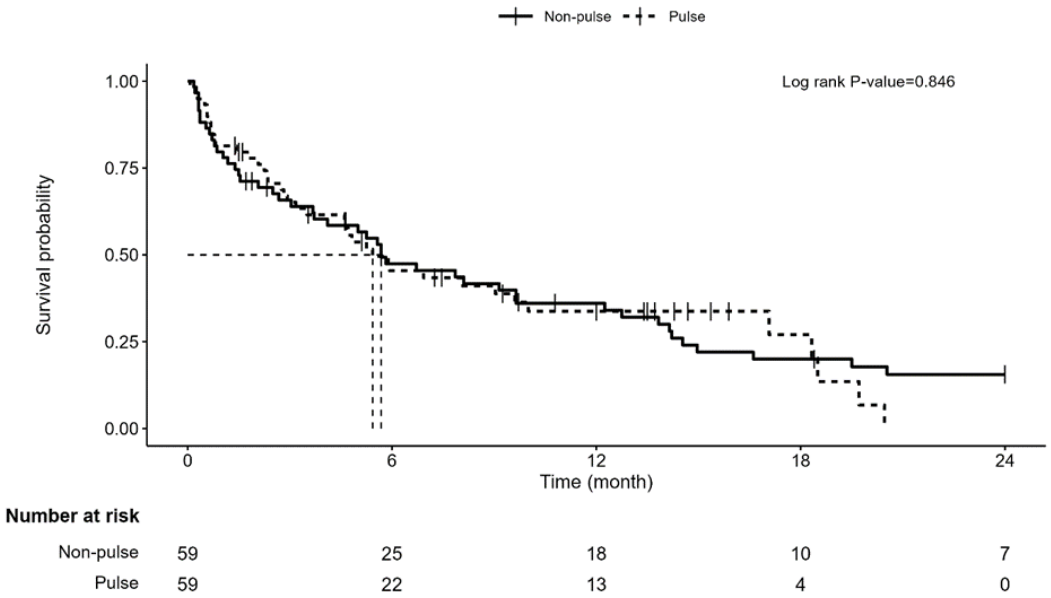
FIGURE 3 Main drug management approaches worldwide.

Eur Respir J. 2020 Apr 3;55(4):1901760.

Steroid

TABLE 2 Clinical data and outcomes of acute exacerbation.

	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)	
Laboratory finding			
White blood cell, $10^3/\mu L$	9.8 (8.3–12.3)	11.2 (9.0–14.4)	0.025
C-reactive protein, mg/dL	3.6 (1.2–7.6)	8.2 (3.0–17.2)	<0.001
PaO_2/FiO_2 ratio, mm Hg[a]	285.9 (160.9–362.5)	252.0 (177.9–328.6)	0.904
Quantitative CT analysis			
Emphysema, %	0.5 (0.2–2.2)	1.0 (0.3–3.0)	0.083
Reticulation, %	18.9 (11.3–30.1)	22.2 (12.7–30.8)	0.380
Ground glass opacity, %	19.7 (10.7–35.3)	16.1 (5.4–31.5)	0.192
Consolidation, %	2.0 (0.5–6.6)	6.0 (2.0–14.5)	<0.001
Honeycombing, %	1.8 (0.2–8.4)	3.2 (0.3–14.0)	0.080
Lung volume, mL	2756 (2260–3420)	2722 (2276–3205)	0.575
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



No significant difference between steroid pulse group vs non-pulse group among patients with AE-IPF after PSM

Respirology. 2024 Mar;29(3):235-242.

Steroid

Table 1 Cohort characteristics

Characteristics[†]	Corticosteroids ($n = 37$)	No corticosteroids ($n = 45$)	*P*-value
Age (years)	66.5 ± 10.2	67.0 ± 10.0	0.79
Sex			0.66
Female	21 (57%)	23 (51%)	
Male	16 (43%)	22 (49%)	
Race			0.63
Asian	3 (8%)	2 (4%)	
Black	2 (5%)	4 (9%)	
White	21 (57%)	30 (67%)	
Other	11 (30%)	9 (20%)	
Ethnicity			0.77
Hispanic	7 (19%)	7 (16%)	
Non-Hispanic	30 (81%)	38 (84%)	
Charlson Comorbidity Index	1 (0–1)	0 (0–2)	0.52
Preadmission PFT[‡]			
FVC (% predicted)	56 ± 15.7	72 ± 21.7	<0.001
FEV_1 (% predicted)	61 ± 18.7	76 ± 20.3	0.003
TLC (% predicted)	56 ± 13.2	69 ± 22.0	0.005
DL_{CO} (% predicted)	35 ± 13.6	48 ± 19.4	0.001
Baseline supplemental O_2	27 (73%)	12 (27%)	<0.001
Admission O_2 requirements			<0.001
None	2 (5%)	20 (44%)	
Nasal cannula/face mask	12 (32%)	20 (44%)	
HFNC	12 (32%)	2 (4%)	
NPPV	5 (14%)	1 (2%)	
Intubation	6 (16%)	2 (4%)	
Initial triage location			<0.001
Floor	16 (43%)	40 (89%)	
ICU	21 (57%)	5 (11%)	
DNR at admission	3 (8%)	1 (2%)	0.32
Hospital course events			
Antibiotics	24 (65%)	11 (24%)	<0.001
ICU admission	23 (62%)	6 (13%)	<0.001
Mechanical ventilation	10 (27%)	1 (2%)	0.002

58% of pts were triggered AE-IPF such as procedure, infection, drug, or aspiration

Table 2 Risk of in-hospital mortality in corticosteroid-treated subjects versus subjects receiving usual care, unadjusted, adjusted and treatment propensity-adjusted models

	HR	95% CI	*P*-value
Unadjusted	2.67	0.74–9.64	0.13
Adjusted[†]	1.52	0.37–6.18	0.56
Propensity score weighted[‡]	1.31	0.26–6.55	0.74

Steroid was not associated with mortality?

Respirology. 2020 Jun;25(6):629-635.

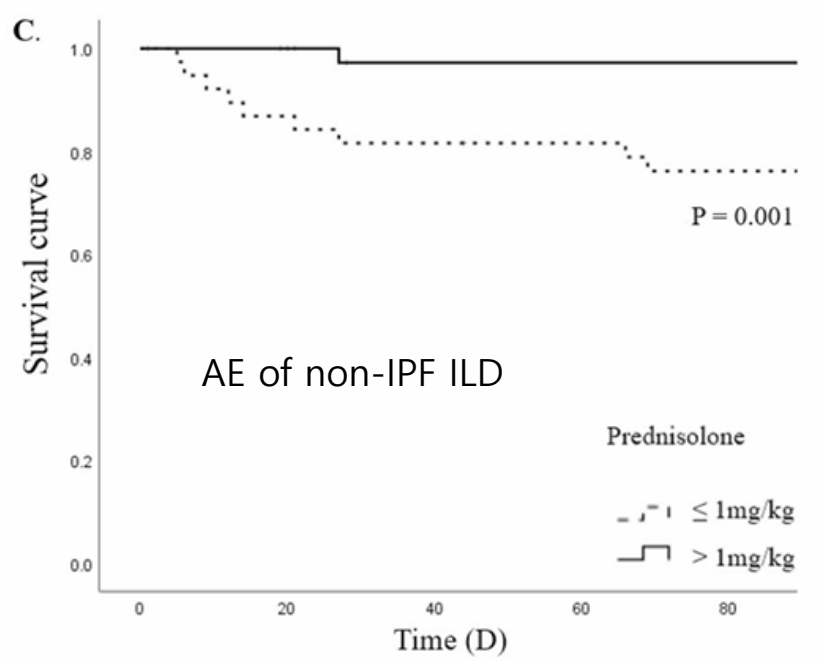
Steroid

Variable	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, years	0.993	0.968–1.019	0.603	0.989	0.957–1.009	0.200
Sex, male	1.228	0.624–2.415	0.552	0.777	0.377–1.599	0.493
Initial P/F ratio	0.998	0.998–1.001	0.241	0.995	0.992–0.999	0.006
FVC (%), predicted	0.994	0.975–1.014	0.540			
DLco (%), predicted	0.976	0.952–1.001	0.059			
Prednisolone > 1 mg/kg	0.380	0.193–0.747	0.005	0.221	0.102–0.480	< 0.001
Use of vasopressors within 3 days	1.852	0.881–3.890	0.104	1.451	0.630–3.340	0.382
Need for mechanical ventilator	3.877	2.068–7.267	< 0.001	4.205	2.059–8.589	< 0.001

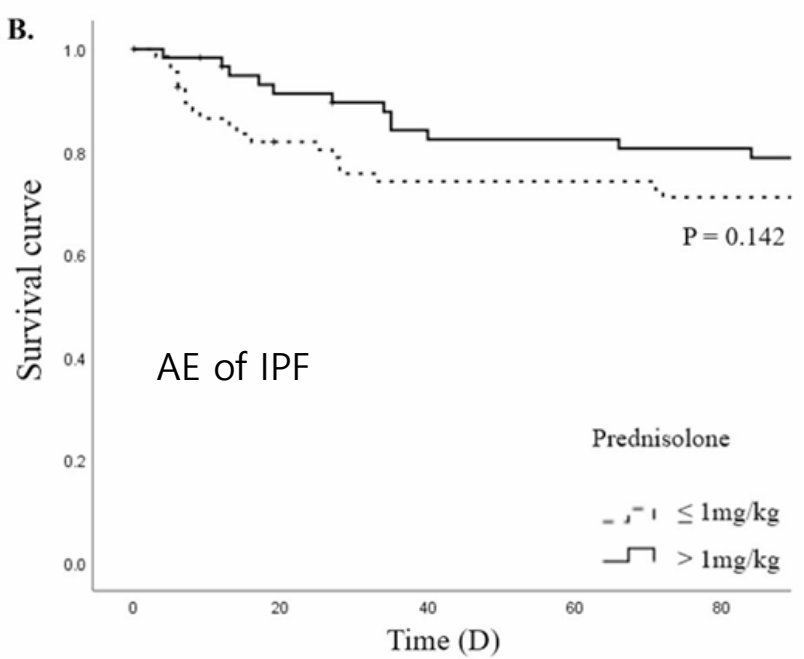
Table 5. Cox regression analysis of risk factors related to 90-day mortality in AE-ILD.

Sci Rep. 2021 Mar 11;11(1):5762.

Steroid



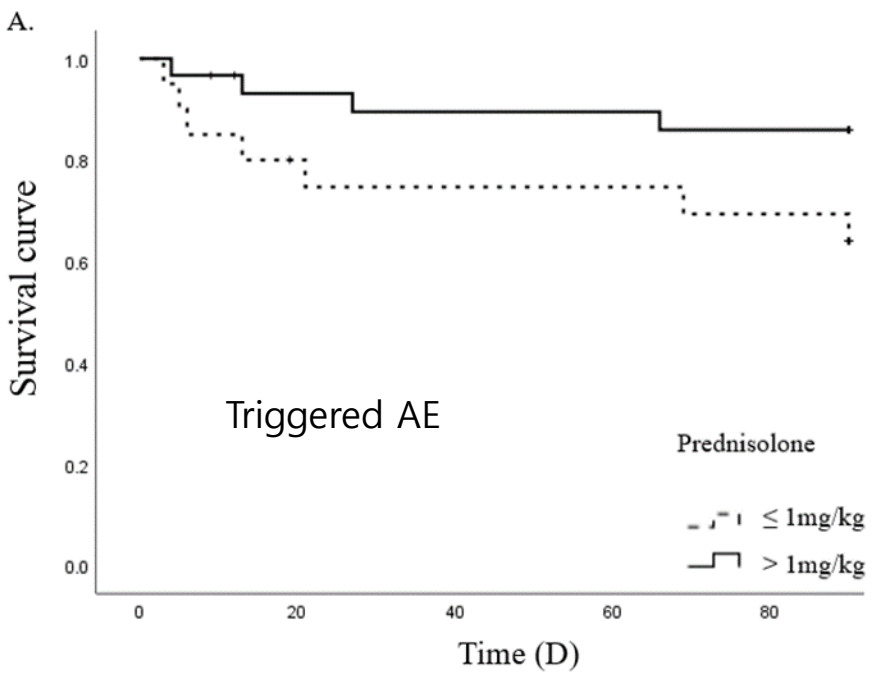
Improved 90-day survival with high dose steroid in pts with AE of non-IPF ILD



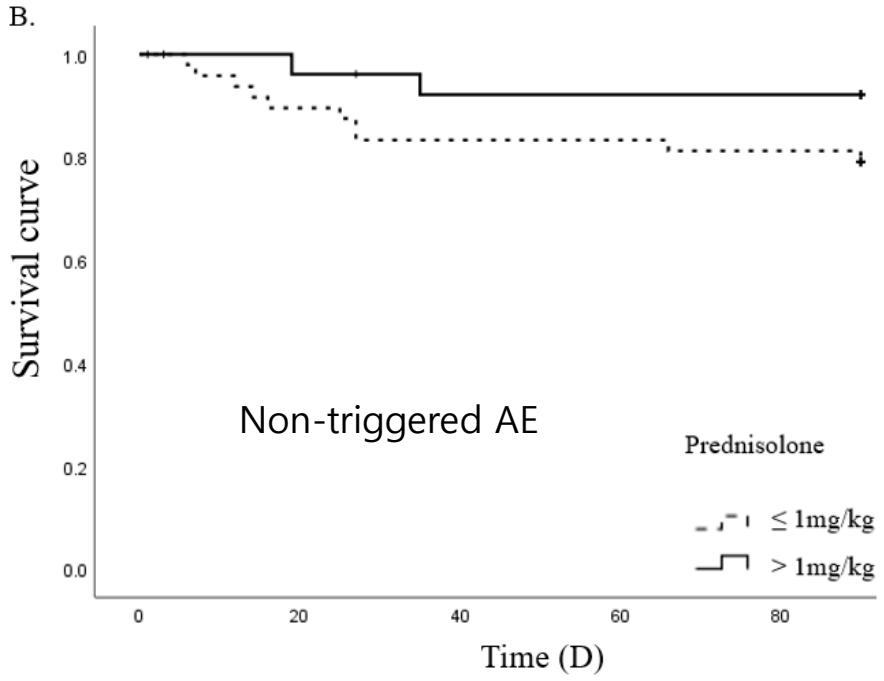
No difference in 90-day survival according to steroid dose in pts with AE-IPF

Sci Rep. 2021 Mar 11;11(1):5762.

Steroid in triggered AE-ILD



A trend toward improved survival with high dose steroid in triggered AE-ILD (p = 0.074)



No difference in survival according to steroid dose in non-triggered AE-ILD

Sci Rep. 2021 Mar 11;11(1):5762.

Steroid in triggered AE-ILD

Steroids in Idiopathic Pulmonary Fibrosis Acute Exacerbation: Defenders or Killers?

To the Editor:

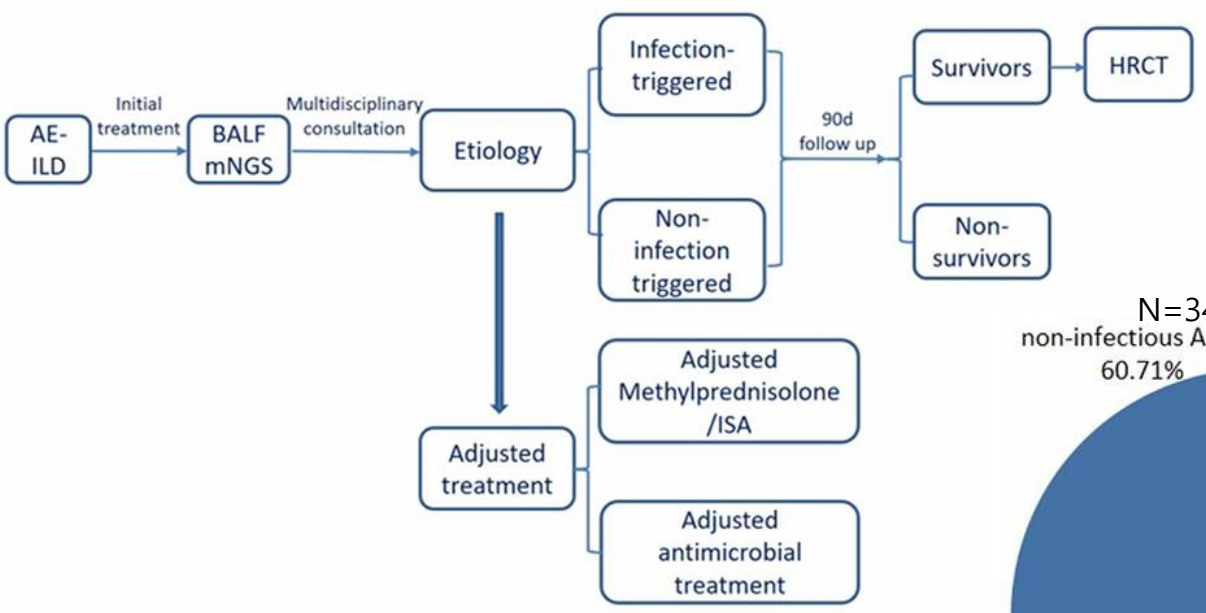
exacerbations is a clinically occult infection that triggers the rapid development of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) upon usual interstitial pneumonia (UIP) lung (3). As in ARDS, with which IPF exacerbations share the histological pattern of diffuse alveolar damage, the treatment of IPF exacerbations should consist of excellent supportive care, investigation for the possibility of reversible causes (especially among but not limited to the list of ARDS causes), and immediate cessation of any immunosuppressive medication (3). The rapid deterioration of IPF should be considered to be exactly this (i.e., an ARDS of known/proven or unknown/unproven [acute exacerbation of IPF] cause upon UIP), and we have proposed the following algorithm (Figure 1) to investigate and treat these patients. The discrepancy of the new guidelines regarding the use of corticosteroids in stable and exacerbated IPF seems quite surprising and unjustified according to current scientific evidence.

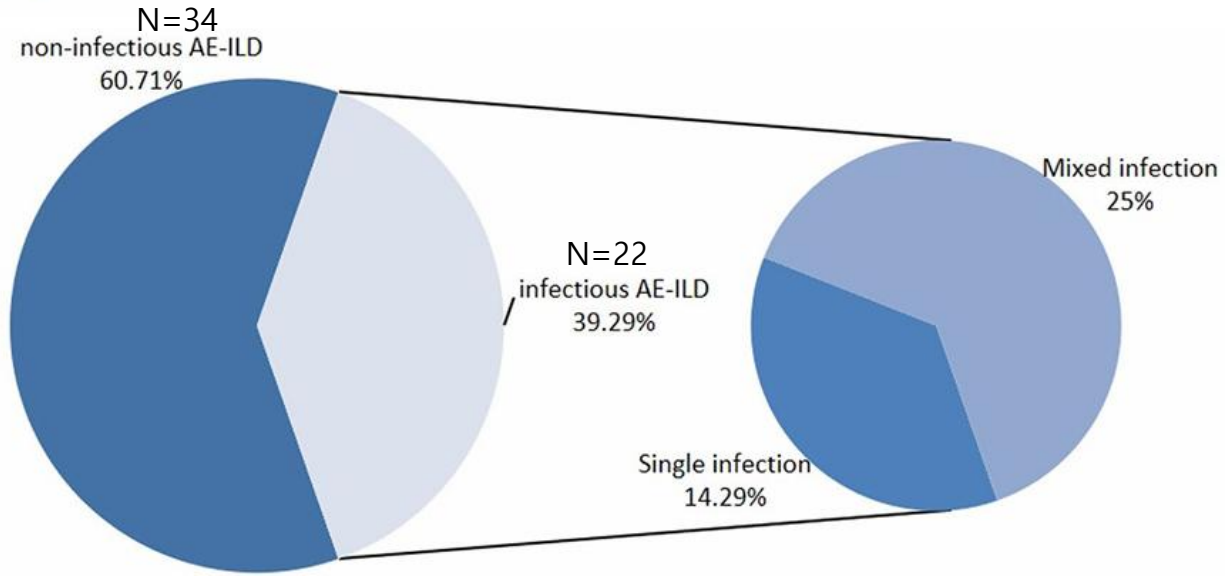
2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia

Acute respiratory distress syndrome
2A. We "suggest" administering corticosteroids to adult hospitalized patients with acute respiratory distress syndrome
Community-acquired bacterial pneumonia
3A. We "recommend" administering corticosteroids to adult patients hospitalized with severe bacterial community-acquired pneumonia
3B. We make "no recommendation" for administering corticosteroids for adult patients hospitalized with less severe bacterial community-acquired pneumonia

Am J Respir Crit Care Med. 2012 Mar 1;185(5):587-8.
Crit Care Med. 2024 May 1;52(5):e219-e233.

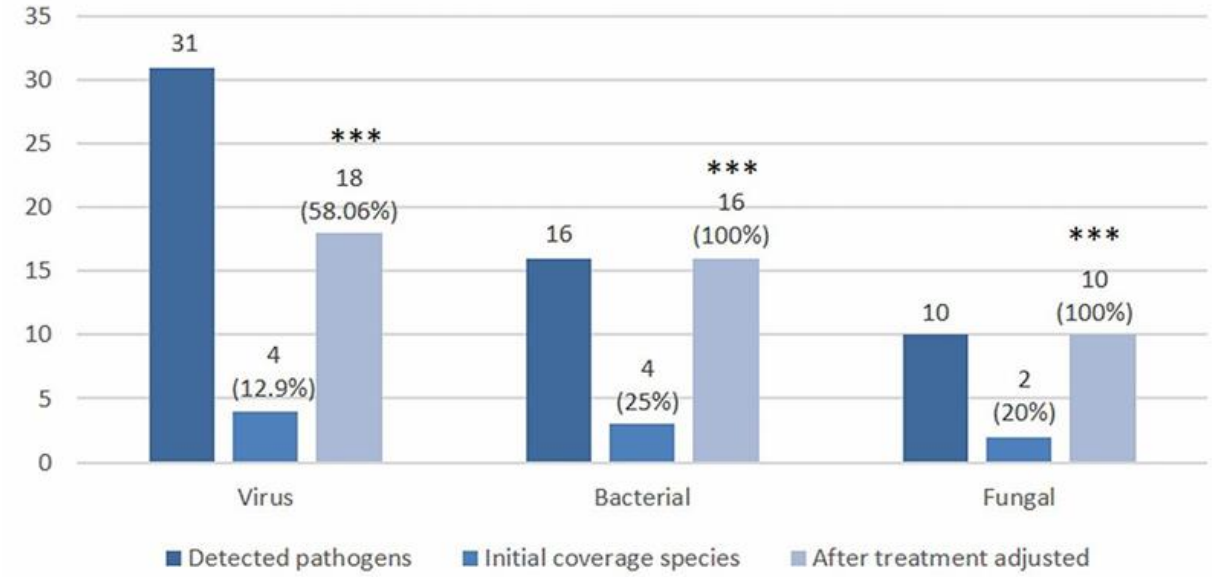
Adjustment of treatment





BMC Pulm Med. 2024 Aug 20;24(1):400.

Adjustment of treatment



Additional microorganisms were detected by mNGS in infectious AE-ILD patients

Antimicrobial therapies were adjusted

BMC Pulm Med. 2024 Aug 20;24(1):400.

Table 2 Antimicrobial treatment adjustments based on mNGS findings

Patient No.	mNGS findings (number of unique reads)	Current treatment	Treatment adjustments	Classification of ILD
1	*Pneumocystis jirovecii* (233)	Sulperazon, Methylprednisolone (80 mg)	Added Compound Sulfamethoxazole, Caspofungin	IPAF
2	*Pneumocystis jirovecii* (22), *Human-gammaherpesvirus-4* (109), *Human-betaherpesvirus-5* (6)	Tazocin, Methylprednisolone (40 mg)	Added Compound Sulfamethoxazole	DM-ILD
3	*Acinetobacter_baumannii* (100)	Cefoxitin, Methylprednisolone (40 mg)	Cefoxitin changed to Sulperazon	ASS-ILD
4	*Human_alphaherpesvirus_1* (145), *Human_betaherpesvirus_7* (48), *Human_gammaherpesvirus_4* (43)	Moxifloxacin, Methylprednisolone (40 mg)	Added Valacyclovir	RA-ILD
6	*Human_gammaherpesvirus_4* (3857), *Candida_albicans* (3418)	Biapenem, Methylprednisolone (40 mg)	Added Valacyclovir; Added Caspofungin	DM-ILD
7	*Human_gammaherpesvirus_4* (189), *Rhinovirus_B* (75), *Human_betaherpesvirus_5* (16), *Klebsiella_aerogenes* (528), *Pichia_kudriavzevii* (172)	Moxifloxacin, Methylprednisolone (80 mg)	Moxifloxacin changed to Ceftaxime sodium; Added Penciclovir; Added Voriconazole	IPAF
8	*Influenza_B_virus* (201), *Aspergillus_flavus* (2)	Cefoxitin	Added Arbidol; Added Voriconazole	IPAF
9	*Human_betaherpesvirus_5* (5), *Pseudomonas_aeruginosa* (637458)	Ceftaxime sodium	Ceftaxime sodium changed to Tazocin; Added Valacyclovir	IPF
10	*Human_gammaherpesvirus_4* (10180), *Human_betaherpesvirus_7* (32), *Human_polyomavirus_4* (3), *Nocardia_abscessus* (163), *Klebsiella_pneumoniae* (92)	Cefoxitin, Methylprednisolone (40 mg)	Cefoxitin changed to Ceftaxime sodium; Added Compound Sulfamethoxazole, Ganciclovir	chronic HP
11	*Tropheryma_whipplei* (10309)	None	Added Ceftriaxone, Methylprednisolone (40 mg)	RA-ILD
12	*Human_alphaherpesvirus_1* (172), *Human_betaherpesvirus_7* (7), *Pneumocystis_jirovecii* (35)	Cefoxitin, Methylprednisolone (40 mg), Cyclophosphamide	Added Compound Sulfamethoxazole, Caspofungin; Added Valacyclovir	IPAF
13	*Klebsiella_pneumoniae* (49)	Cefoxitin, Methylprednisolone (40 mg)	Cefoxitin changed to Tazocin; Methylprednisolone increased to 80 mg	chronic HP
14	*Human_betaherpesvirus_5* (20), *Methylobacterium_radiotolerans* (3911), *Aspergillus_fumigatus* (159)	Levofloxacin, Methylprednisolone (40 mg)	Added Voriconazole	ASS-ILD
15	*Pneumocystis jirovecii* (5)	Methylprednisolone (28 mg)	Added Compound Sulfamethoxazole, Caspofungin; Methylprednisolone increased to 80 mg; Added cyclophosphamide	ASS-ILD
16	*Human_betaherpesvirus_5* (89)	Methylprednisolone (40 mg)	Added Ganciclovir	chronic HP
17	*Rhinovirus_A* (295), *Human_betaherpesvirus_5* (40), *Human_gammaherpesvirus_4* (12), *Methylobacterium_radiotolerans* (9969), *Mycobacterium_avium_complex_(MAC)* (8335), *Aspergillus_fumigatus* (1871)	Ceftaxime sodium, Methylprednisolone (40 mg)	Changed ceftaxime sodium to Moxifloxacin; Added Valacyclovir; Added Voriconazole	RA-ILD
18	*Acinetobacter_baumannii* (92869), *Klebsiella_pneumoniae* (5423), *Human_gammaherpesvirus_4* (82), *Human_betaherpesvirus_7* (21), *Mycobacterium_avium_complex_ (MAC)* (191), *Candida_parapsilosis* (426)	Cefoxitin	Cefoxitin changed to Imipenem and Cilastatin; Added Voriconazole	IPF
20	*Pseudomonas aeruginosa* (27053)	Moxifloxacin	Moxifloxacin changed to Sulperazon	chronic HP
21	*Human_betaherpesvirus_5* (448), *Human_betaherpesvirus_7* (98), *Human_alphaherpesvirus_1* (46), *Klebsiella_pneumonia* (95,756), *Enterobacter_hormaechei* (52,916), *Mycobacterium_tuberculosis_complex* (1162), *Candida_albicans* (1151)	Cefoxitin; Methylprednisolone (20 mg)	Cefoxitin changed to Sulperazon; Added Antituberculosis treatment; Methylprednisolone decreased to 12 mg	RA-ILD

Adjustment of treatment

Table 3 Methylprednisolone/ISA adjustment based on negative mNGS findings

Patient No.	Current Treatment	Treatment adjustments	Classification of ILD
23	Moxifloxacin; Methylprednisolone (40 mg)	Methylprednisolone increased to 160 mg	ASS-ILD
24	Tazocin; Methylprednisolone (40 mg)	Methylprednisolone increased to 320 mg	DM-ILD
27	Meropenem; Methylprednisolone (40 mg)	Methylprednisolone increased to 80 mg	ASS-ILD
28	Compound Sulfamethoxazole; Methylprednisolone (40 mg)	Methylprednisolone increased to 80 mg; Added Cyclophosphamide	MCTD-ILD
29	Cefoxitin	Added Methylprednisolone (40 mg)	iNSIP
31	Ceftaxime sodium	Added Methylprednisolone (40 mg)	IPAF
36	Imipenem and Cilastatin; Methylprednisolone (40 mg)	Methylprednisolone increased to 200 mg; Added cyclophosphamide	ASS-ILD
40	Methylprednisolone (16 mg)	Methylprednisolone increased to 20 mg; Added MMF; Added Compound Sulfamethoxazole	IPAF
43	Cefoxitin	Added Methylprednisolone (40 mg)	IPAF
46	Levofloxacin	Added Methylprednisolone (40 mg); Added TW	ASS-ILD
47	Ampicillin sulbactam	Added Methylprednisolone (40 mg); Added Cyclophosphamide	AAV-ILD
48	Tazocin; Methylprednisolone (40 mg)	Methylprednisolone increased to 120 mg; Added Compound Sulfamethoxazole	IPAF

Steroid and/or other immunosuppressants were increased or added in non-infectious AE-ILD patient with negative mNGS

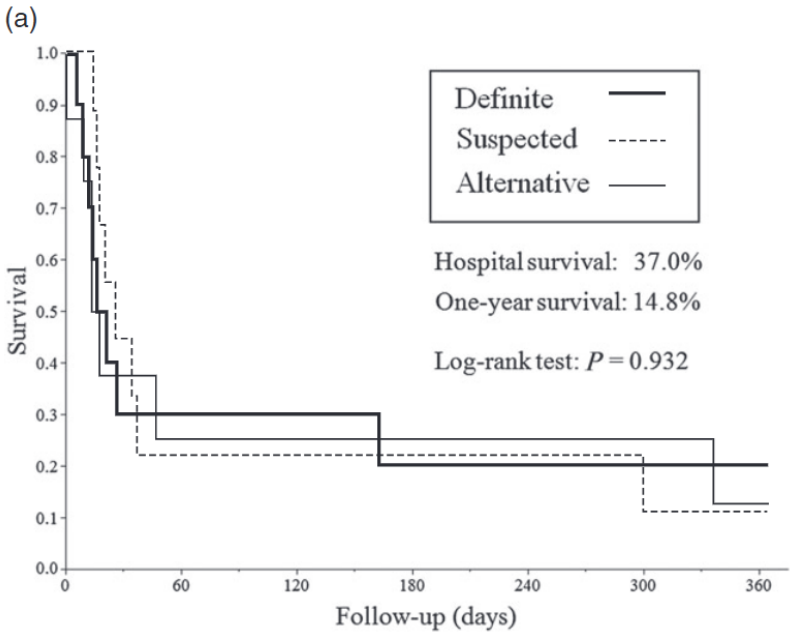
BMC Pulm Med. 2024 Aug 20;24(1):400.

Prognosis

Prognosis is similar?

Table 5 Summary of the CT findings at admission in 27 patients with fibrotic lung disease

Characteristic	All patients *n* (%)	Definite AE-ILD *n* (%)	Suspected AE-ILD *n* (%)	Alternative aetiology *n* (%)	*P*-value
Number of patients	23	8	8	7	
Pattern of ground glass opacities					0.433
Diffuse	17 (73.9)	7 (87.5)	6 (75.0)	4 (57.1)	
Multicentric	6 (26.1)	1 (12.5)	2 (25.0)	3 (42.9)	
Peripheral	0	0	0	0	
Consolidation	9 (39.1)	4 (50.0)	4 (50.0)	1 (14.3)	0.362
Traction bronchiectasis	17 (73.9)	5 (50.0)	6 (75.0)	7 (100.0)	0.147
Honeycombing	10 (43.5)	2 (25.0)	3 (37.5)	5 (71.4)	0.243
Pleural effusions	10 (43.5)	5 (62.5)	3 (37.5)	2 (28.6)	0.454
Mosaic attenuation	6 (26.1)	1 (12.5)	3 (37.5)	2 (28.6)	0.619



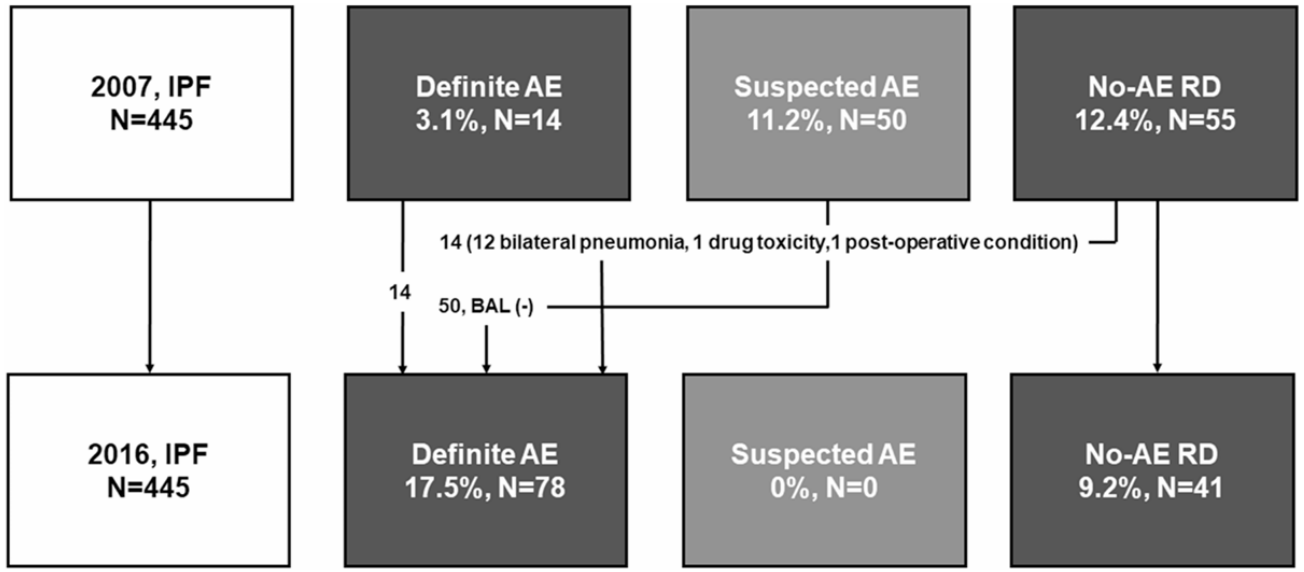
Patients with fibrotic ILD

Respiratory failure due to infection vs exacerbation

- No difference between CT findings
- No difference between survival

Respirology. 2010 Aug;15(6):909-17.

Prognosis is similar?

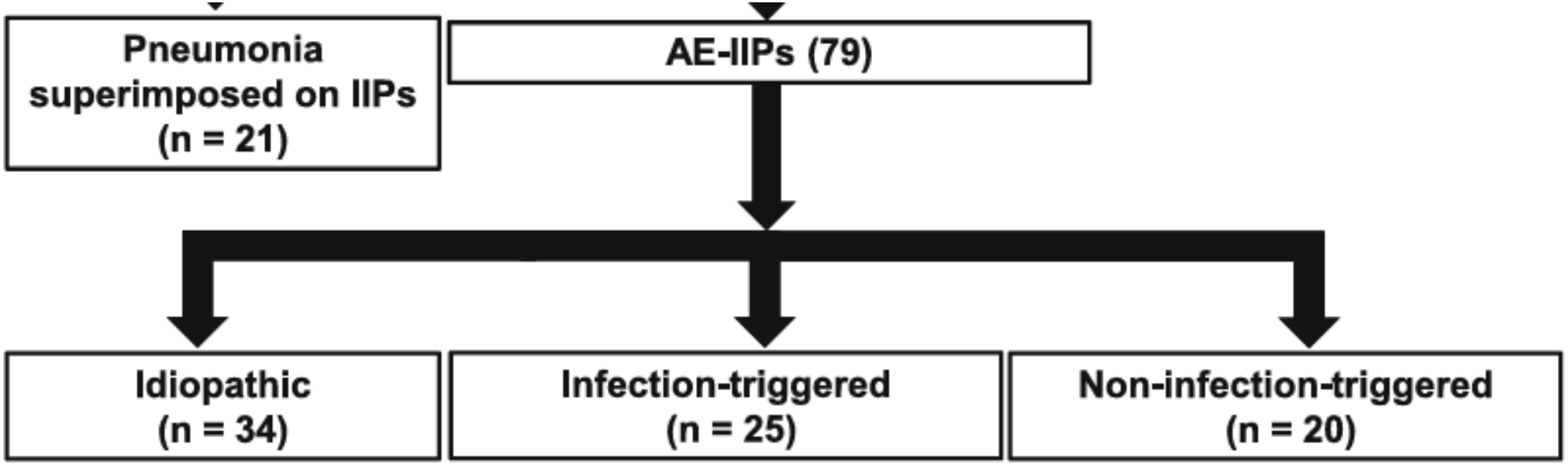


2007 definition
In-hospital mortality of AE-IPF: 32.8%

2016 revised definition
In-hospital mortality of AE-IPF: 29.5%
In-hospital mortality of idiopathic AE: 32.8%
In-hospital mortality of triggered AE: 14.3%
(p=0.211)

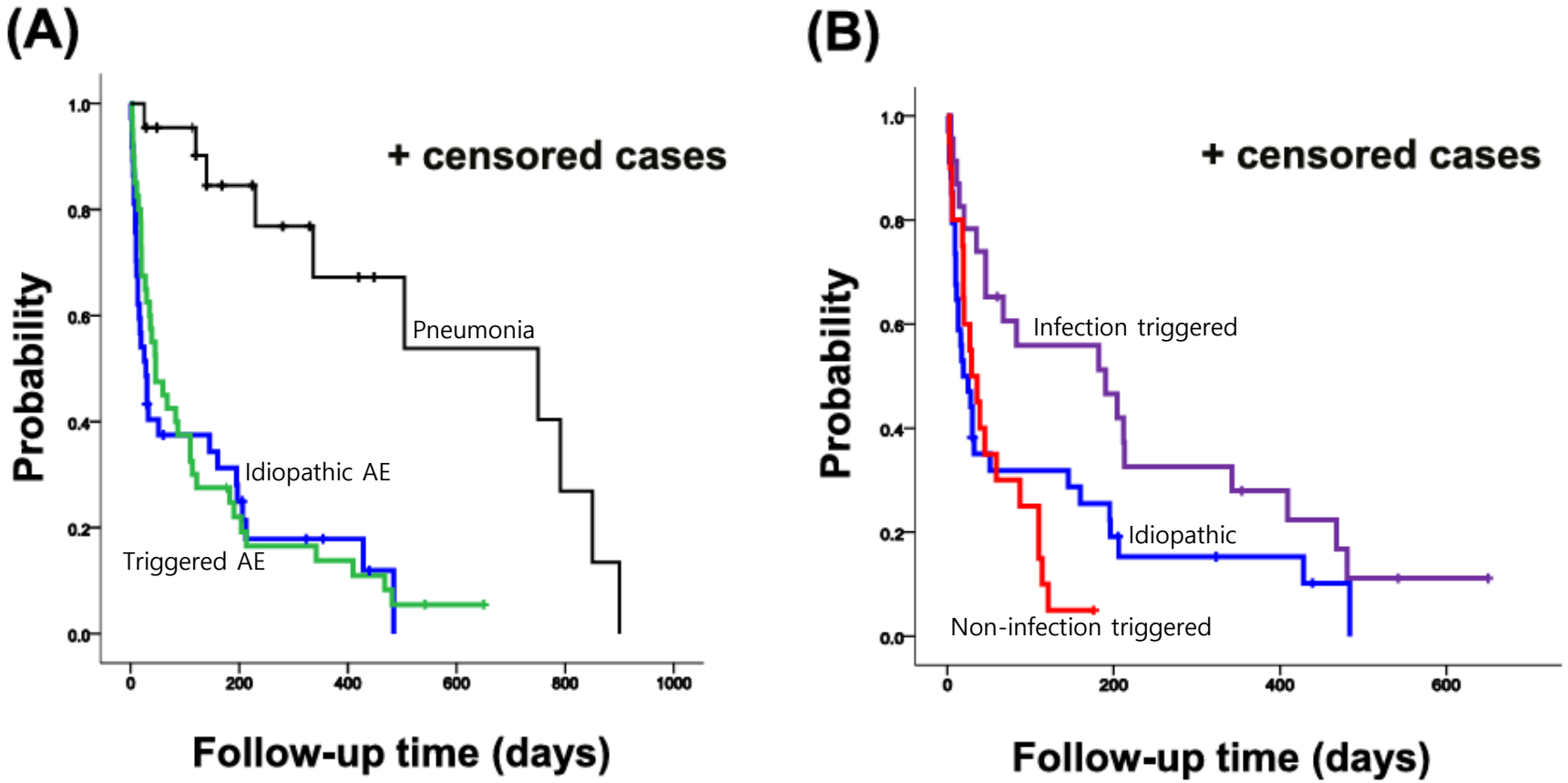
Sci Rep. 2022 May 25;12(1):8817.

Prognosis is different?



Respir Res. 2019 Dec 18;20(1):287.

Prognosis is different?



Respir Res. 2019 Dec 18;20(1):287.

Prognosis is different?

Table 6 Mortality and cause of death

	Total *n* = 79	Idiopathic *n* = 34	Infection-triggered *n* = 25	Non-infection-triggered *n* = 20	*p*
Mortality					
14 days	22 27.84%	14 41.18%	4 16%	4 20%	*0.049*
28 days	37 46.83%	22 64.71%	5 20%	10 50%	*0.029*
56 days	41 51.89%	21 61.76%	8 32%	12 60%	*0.025*
90 days	50 63.29%	24 70.59%	11 44%	15 75%	*0.022*

Respir Res. 2019 Dec 18;20(1):287.

Summary

- Infection may play a role in exacerbation of ILD
- BAL may be useful in patients at risk of opportunistic infection
- Steroid may be useful in patients with triggered exacerbation of ILD
- Prognosis of infection-triggered exacerbation of ILD may be better than idiopathic exacerbation