IPF 급성악화의 진단과 치료

울산대학교병원

제갈양진

42/M

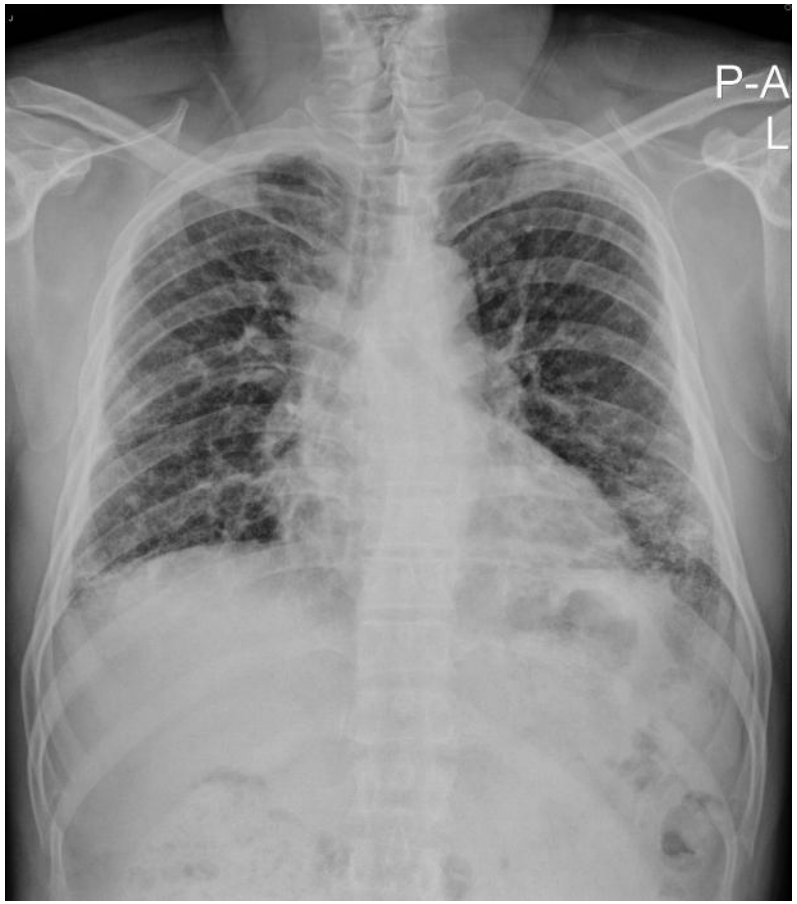
20PY exsmoker 5-6개월 전 금연

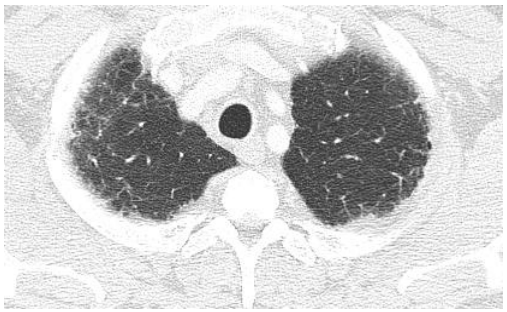
2년 전부터 마른기침

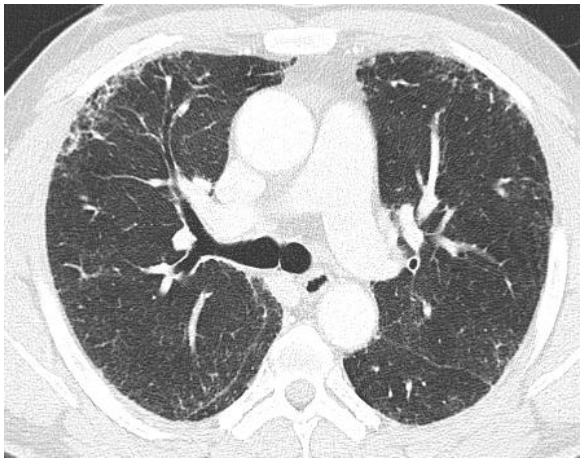
5-6개월 전 부터 호흡곤란

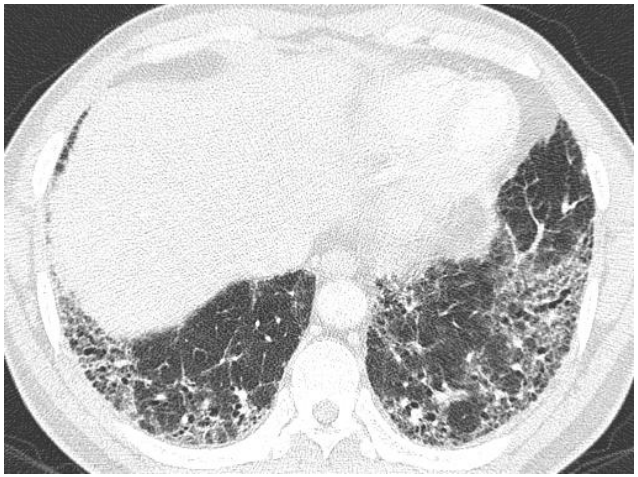
Inspiratory crakles on BLLF

FVC 83%, TLC 75%, DLco54%



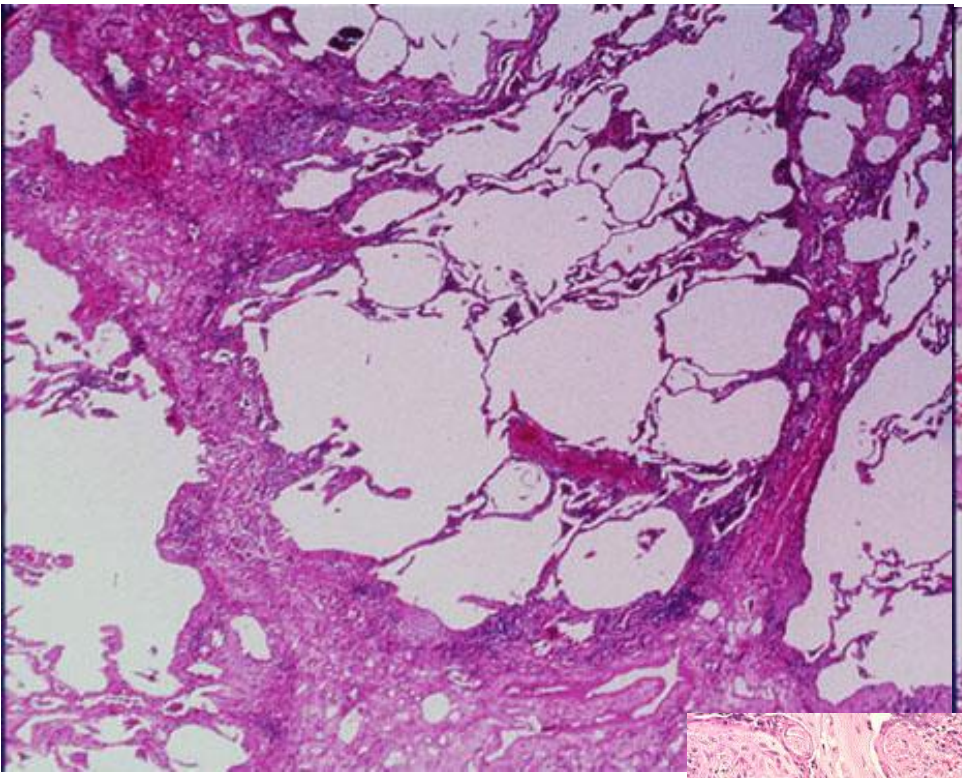


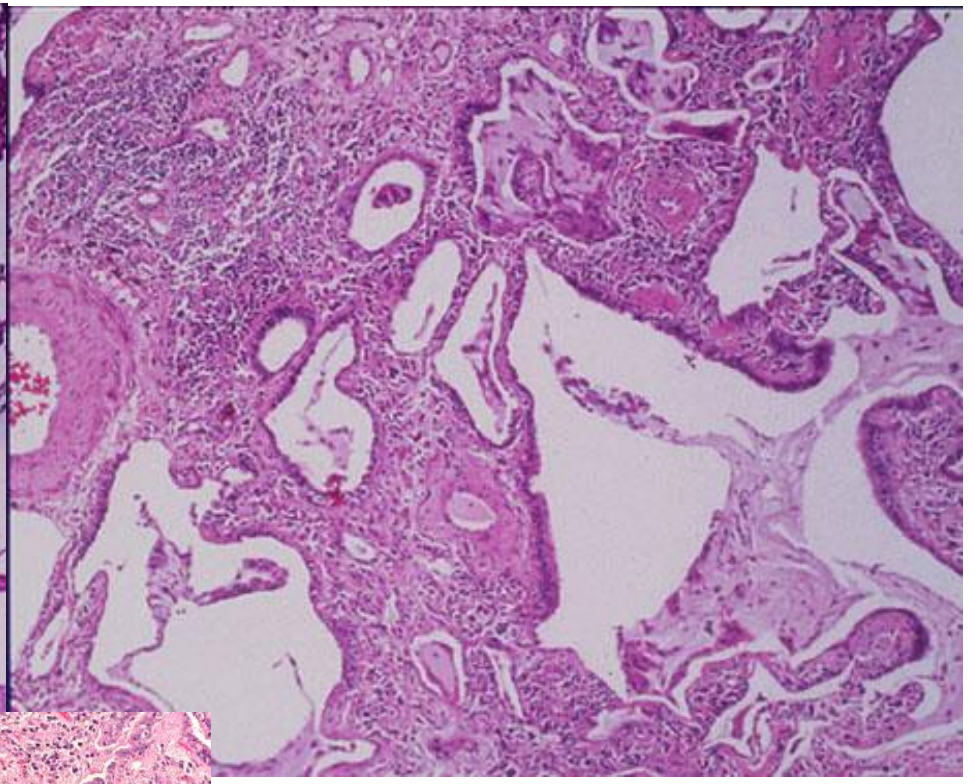


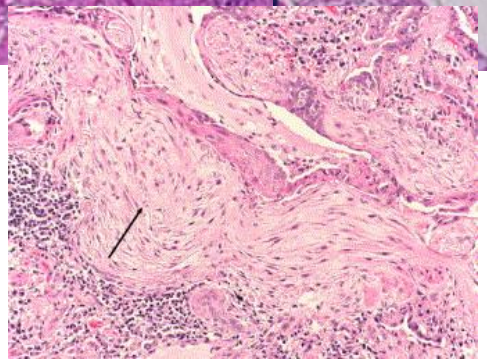


2010-11-10

Pathology



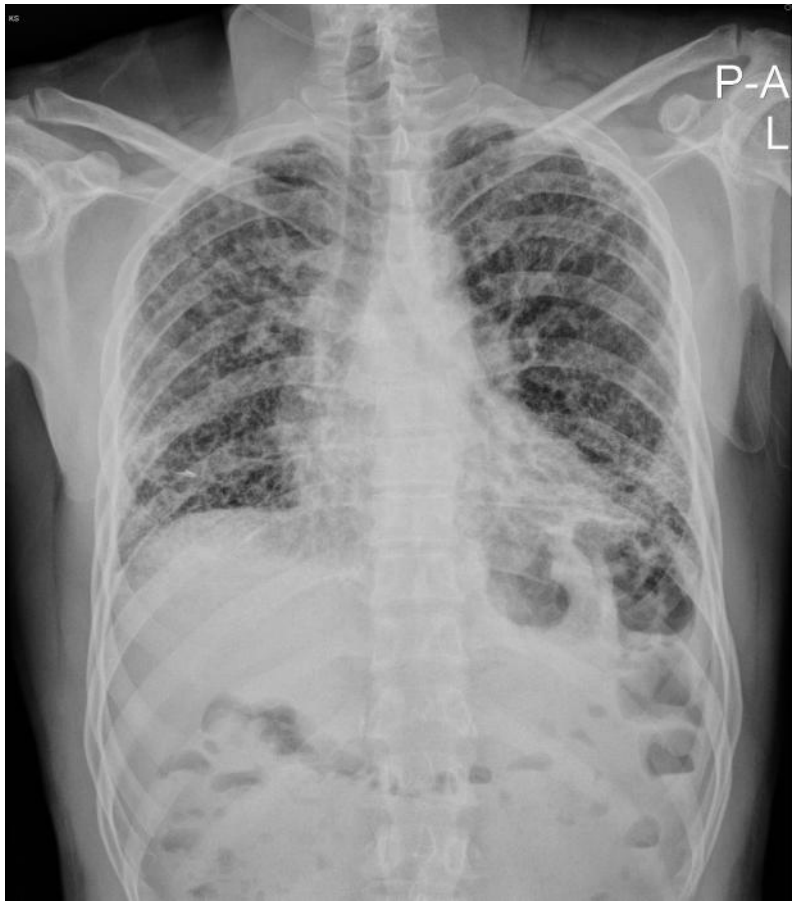




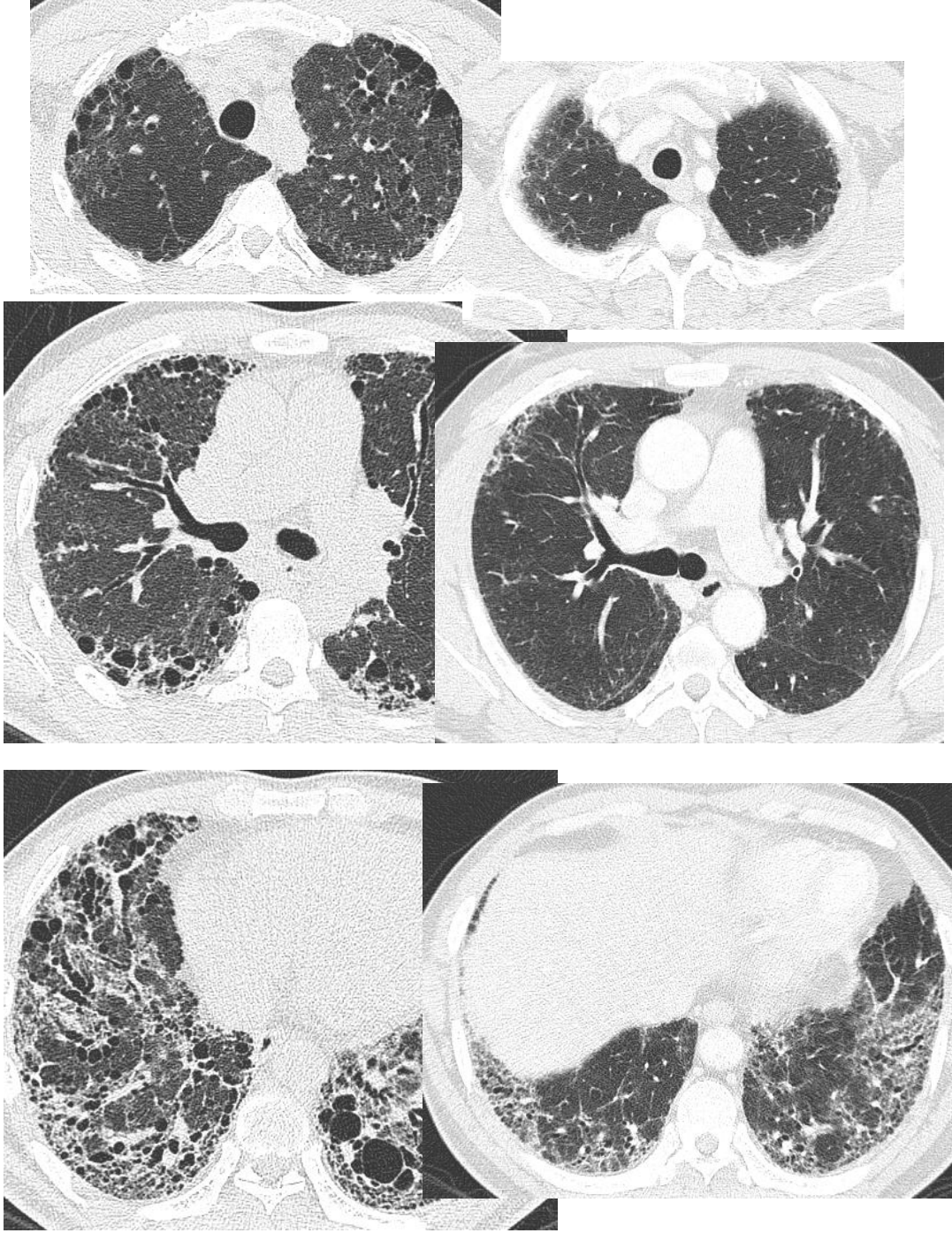
UIP

- 2010년 12월 16일 Biopsy 상 UIP 이기는 하나 CT 상 honeycombing 이 심하지 않아 PD + AZAT 시작함
- 3개월 후 CT , PFT 악화되어 tapering 중 Follow up loss

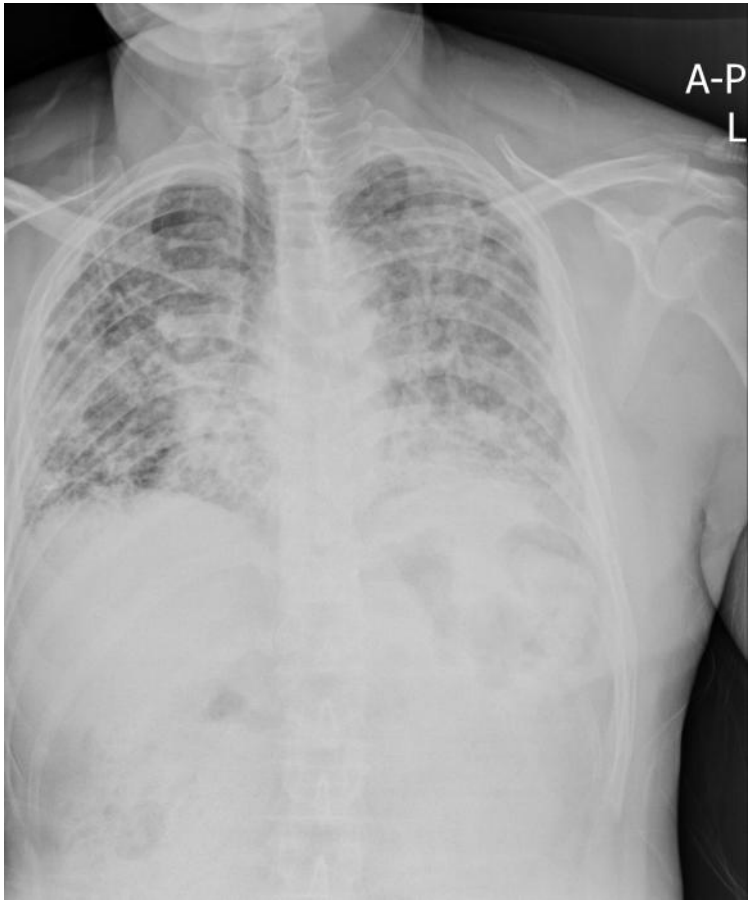
2년 후 서서히 악화되는
호흡곤란



2012-01-22



6개월 후 -10일전부터
시작된 호흡곤란



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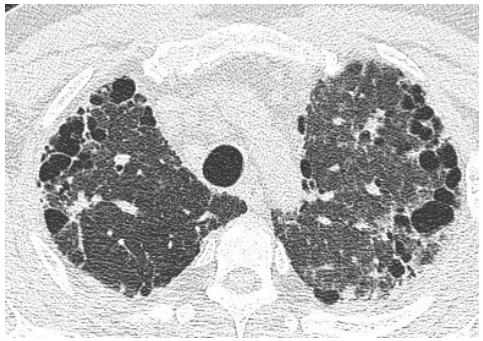
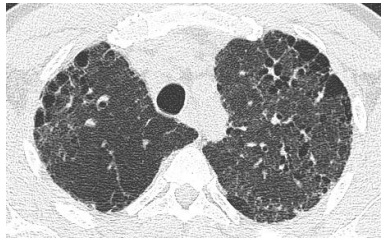
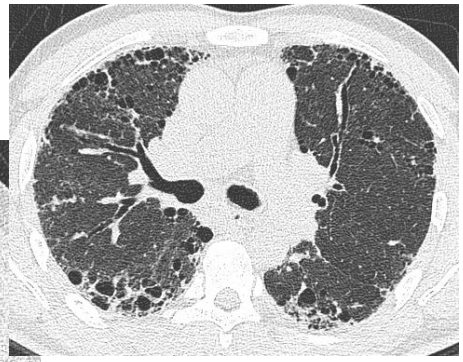
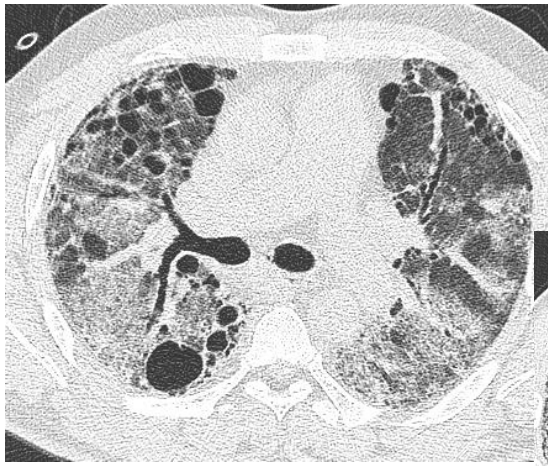
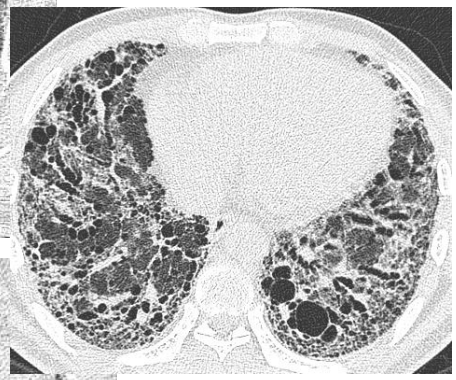
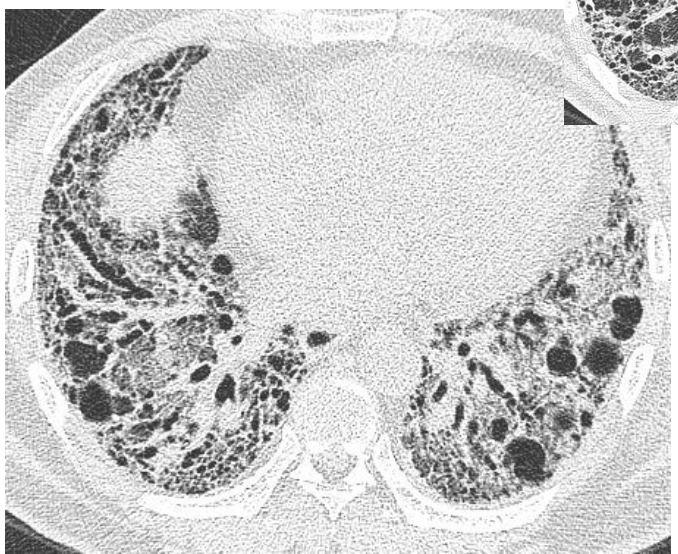












ABGA

7.437-46.3-45.3-29.9-81.4%

(1Month ago 7.366-39.6-63.3-22.2-89.4%)

BAL

Neutrophil 37%

Lymphcyte 32%

Macrophage 31%

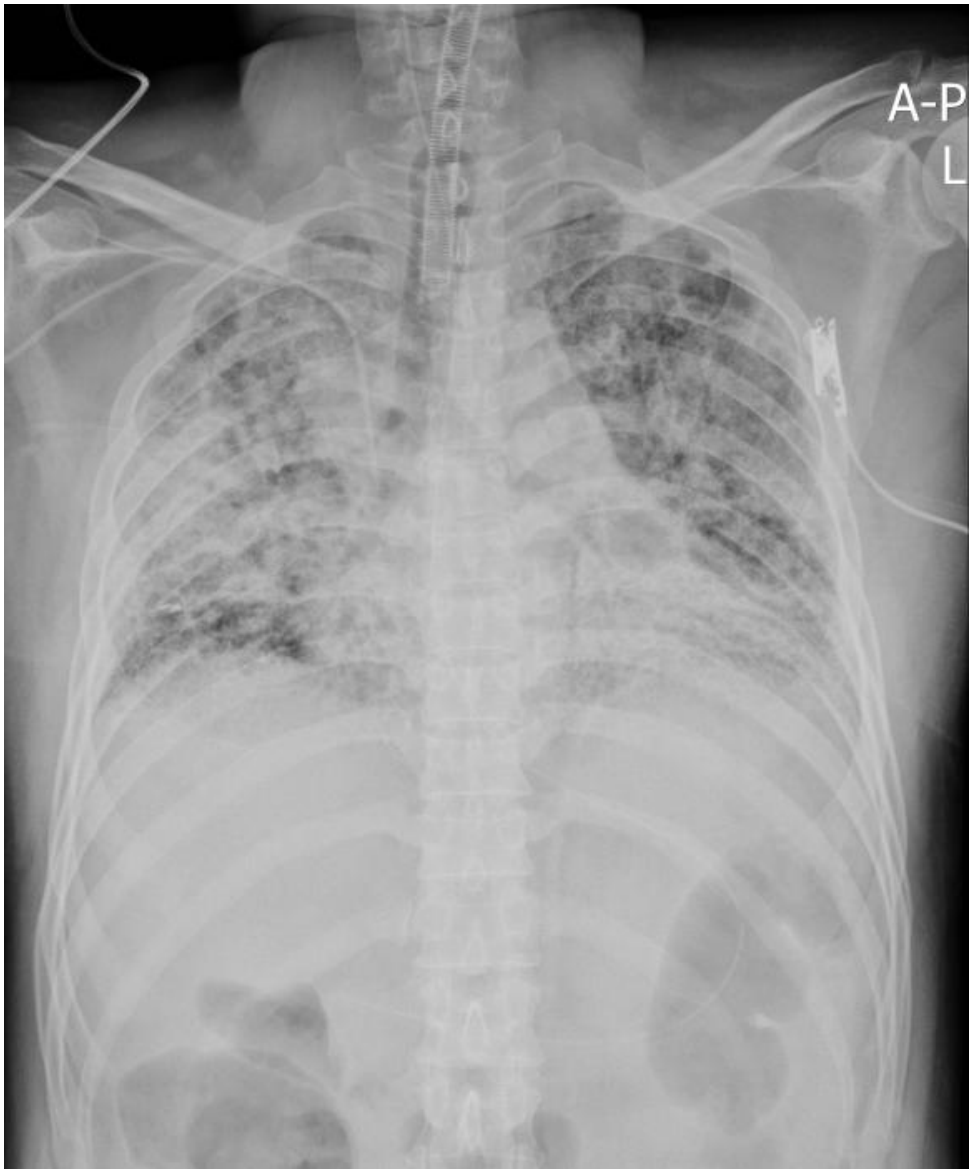
Bacterial culture (-)

Respiratory virus PCR (-)

CMV(-)

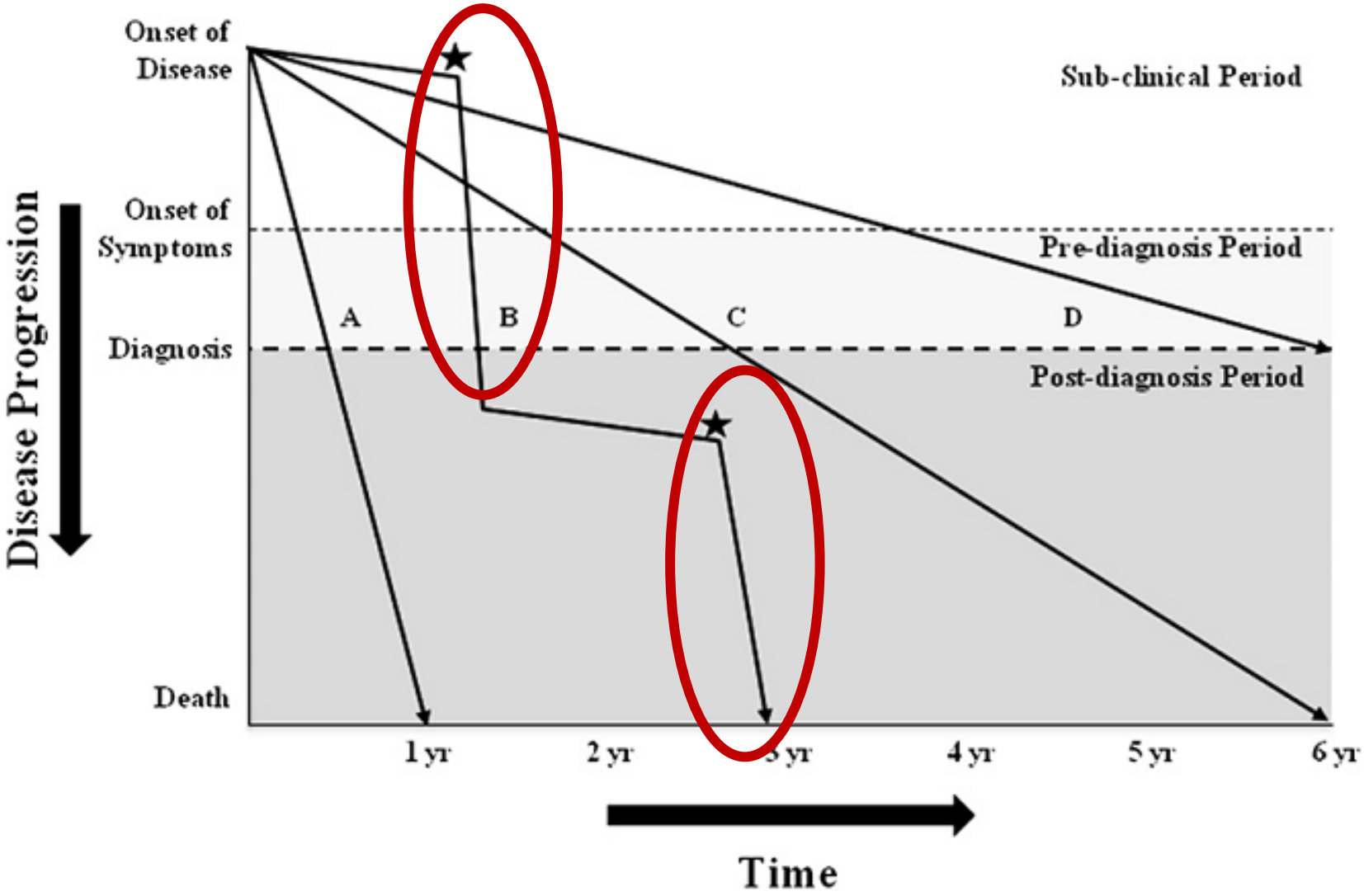
Galactomannan (-)

Pneumocysitis jiroveci(-)



2012-06-26

Clinical courses of IPF



Ley et al. Am J Respir Crit Care Med 2011;183:431-40

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.

(1) Exacerbation of dyspnea within a few weeks

(2) Newly developing diffuse pulmonary infiltrates on chest x-ray films

(3) deterioration of hypoxemia

(4) Absence of apparent infectious agents

Kondoh et al. Chest 1993;103:1801-12

Diagnostic criteria by Collard et al.

Previous or concurrent **diagnosis of IPF**

Unexplained worsening or development of **dyspnea within 30 days**

HRCT with **new bilateral ground-glass abnormality** and/or **consolidation** superimposed on a background reticular or honeycomb pattern consistent with **usual interstitial pneumonia pattern**

No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage

Exclusion of alternative causes, including the following:

- Left heart failure
- Pulmonary embolism
- Identifiable cause of acute lung injury

Collard et al. Am J Respir Crit Care Med 2007;176:636-43

Incidence of *AE* in IPF

Incidence of acute exacerbation of IPF reported in randomized controlled clinical trials

Name	Pirfenidone Azuma[14]		Pirfenidone Taniguchi[15]			CAPACITY1[16]			CAPACITY2[16]	
AEx Criteria	JRS†		JRS†			Collard + Pao_2			Collard + Pao_2	
Duration	9 mo		52 wk			77 wk			77 wk	
	PR	Control	PR-High	PR-Low	Control	PR-High	PR-Low	Control	PR-High	Control
No.	72	35	108	55	104	174	87	174	171	(173)
AEx (%)	0	13.9	5.6	5.5	4.8	1.1	1.1	1.7	1.2	0.6

Name	Kubo[17]		IFIGENIA[18]		INSPIRE[19]		BUILD-1[20]		BUILD-3[21]		Imatinib[22]	
AEx Criteria[a]	[b]		Respiratory failure		Acute respiratory failure		Acute decom-pensation of IPF		Acute exac-erbation of IPF		Acute worsening of IPF	
Duration	3 y		1 y		537 d		12 mo		20 mo		96 wk	
	AC	Control	NAC	Control	IF-g	Control	Bos	Control	Bos	Control	Ima	Control
No.	23	33	80	75	551	275	71	83	407	209	59	60
AEx (%)	16	21	6	1	2	—	1.4	3.6	4.7	2.9	8.5	1.7

Kim DS et al. Clin Chest Med 2012;33:59-68

Incidence of AE in IPF

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. Eur Respir J 2011;37:356-63

Etiology of RD

Aetiology	Cases n (%)#	Documented organisms¶ (n)
Total RD	163 (35.4)	
Bilateral lesions	140 (30.4)	
AE	90 (19.5)	
Definite	57 (12.4)	
Suspected	33 (7.2)	
Infection	37 (8.0)	
Definite	21 (4.6)	
Bacterial	9 (2.0)	*Streptococcus pneumoni*
		MRSA (1)
		Haemophilus influenzae (4)
		Legionella spp. (1)
		Klebsiella pneumoniae (1)
Viral	7 (1.5)	CMV (7; 2 mixed infections with RSV or *Pneumocystis jiroveci*)
		Influenza virus (1)
		RSV (1)
Fungal	2 (0.4)	*Candida* spp. (1)
		Aspergillus spp. (1)
Parasitic	2 (0.4)	*Pneumocystis jiroveci* (2)
Mycobacterial	1 (0.2)	*Mycobacterium tuberculosis* (1)
Suspected+	16 (3.5)	
Heart failure	5 (1.1)	
PTE	2 (0.4)	
AEP	1 (0.2)	
Uncertain§	5 (1.1)	
Focal lesion	23 (5.0)	
Pneumothorax	9 (2.0)	
Infection	14 (3.0)	*Klebsiella pneumoniae* (1)
		Klebsiella oxytoca (1)
		Streptococcus pneumoniae (1)

Total RD	163 (35.4)
AE	90 (19.5)
Infection	37 (8.0)
Definite	21 (4.6)
Bacterial	9 (2.0)

Song et al. Eur Respir J 2011;37:356-63

Pathogenesis

- *Accelerated IPF*
  - epithelial damage
  - cytokines
  - cellular inflammation
  - matrix metaloproteinase
  - coagulation abnormality
- *Triggering factor*
  - viral infection
  - silent aspiration
  - sequel of direct infective insults

Plasma biomarkers

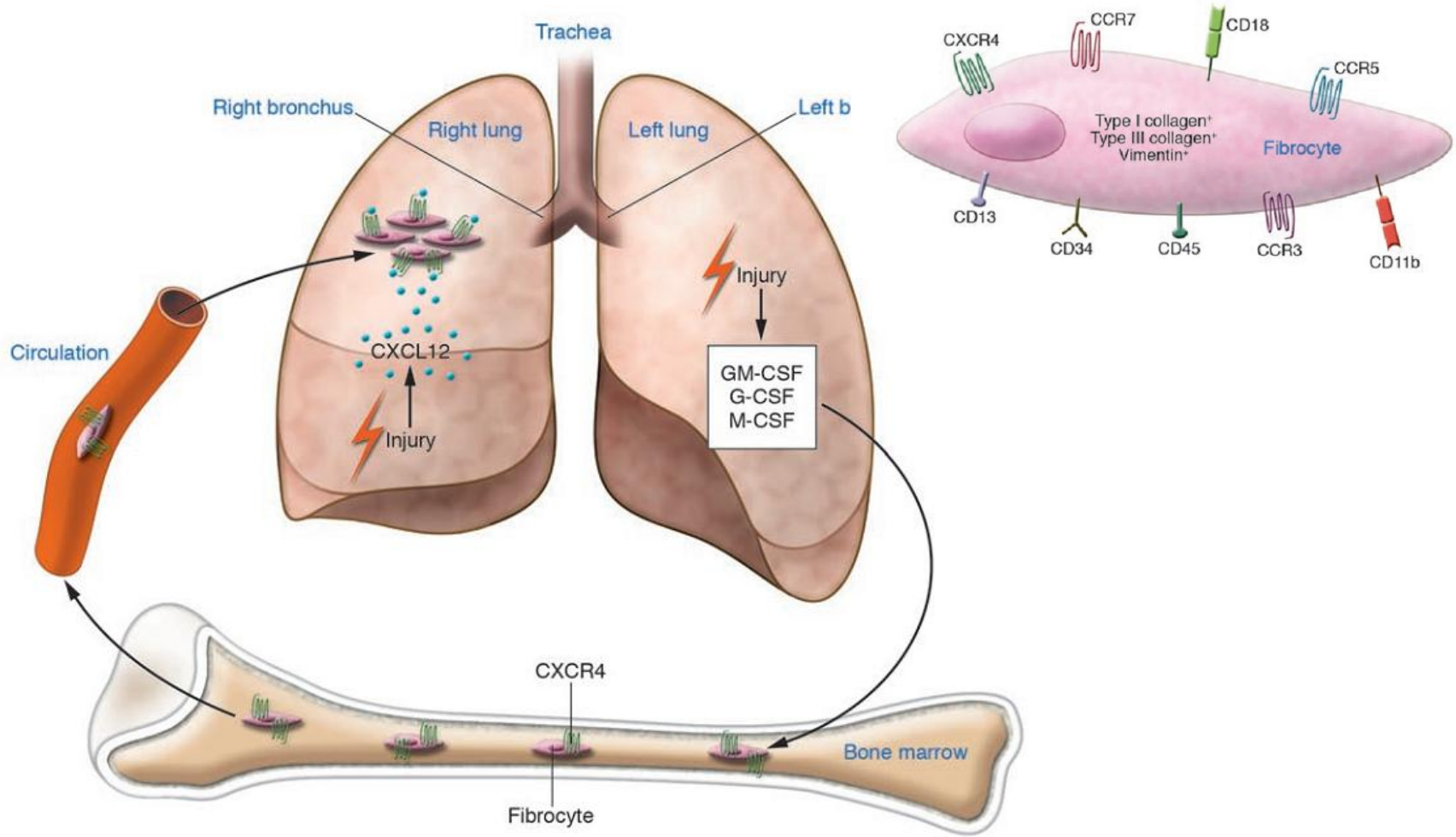
Table 3. *Plasma biomarkers in acute exacerbation of IPF vs. ALI*

Variable	AEx IPF *n* = 47	Early ALI *n* = 10	Late ALI *n* = 20	*P* Value AEx IPF vs. Early ALI	*P* Value AEx IPF vs. Late ALI
KL-6, units	1,791 (1,155, 2,866)	535 (163, 740)	595 (357, 1198)	<0.0001	<0.0001
SP-D, ng/ml	361 (228, 586)	121 (83, 456)	117 (85, 265)	0.03	0.0004
RAGE, pg/ml	366 (208, 690)	1,060 (511, 1,855)	531 (286, 864)	0.01	0.19
Von Willebrand factor, %	89 (59, 180)	205 (160, 275)	129 (96, 206)	0.008	0.11
IL-6, pg/ml	10 (6, 19)	307 (42, 1,451)	23 (11, 81)	0.001	0.03
Protein C, %	135 (93, 199)	54 (37, 69)	94 (64, 107)	<0.0001	0.0002
Thrombomodulin, ng/ml	5.0 (3.2, 7.0)	9.0 (6.8, 10.6)	8.5 (7.3, 13.1)	0.002	<0.0001
PAI-1, ng/ml	70 (49, 85)	97 (75, 109)	51 (41, 62)	NP	NP

NP, not performed (due to insignificant *P* value on Kruskal-Wallis test across all 3 groups). Values are median (25th percentile, 75th percentile).

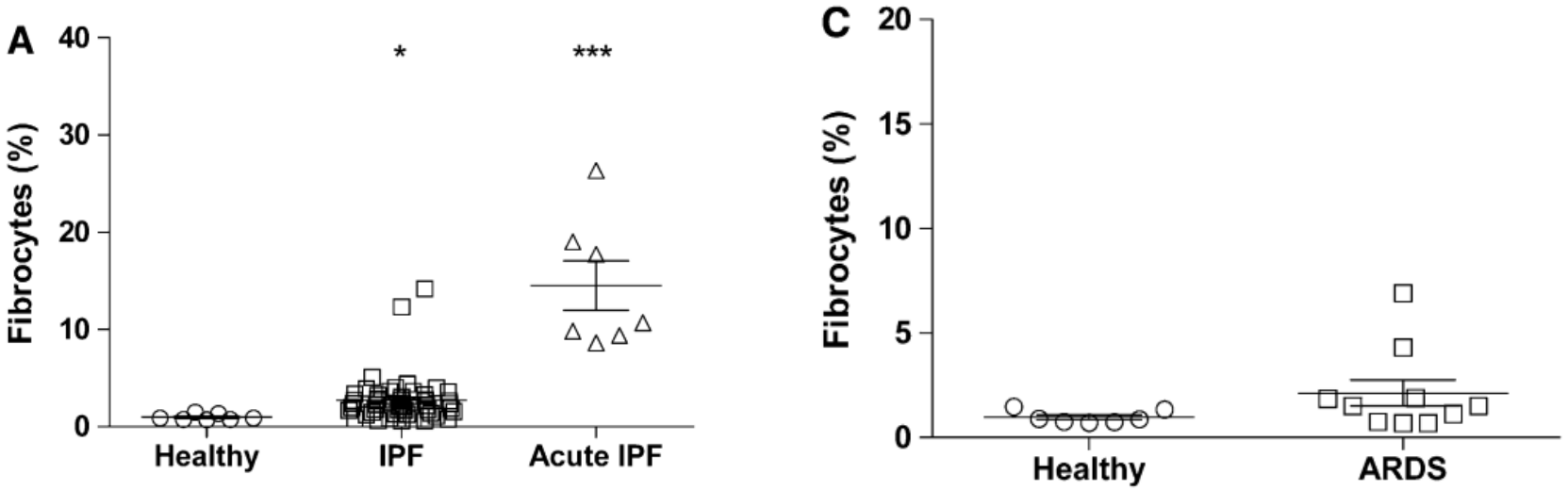
Collard et al. Am J Physiol Lung Cell Mol Physiol 2010;299:L3-7

Fibrocyte



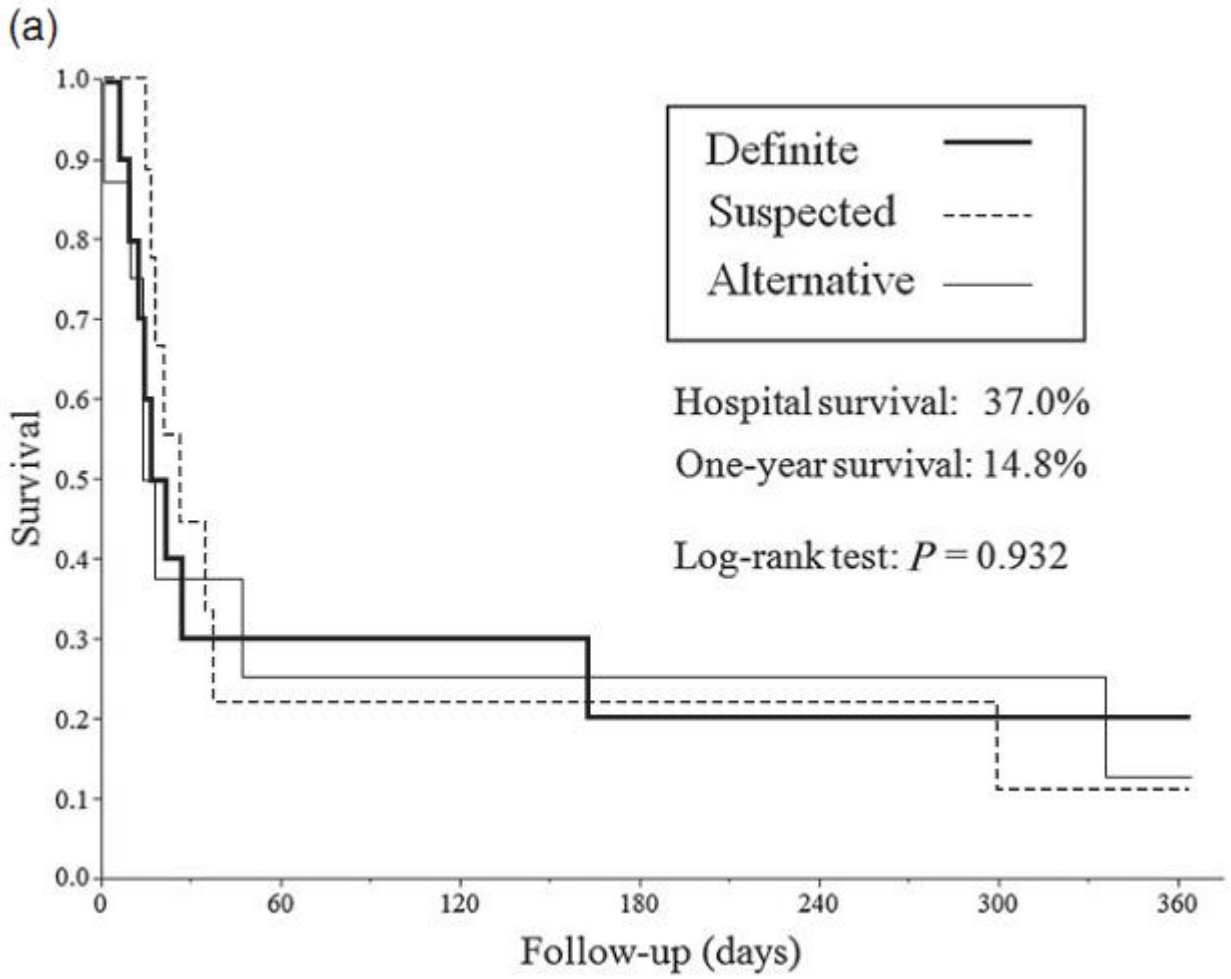
Strieter et al J. Clin. Invest 2007

Fibrocyte



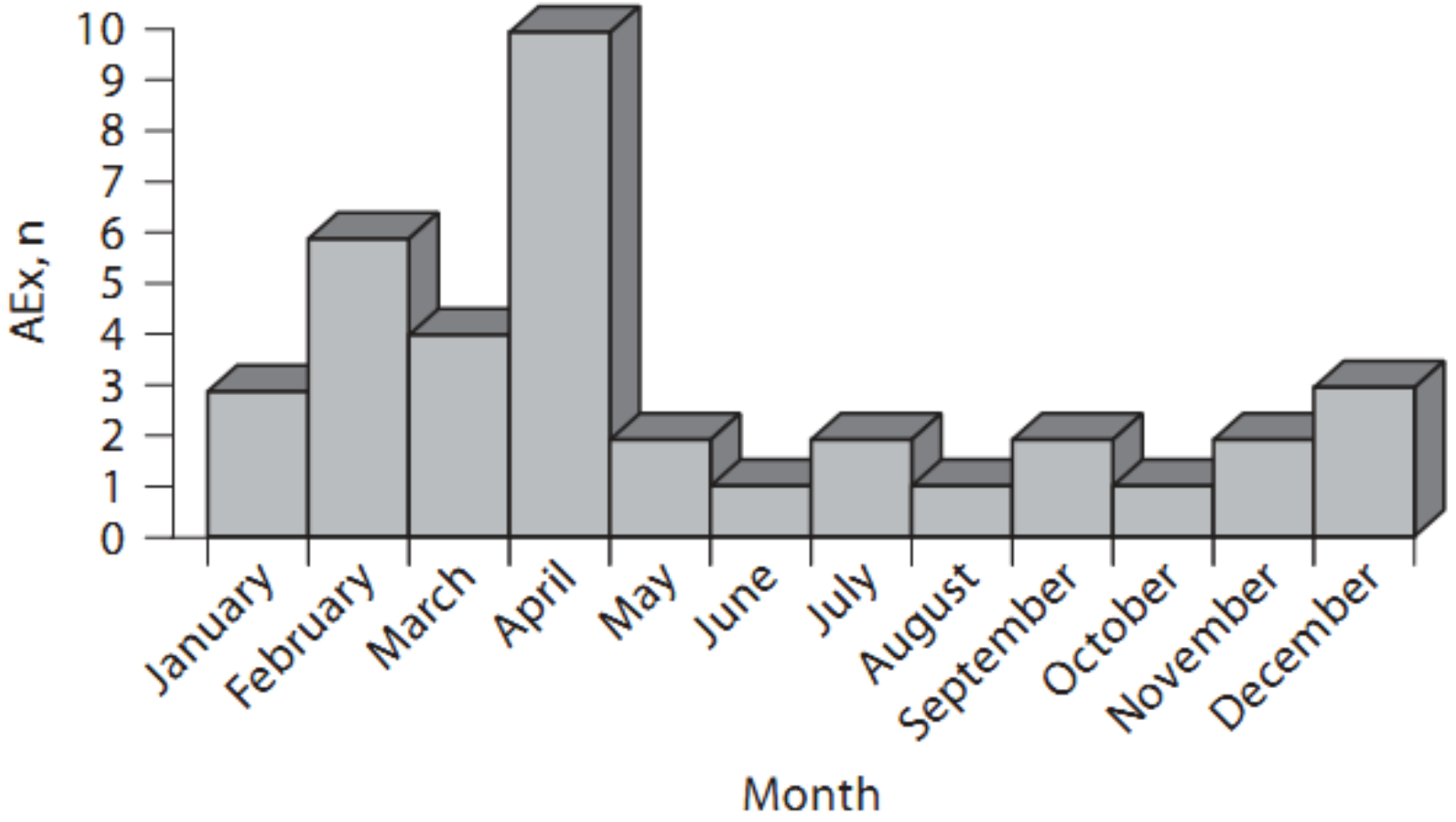
Moeller et al. Am J Respir Crit Care Med 2009;179:588-94

Survival based on etiology



Huie et al. Respirology 2010;15:909-17

Variation in the occurrence of AE



Simom-Blancal et al. Respiration 2012;83:28-35

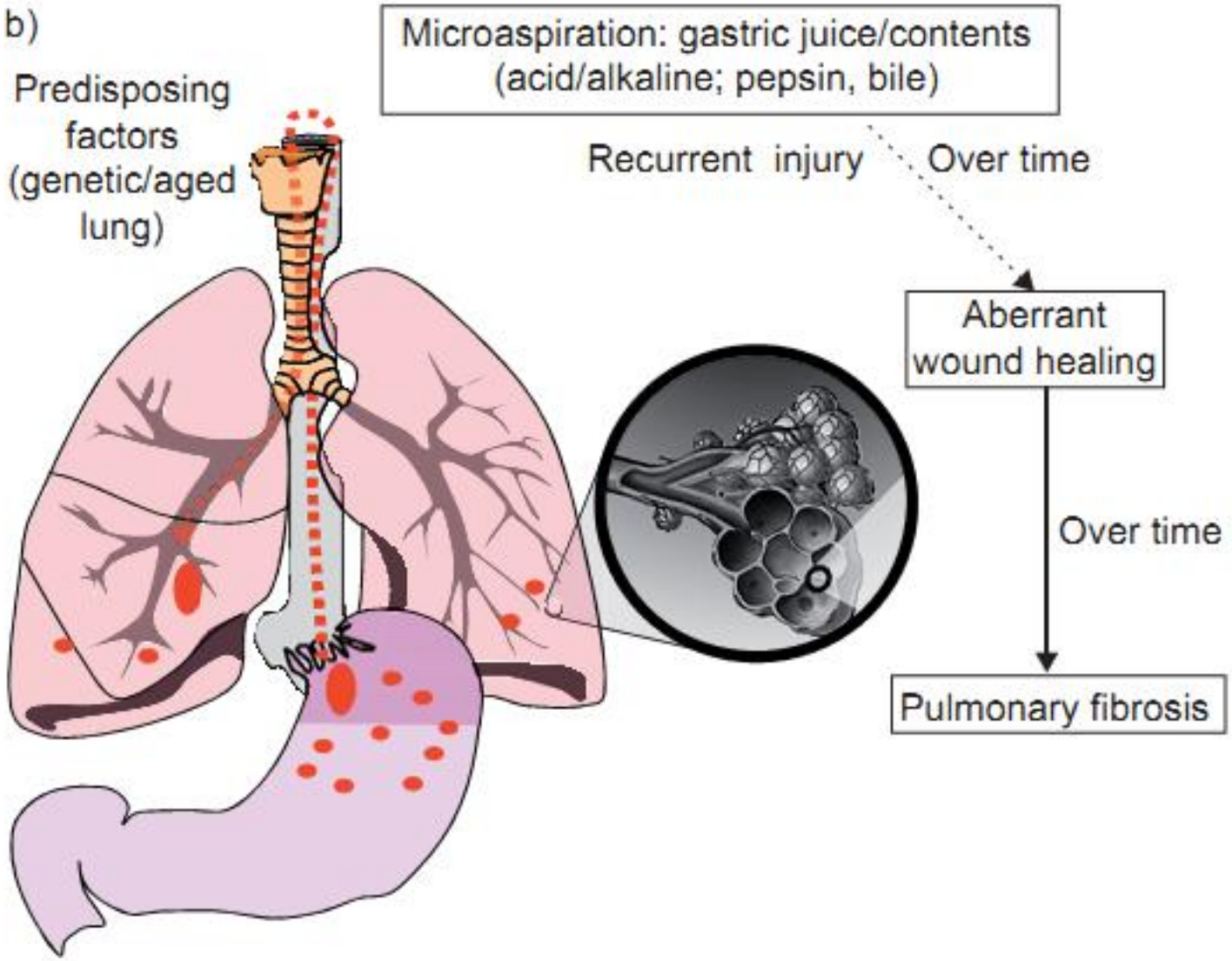
Viral infection

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)	–

Wootton et al. Am J Respir Crit Care Med 2011;183:1698-702

Microaspiration



Raghu et al. Eur Respir J 2012;39:242-5

BAL pepsin

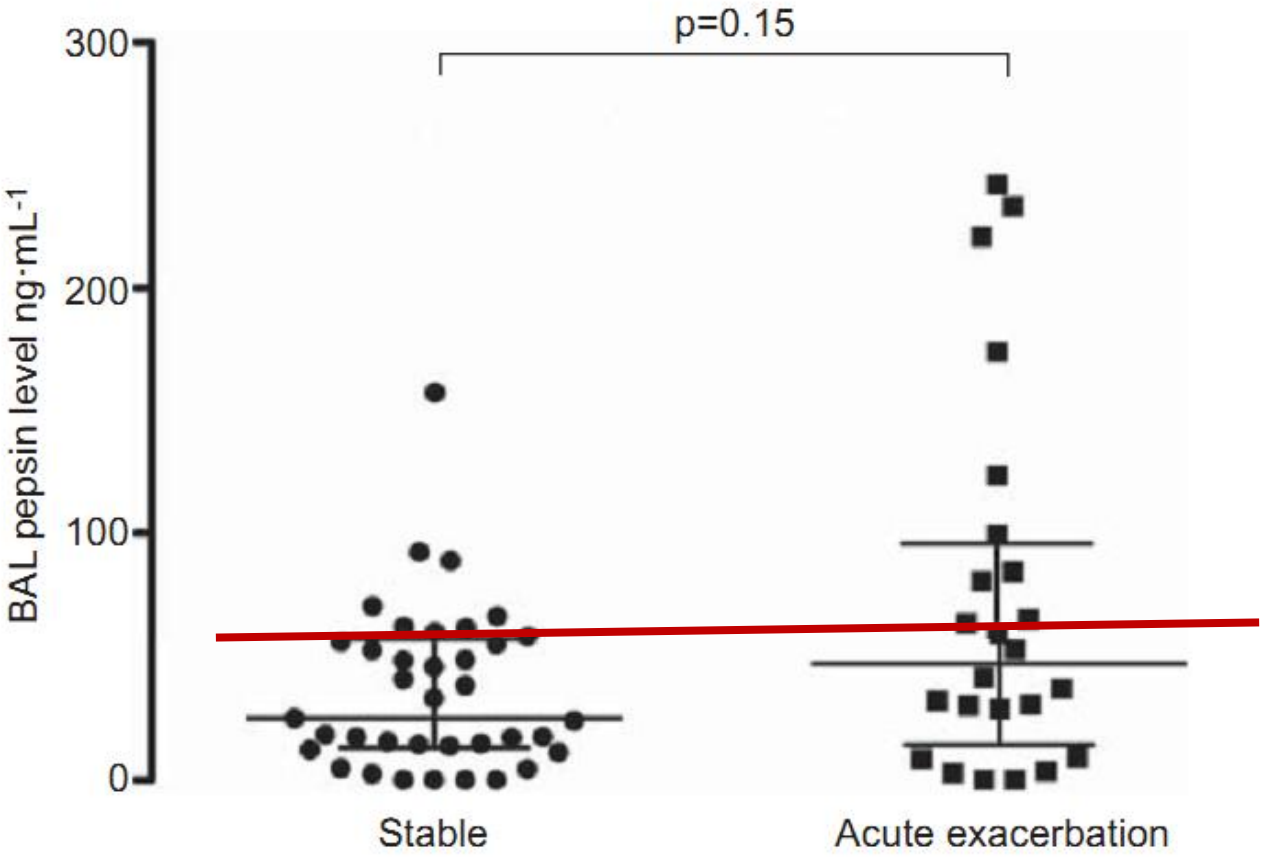


FIGURE 1. Bronchoalveolar lavage (BAL) pepsin levels in patients with stable idiopathic pulmonary fibrosis (IPF) compared with acute exacerbation of IPF. Horizontal lines represent median, 25th percentile and 75th percentile.

Lee et al. Eur Respir J 2012;39:352-8

AE after cancer treatment

Table 3. Incidence of Idiopathic or Iatrogenic Acute Exacerbation of IIPs after Cancer Treatment by Various Modalities

Treatment		AE (n)	(%)	Death (n)	(%)
Chemotherapy	n= 50 §	10	20.0	7	14.0
Chemoradiotherapy	n= 7 §	3	42.9	1	14.3
Surgery	n= 35 §	8	22.9	3	8.6
Radiation only	n= 6 §	1	16.7	1	16.7
Total of therapy group	n= 88	20†	22.7	12	13.6
BSC only	n= 32	10	31.3	10	31.3
Total	n=120	30	25.0	22	18.3

Minegishi et al. Intern Med 2009;48:665-72

Risk factors

- Racial difference
- Pulmonary function
- Smoking
- Pulmonary HTN

Incidence of AE in IPF

Incidence of acute exacerbation of IPF reported in randomized controlled clinical trials

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AEx (%)	0	13.9	5.6	5.5	4.8	1.1	1.1	1.7	1.2	0.6

Name	Kubo[17]		IFIGENIA[18]		INSPIRE[19]		BUILD-1[20]		BUILD-3[21]		Imatinib[22]	
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Duration	3 y		1 y		537 d		12 mo		20 mo		96 wk	
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No.	23	33	80	75	551	275	71	83	407	209	59	60
AEx (%)	16	21	6	1	2	—	1.4	3.6	4.7	2.9	8.5	1.7

Kim DS et al. Clin Chest Med 2012;33:59-68

Risk factors

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
Univariate Cox analysis		
Age	1.021 (0.997–1.047)	0.093
Male sex	0.921 (0.563–1.506)	NS
Smoking	0.629 (0.407–0.972)	0.037
PFT % pred		
FVC	0.975 (0.960–0.989)	0.001
$D_{L,CO}$	0.981 (0.967–0.994)	0.005
TLC	0.970 (0.953–0.987)	0.001
BAL		
Macrophages	0.991 (0.975–1.008)	NS
Lymphocytes	1.001 (0.977–1.025)	NS
Neutrophils	1.010 (0.989–1.031)	NS
Eosinophils	0.994 (0.929–1.064)	NS
CRP	0.786 (0.380–1.622)	NS
Steroids with/without cytotoxic agents[#]	1.045 (0.682–1.602)	NS
Multivariate Cox analysis[¶]		
Smokers	0.585 (0.342–1.001)	0.050
FVC % pred	0.979 (0.964–0.995)	0.011

Song et al. Eur Respir J 2011;37:356-63

Risk factors

TABLE 3 Risk factors at initial assessment for acute exacerbation

Parameter	HR (95% CI)	p-value
Univariate Cox analysis		
Age	1.023 (0.967–1.081)	0.435
Male	0.599 (0.250–1.434)	0.253
Body mass index	1.043 (0.939–1.159)	0.437
FVC % pred	0.999 (0.979–1.019)	0.928
FEV_1 % pred	1.008 (0.987–1.031)	0.438
$D_{L,CO}$ % pred	1.003 (0.967–1.041)	0.873
TLC % pred	0.982 (0.946–1.019)	0.347
LVEF %	0.989 (0.922–1.062)	0.767
RVSP mmHg	1.010 (0.977–1.042)	0.597
mP_{pa} mmHg	1.043 (0.977–1.114)	0.210
PH	2.217 (1.005–4.889)	0.041
P_{pcw} mmHg	0.938 (0.843–1.044)	0.241
Multivariate Cox analysis		
Male	0.587 (0.398–1.139)	0.182
PH	2.510 (1.119–5.628)	0.026

Judge et al. Eur Respir J 2012; 40: 93–100

Diagnosis

Previous or concurrent **diagnosis of IPF**

Unexplained worsening or development of **dyspnea** within 30 days

HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern

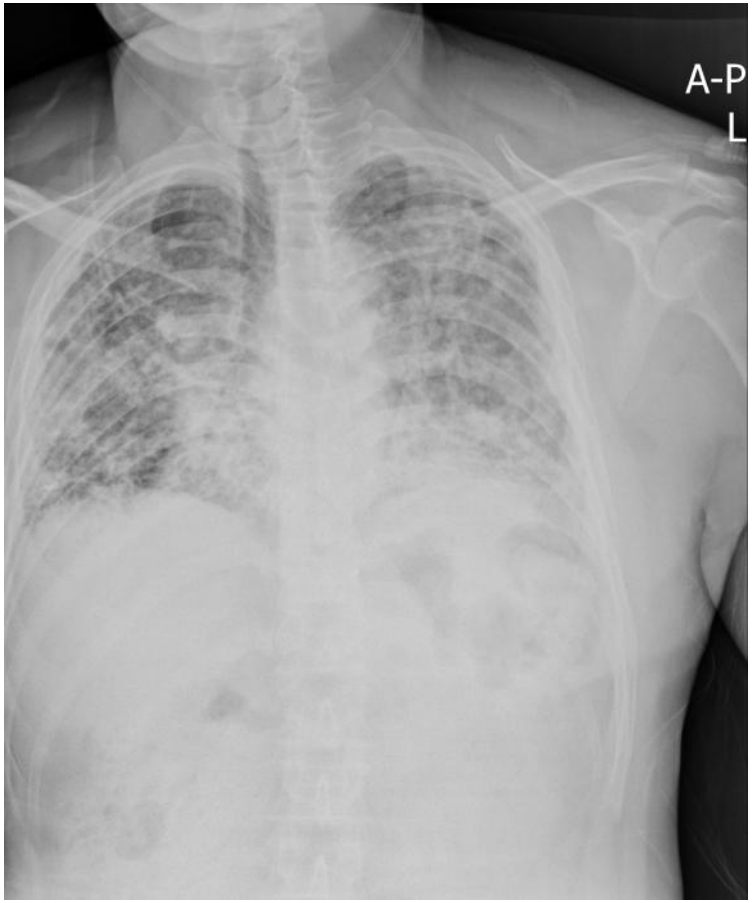
No evidence of pulmonary infection by **endotracheal aspirate or bronchoalveolar lavage**

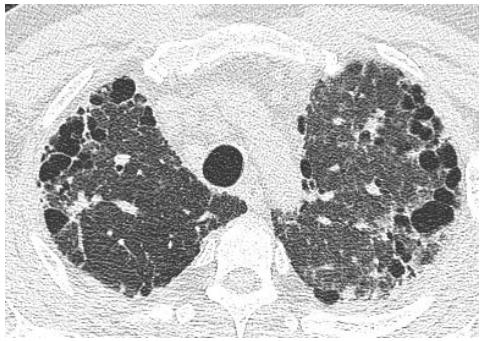
Exclusion of alternative causes, including the following:

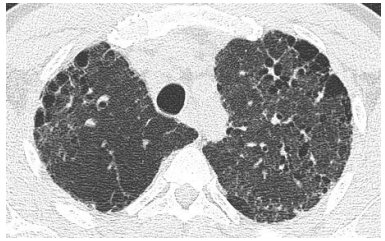
- Left heart failure ▷ **echoCG, proBNP**
- Pulmonary embolism ▷ **d-dimer, embolism CT**
- Identifiable cause of acute lung injury

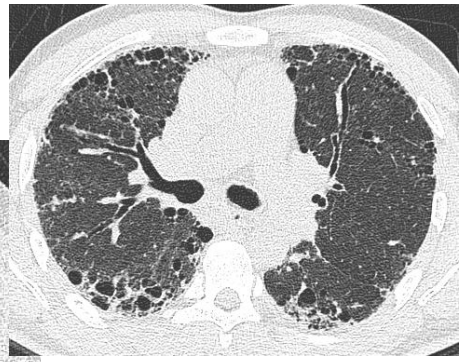
HRCT

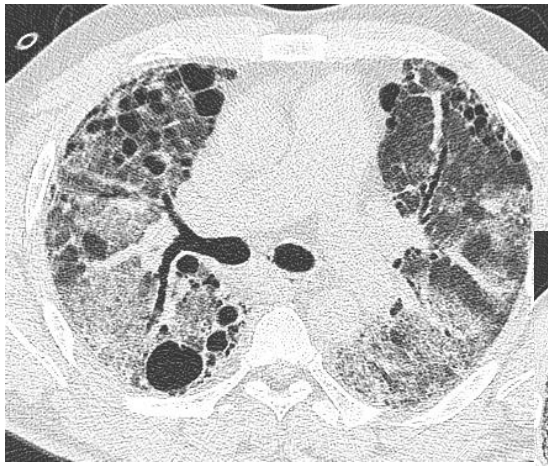
New bilateral ground-glass abnormality and/or consolidation

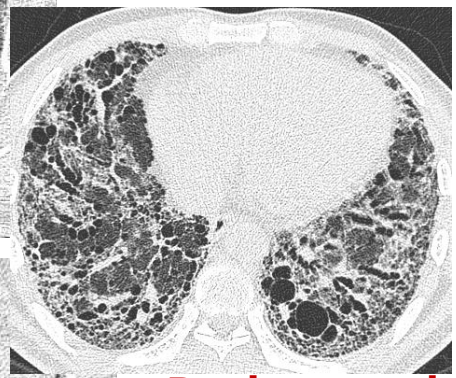


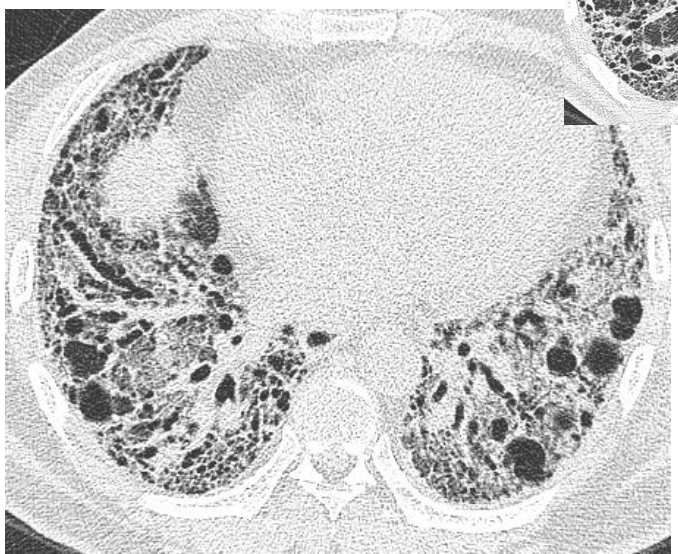






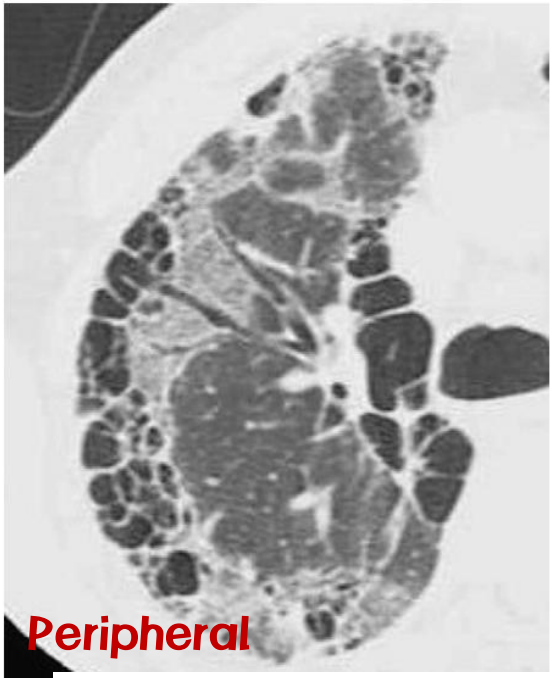


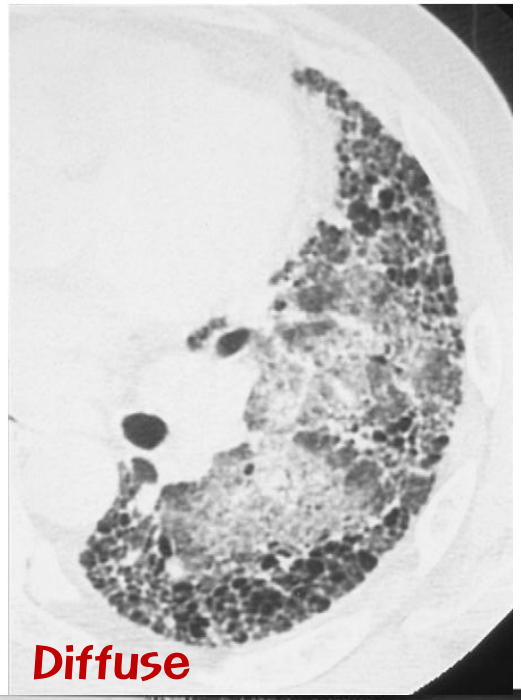


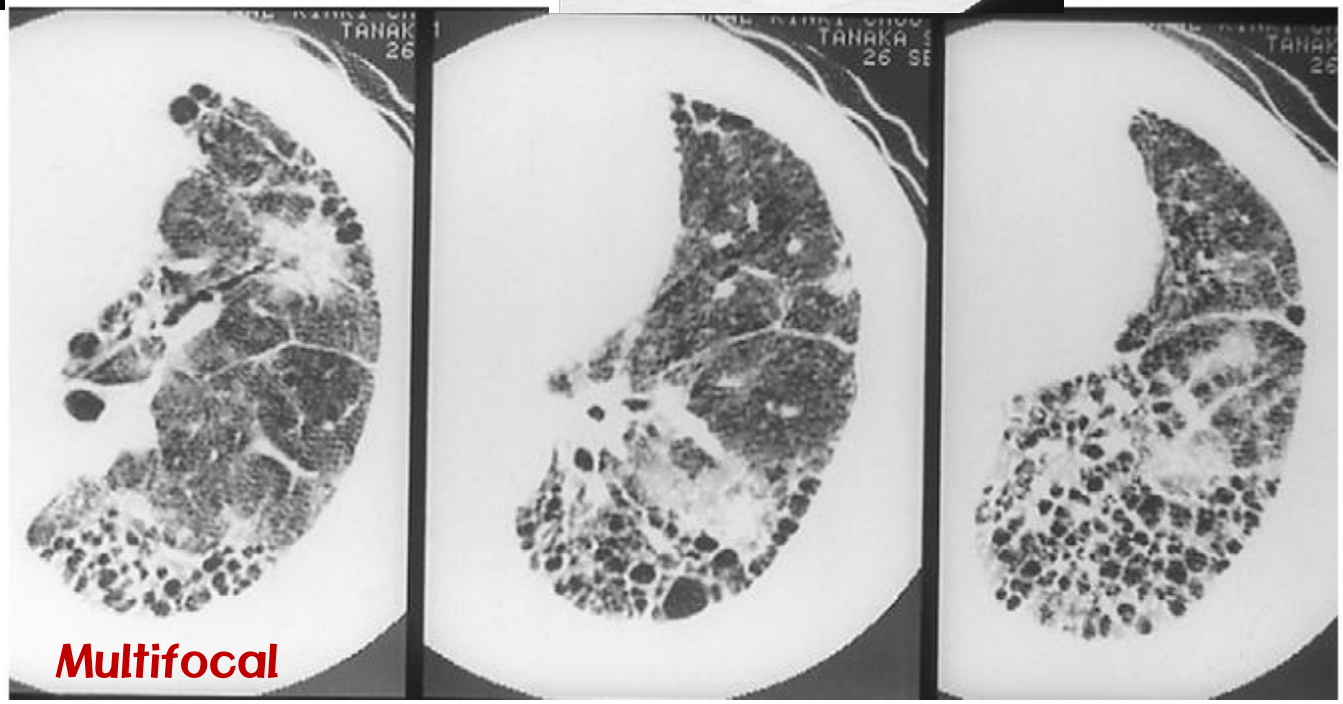


Background reticular or honeycomb pattern

HRCT

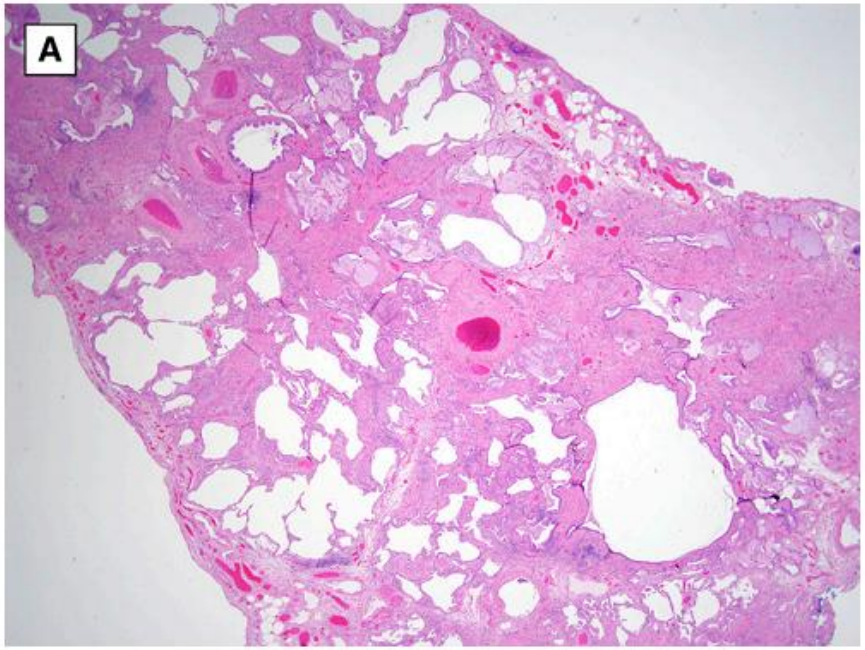




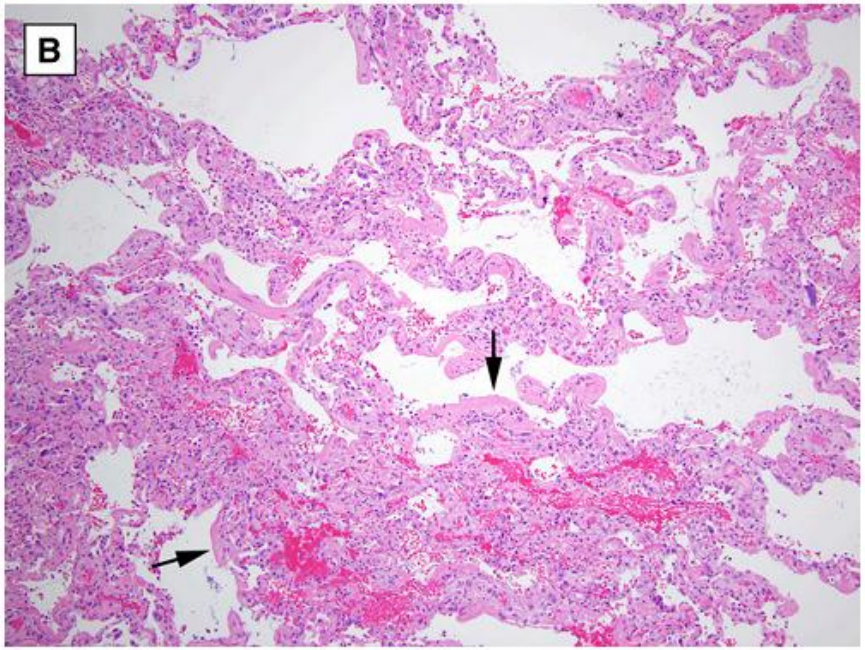


Akiraet al. Am J Respir Crit Care Med 2008;178:372-8

Pathology



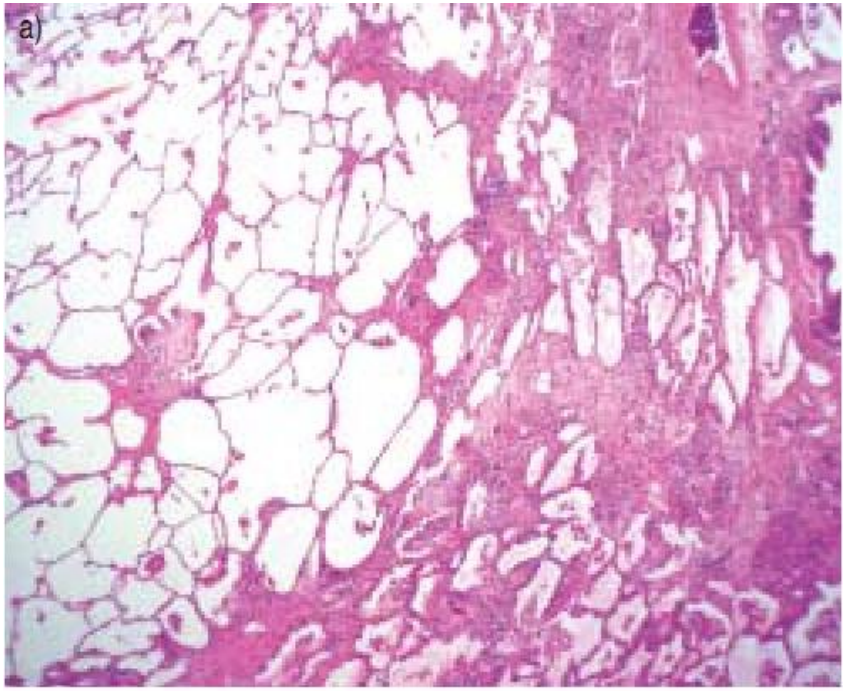
Typical UIP



Diffuse Alveolar Damage

Collard et al. Am J Respir Crit Care Med 2007;176:636-43

Pathology



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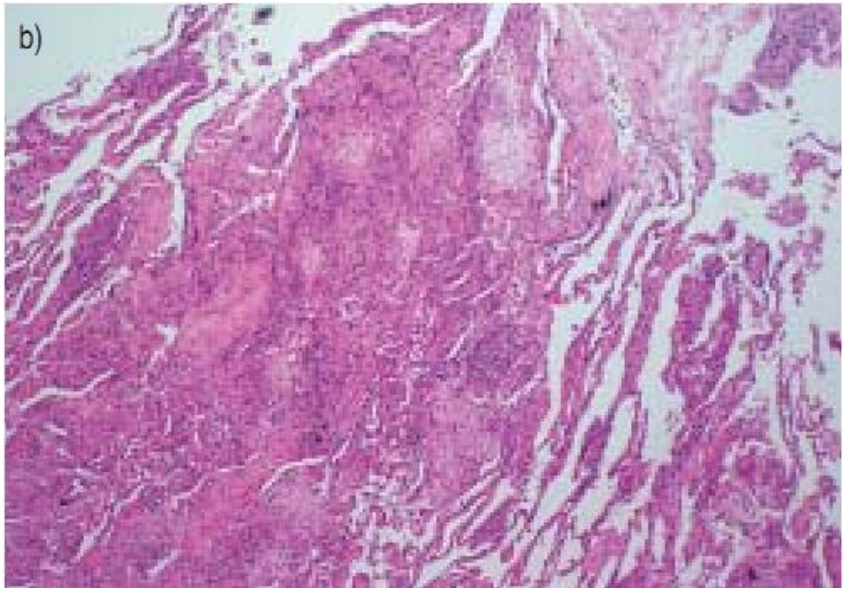


Organizing Pneumonia

DS Kim et al. Eur Respir J 2006; 27: 143–150

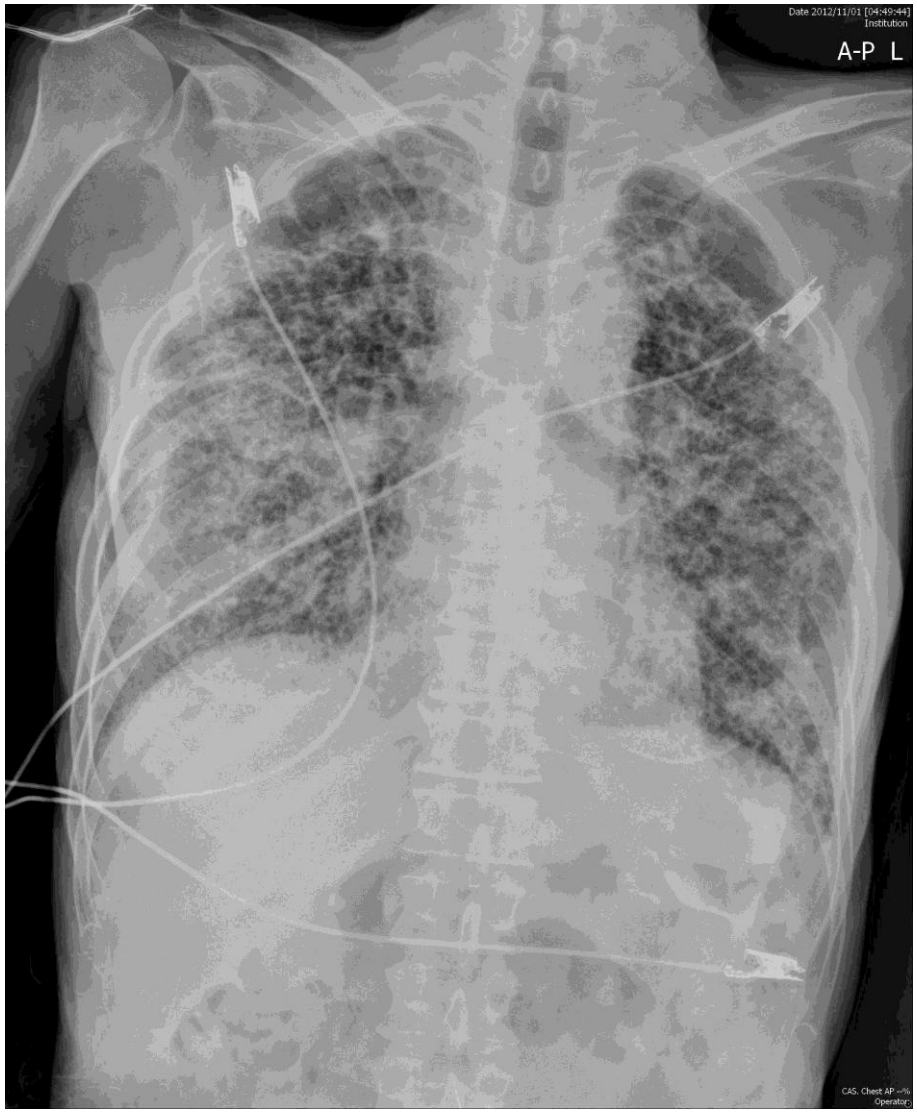
72/M

3년 전 IPF (clinically) 진단

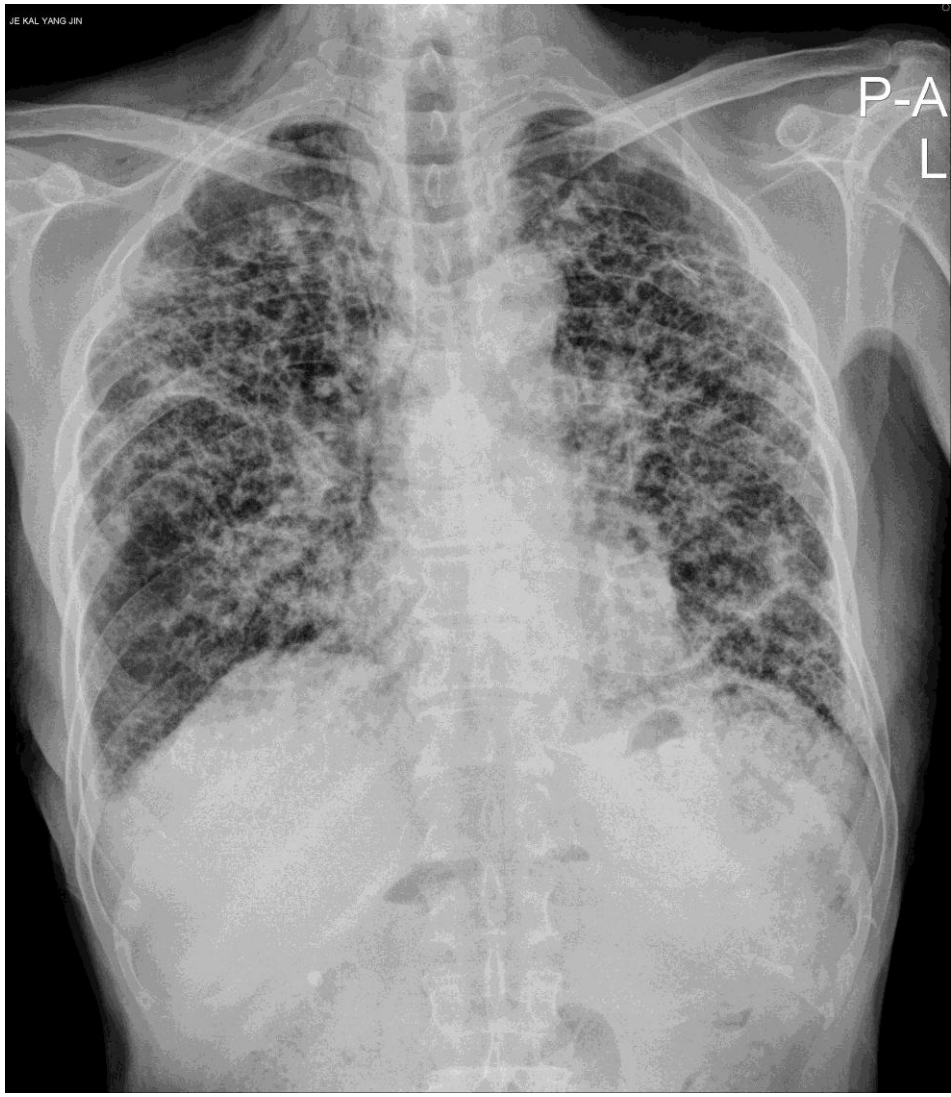
home O_2 1.5-2L 사용 중

2일전부터 열감, 오한 기침 객담

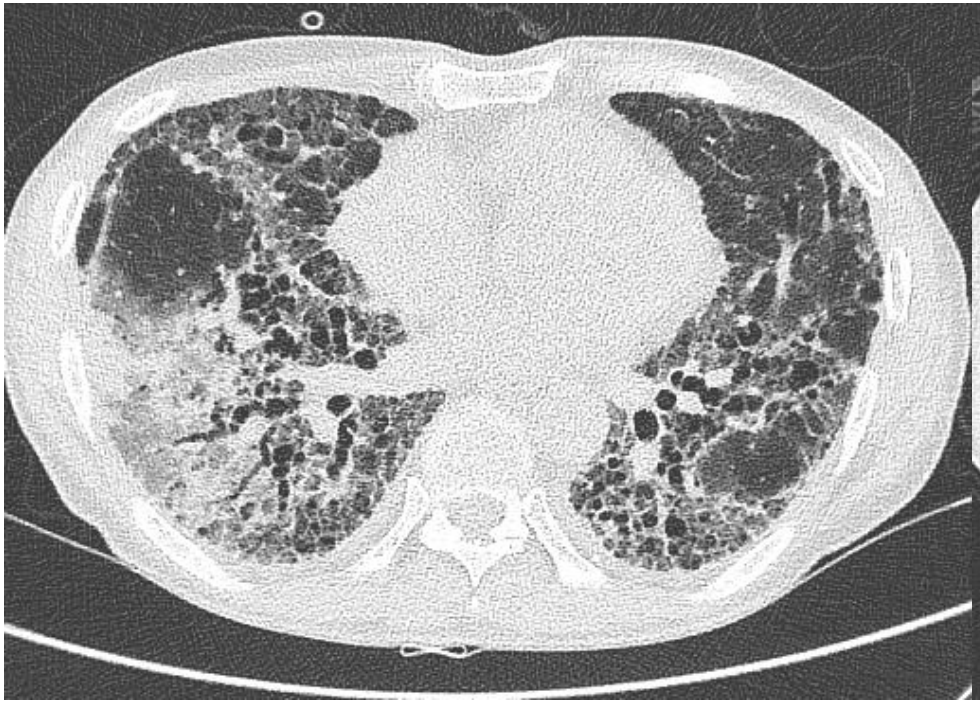
1일전부터 조금만 움직여도 호흡곤란



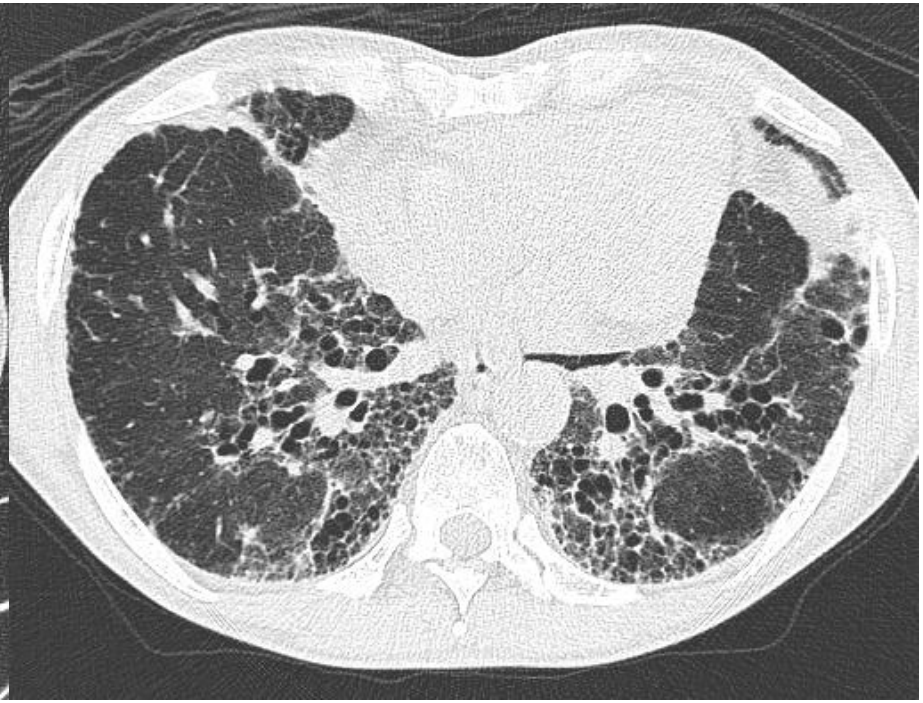
2012-11-01



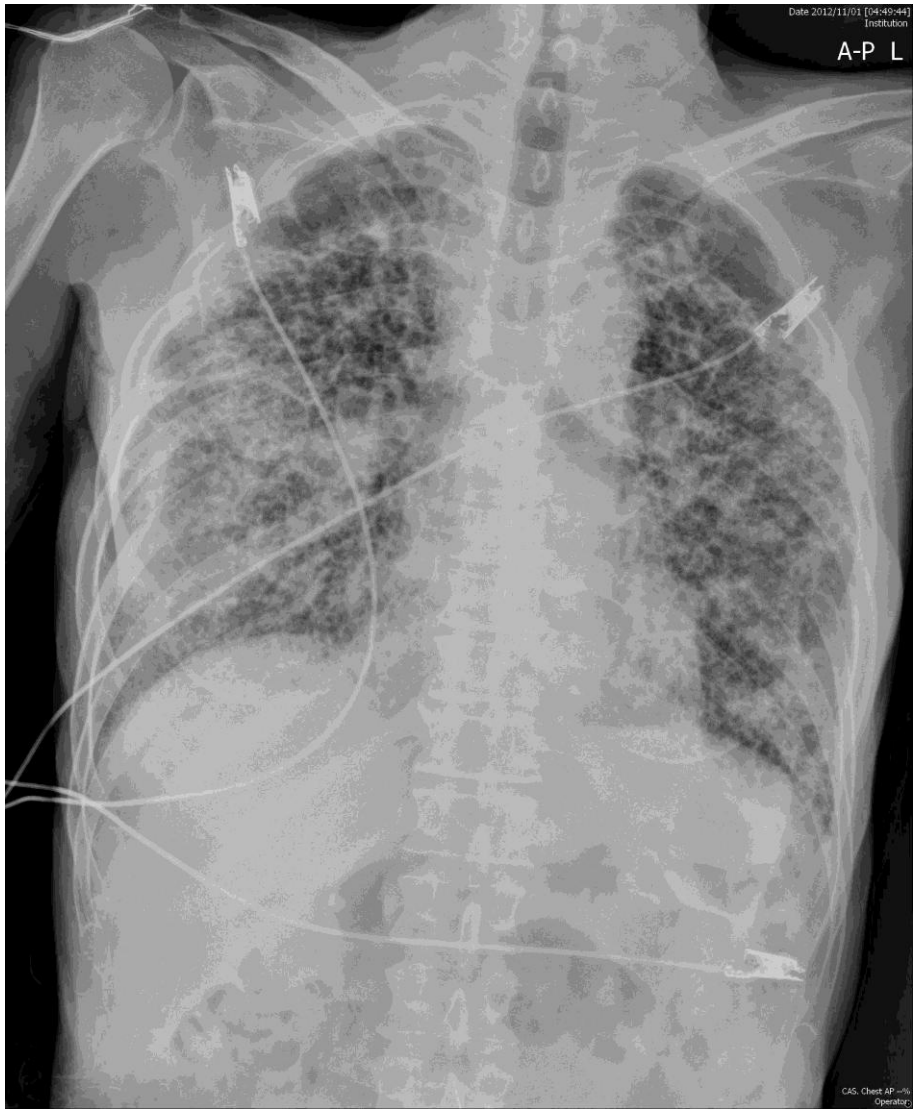
2012-10-05

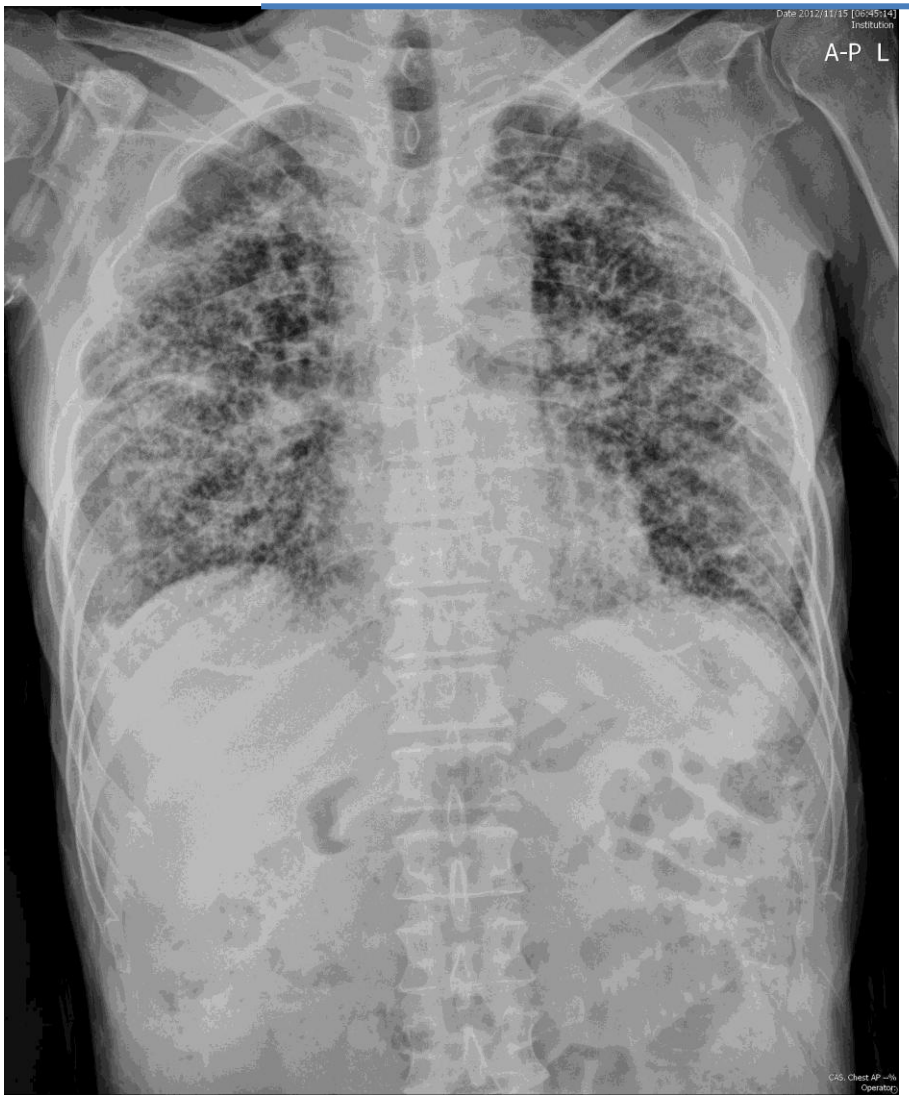


2012-11-01



2012-07-30





2012-11-01

Meropenem+
vancomycin

2012-11-15

73/M

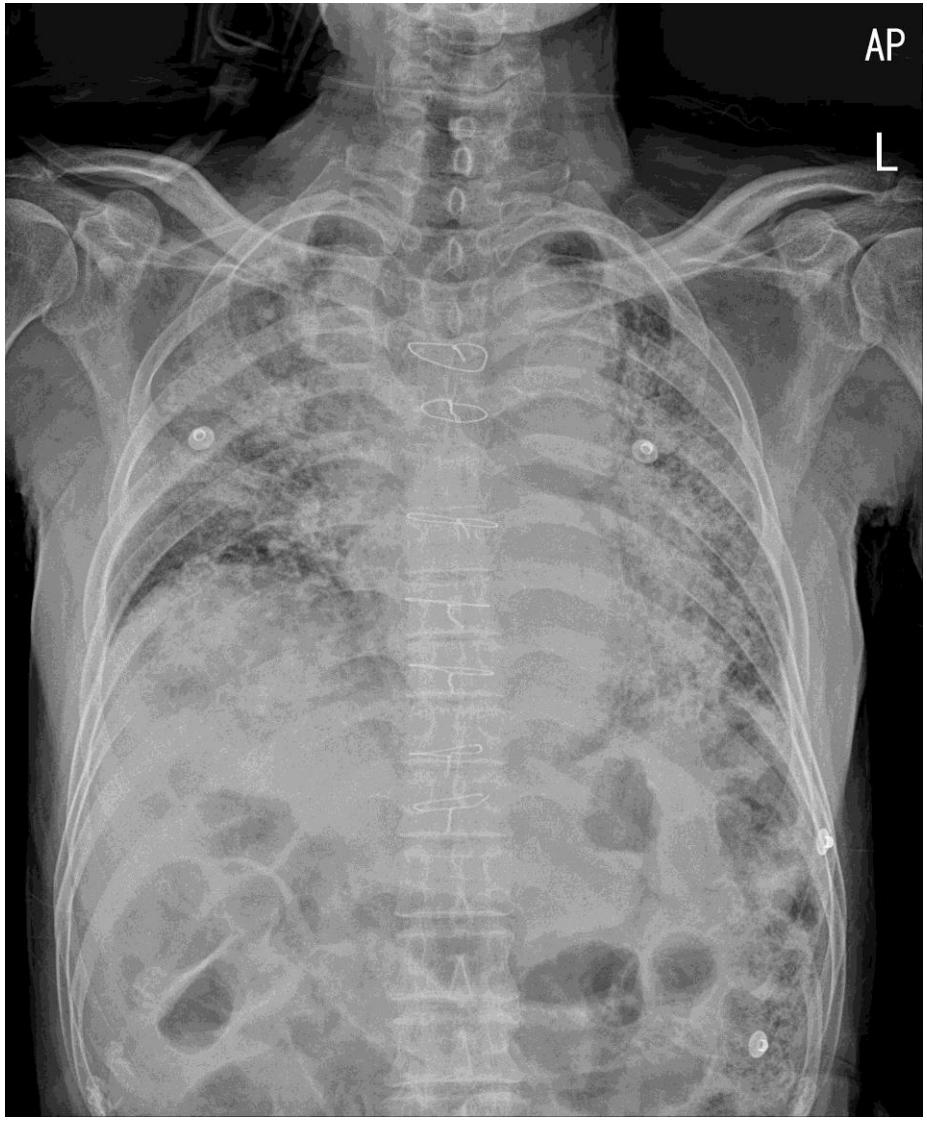
5년 전 aortic valve replacement

9개월 전 IPF (clinically) 진단

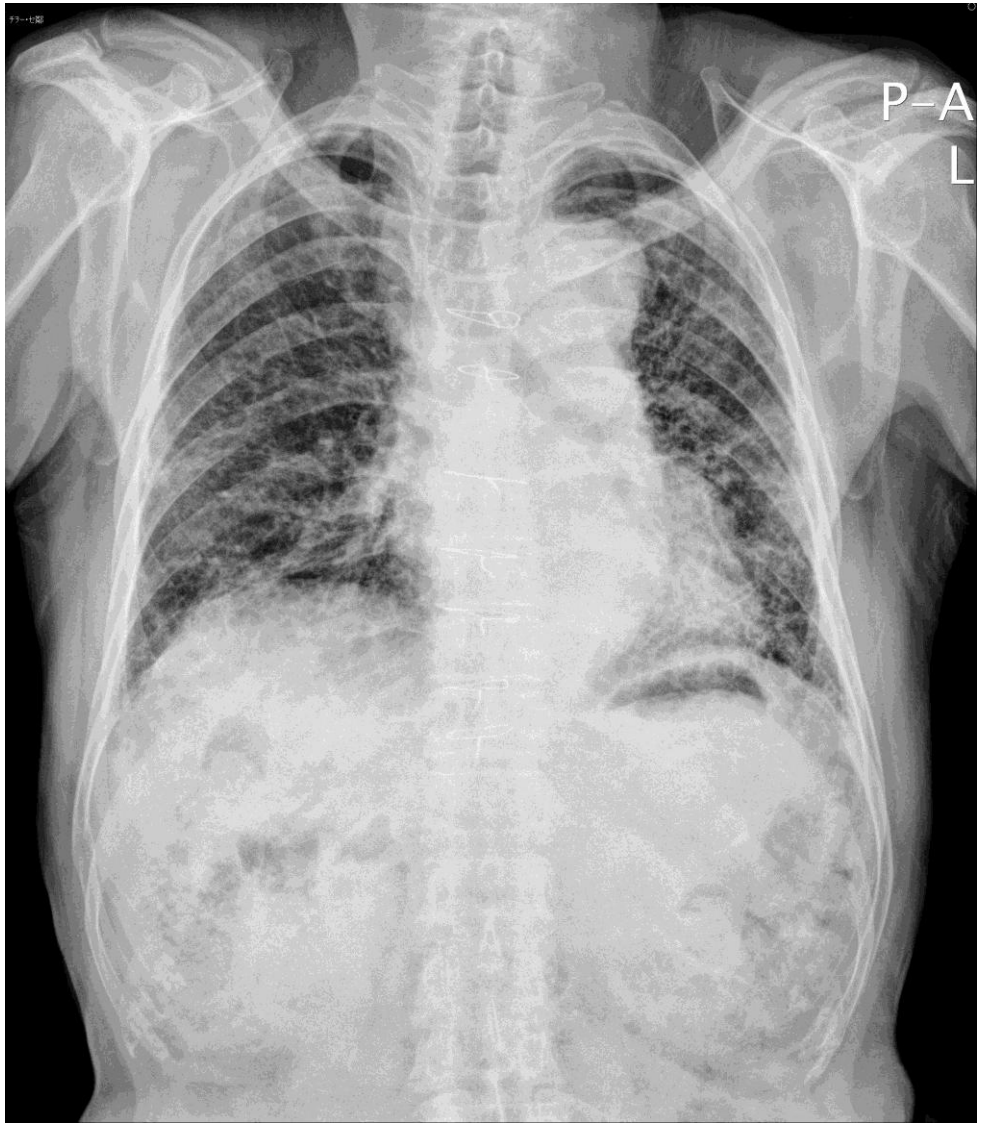
특별한 medication 없이 지내던 중

4일 전부터 호흡곤란 발생

1일 전부터 orthopnea 발생



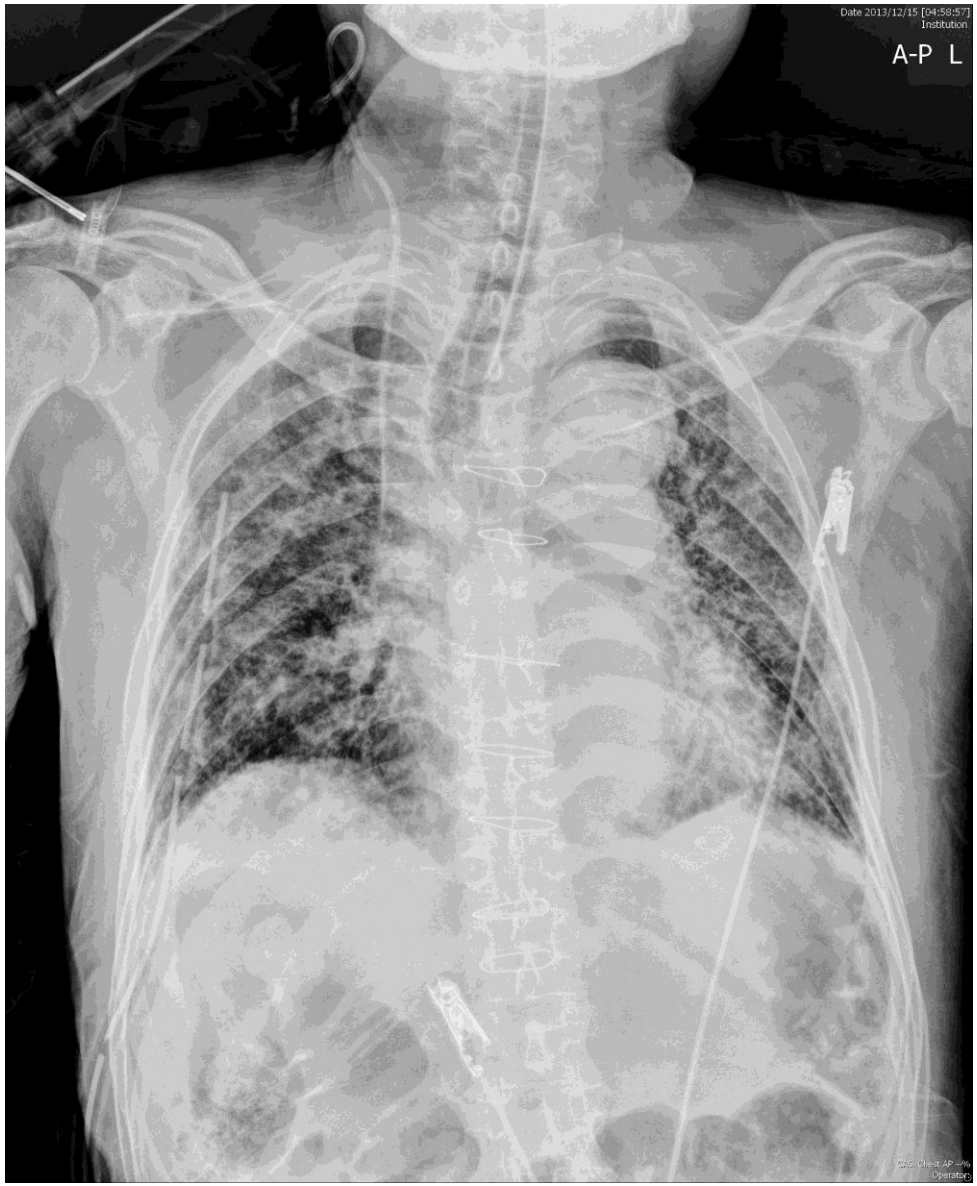
2013-12-13



2013-11-15

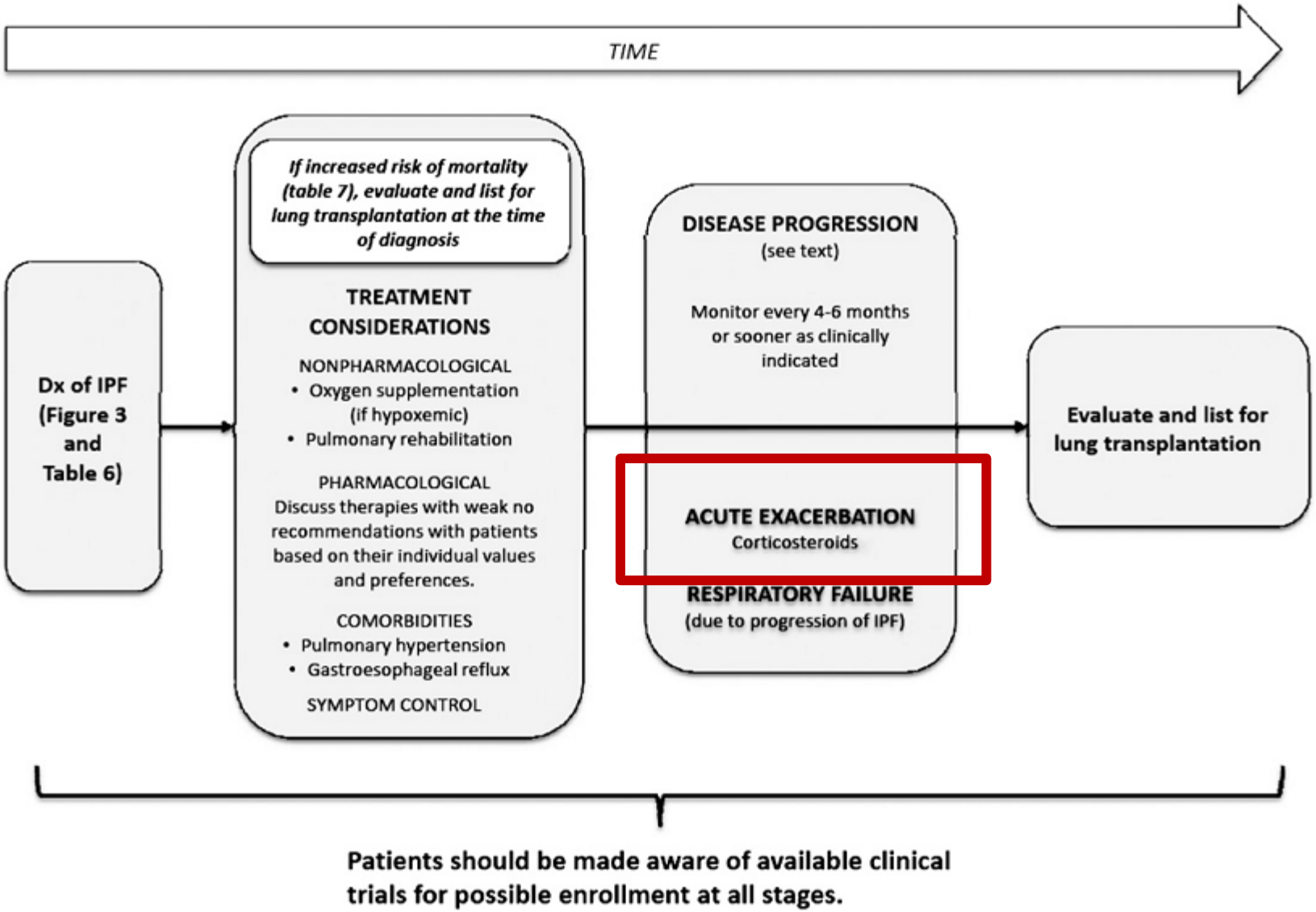
EchoCG

Newly deveoped regional wall motion abnormaltiy(mid interolateal and mid anterolateal) with mild to moderate LV systolic dysfunction **(EF42%)**



2013-12-15

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



Question: Should patients with acute exacerbation of IPF be treated with corticosteroids?

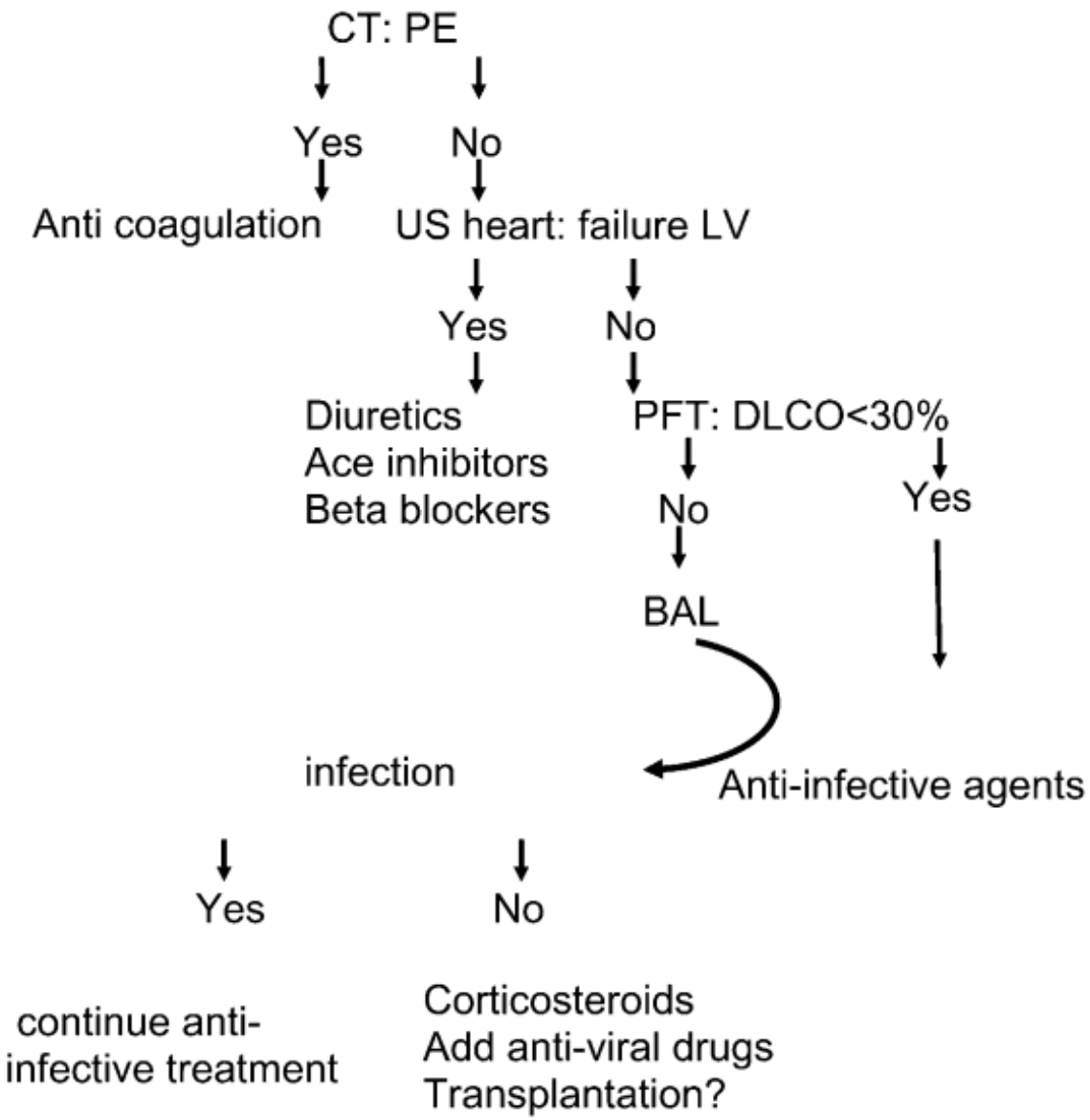
Although high-dose corticosteroids are commonly prescribed for the treatment of acute exacerbation of IPF, **there are no controlled trials on which to judge efficacy**. Cyclosporin A and anticoagulation have also been used without conclusive results

Recommendation: The majority of patients with acute exacerbation of IPF **should be treated** with corticosteroids, but corticosteroids may not be reasonable in a minority (**weak recommendation, very low-quality evidence**).

Values: This recommendation places a high value on anecdotal reports of benefit and the high mortality of acute exacerbation of IPF.

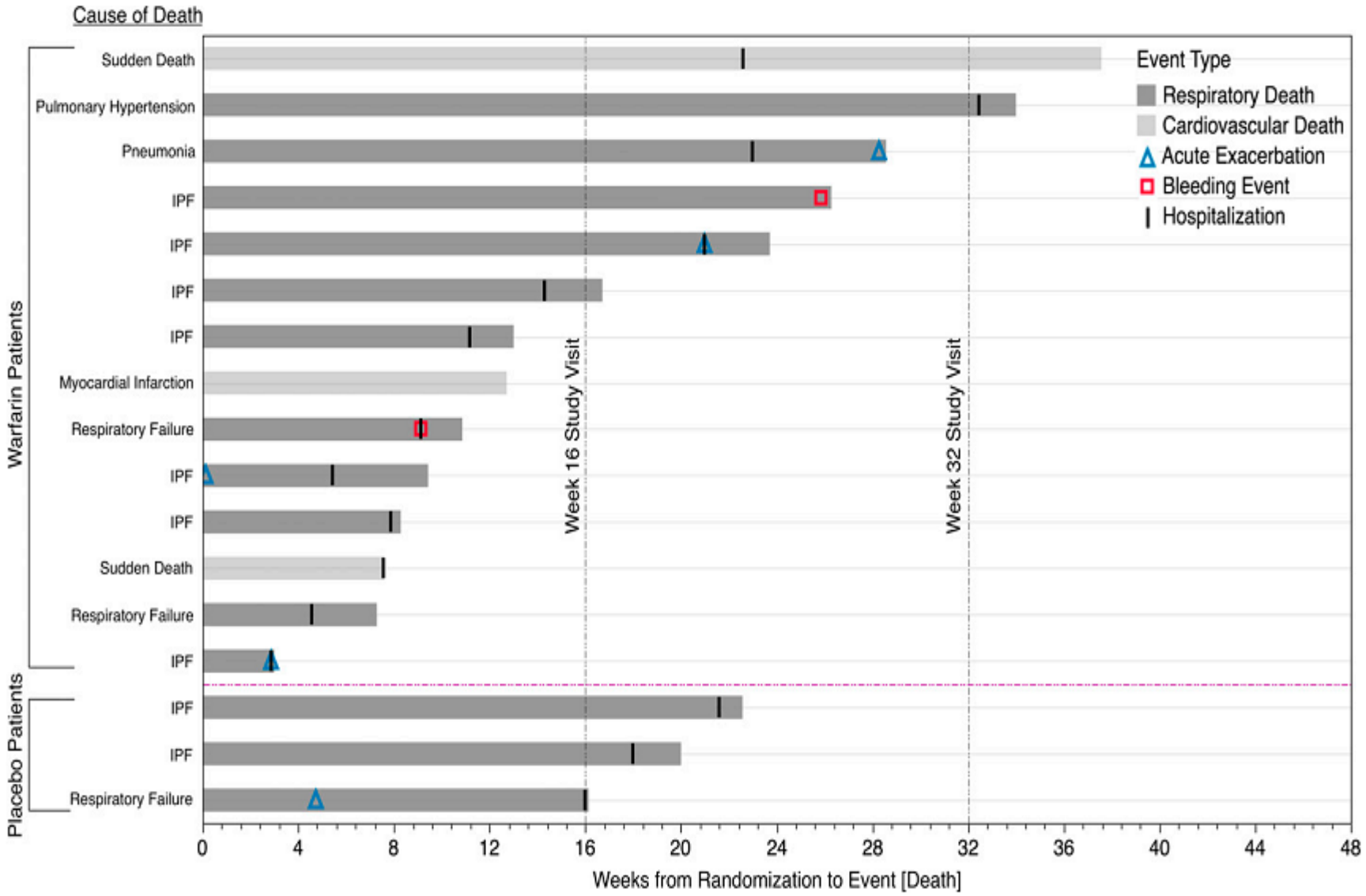
Remarks: Specific recommendations regarding the dose, route, and duration of corticosteroid therapy cannot be made. **Intravenous corticosteroids up to a gram per day** have been reported in a few case series. **There was consensus that supportive care is the mainstay of therapy** for acute exacerbation of IPF. (Vote: 14 for use, 5 against use, 1abstention, 11 absent.)

Algorithm of Dx and Tx



Wuyts et al. Am J Respir Crit Care Med 2008;177:1397

Anticoagulation therapy



Noth et al. Am J Respir Crit Care Med 2012;186:88-95

Pirfenidone

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

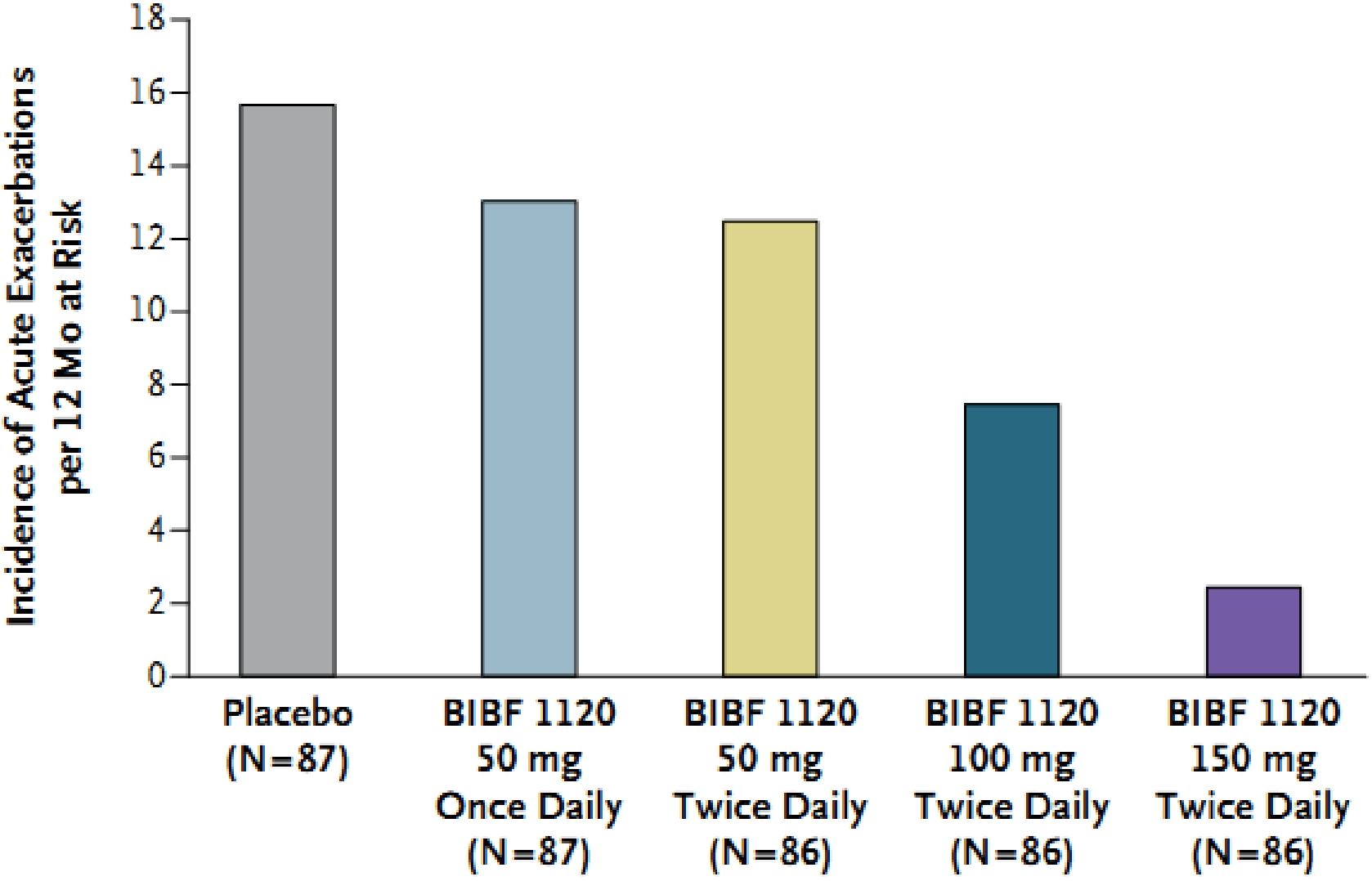
Arata Azuma, Toshihiro Nukiwa, Eiyasu Tsuboi, Moritaka Suga, Shosaku Abe, Koichiro Nakata, Yoshio Taguchi, Sonoko Nagai, Harumi Itoh, Motoharu Ohi, Atsuhiko Sato, and Shoji Kudoh for the members of the Research Group for Diffuse Lung Diseases in Japan; and Ganesh Raghu

Discontinuation of the Study Medication at 9 Months

Reason for Discontinuation	Pirfenidone Number of Patients (%)	Placebo Number of Patients (%)	p Value*
Adverse events	11 (15.1)	2 (5.6)	0.2132
Photosensitivity	5 (6.8)	0 (0.0)	0.1686
Vomiting	1 (1.4)	0 (0.0)	1.0000
Fever	1 (1.4)	0 (0.0)	1.0000
Abnormality of hepatic function	1 (1.4)	0 (0.0)	1.0000
Dizziness	1 (1.4)	0 (0.0)	1.0000
Facial paralysis	1 (1.4)	0 (0.0)	1.0000
Hepatoma	1 (1.4)	0 (0.0)	1.0000
Headache	0 (0.0)	1 (2.8)	0.3303
Acute exacerbation	**0 (0.0)**	**5 (13.9)**	**0.0032**
Progression of disease	1 (1.4)	1 (2.8)	1.0000
Protocol violation	1 (1.4)	0 (0.0)	1.0000

Azuma et al. Am J Respir Crit Care Med 2005;171:1040-7

Nintedanib (BIBF1120)



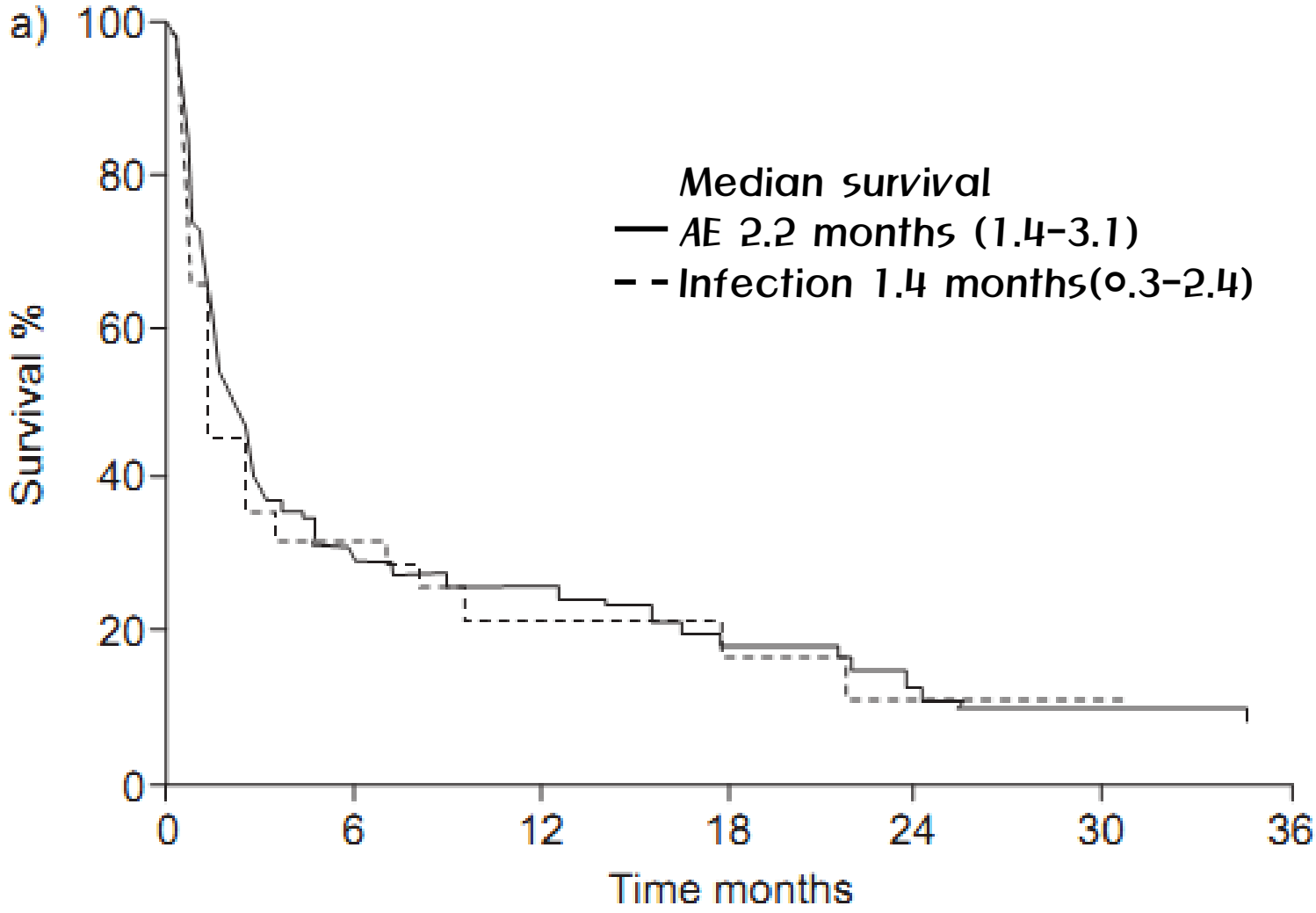
Richeldi et al. N Engl J Med 2011;365:1079-87

Expert opinion

Practical questions	Answers
Do you use BAL for diagnosing AE?	We perform BAL unless there is a high change of triggering the need for mechanical ventilation
Do you use empirical antibiotic treatment?	We use broad-spectrum antibiotic therapy
Do you treat with antivirals?	No, unless the patient is severely lymphopenic
Do you treat for pneumocystis	Yes, we do
Do you use anticoagulation?	No, we do not
Do you use corticosteroids?	Yes, we pulse the patient with three daily doses of methyl prednisolone of 1 g each
Do you use cyclophosphamide for AE-IPF?	No

Collard et al. Am J Respir Crit Care Med 2007;176:636-43

Prognosis



Song et al. Eur Respir J 2011;37:356-63

HRCT and prognosis

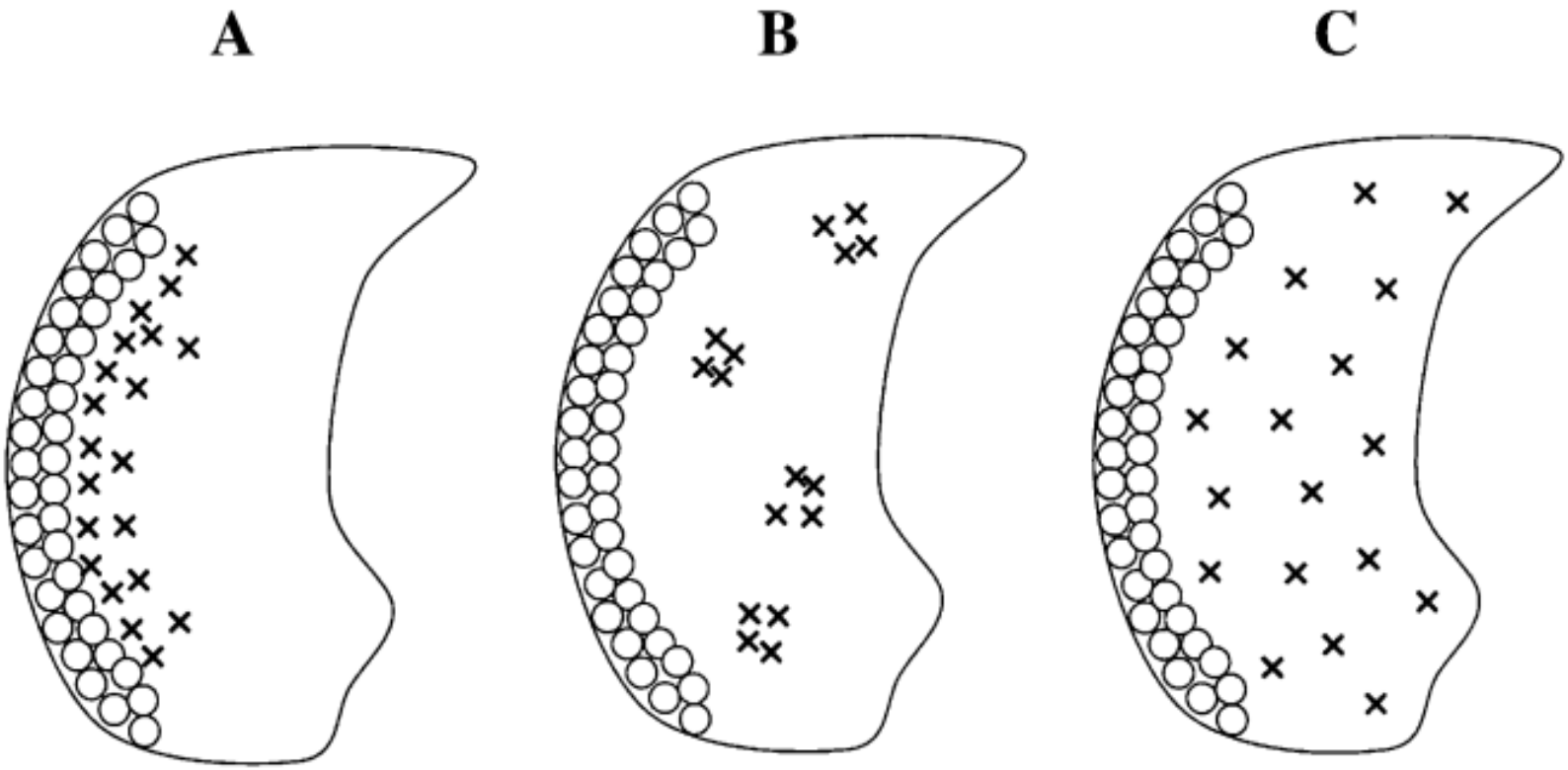
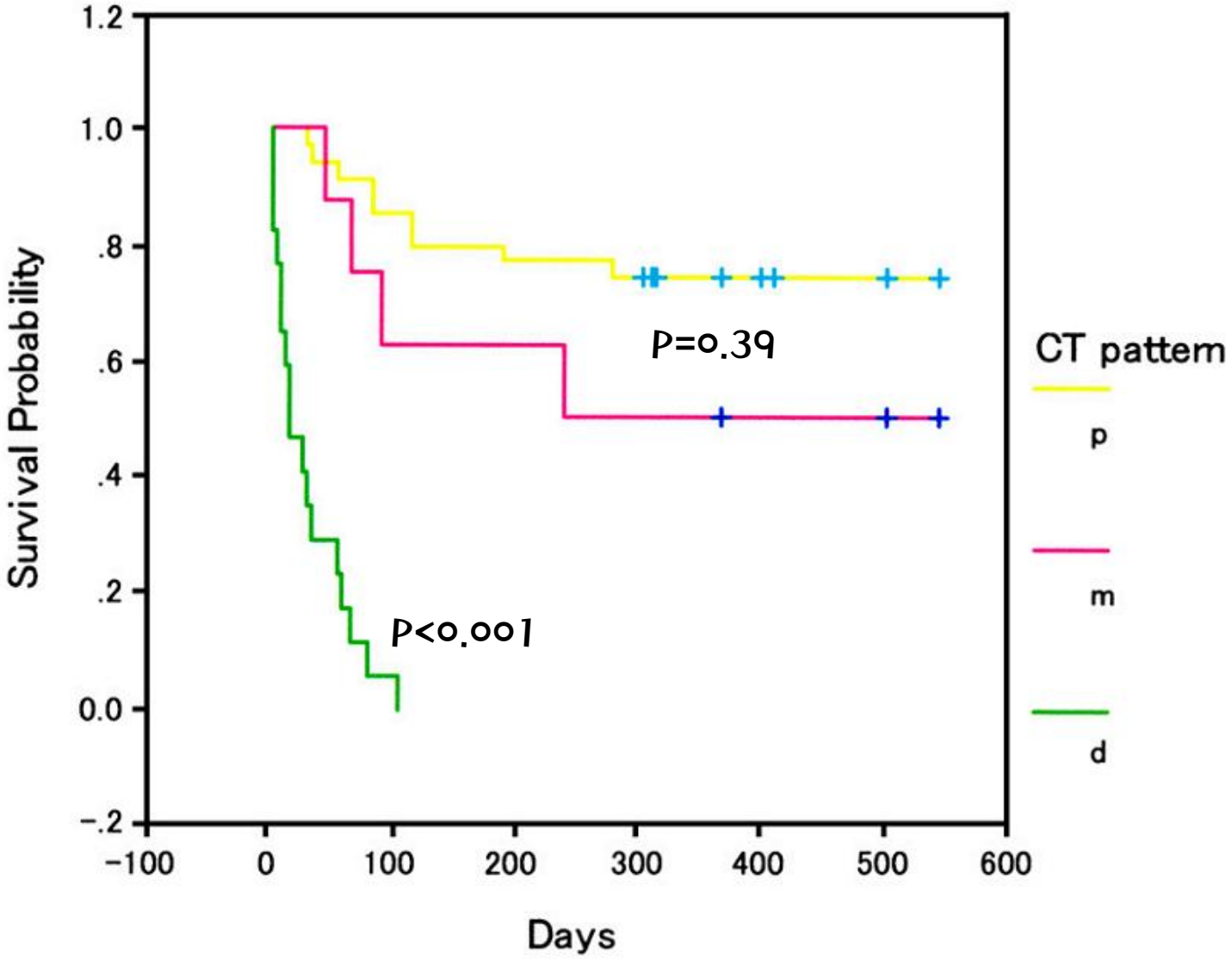


Figure 1. Scheme of computed tomography (CT) patterns. (*A*) Peripheral pattern; (*B*) multifocal pattern; (*C*) diffuse pattern.

Akiraet al. Am J Respir Crit Care Med 2008;178:372-8

HRCT and prognosis



Akiraet al. Am J Respir Crit Care Med 2008;178:372-8

HRCT sore and Survival

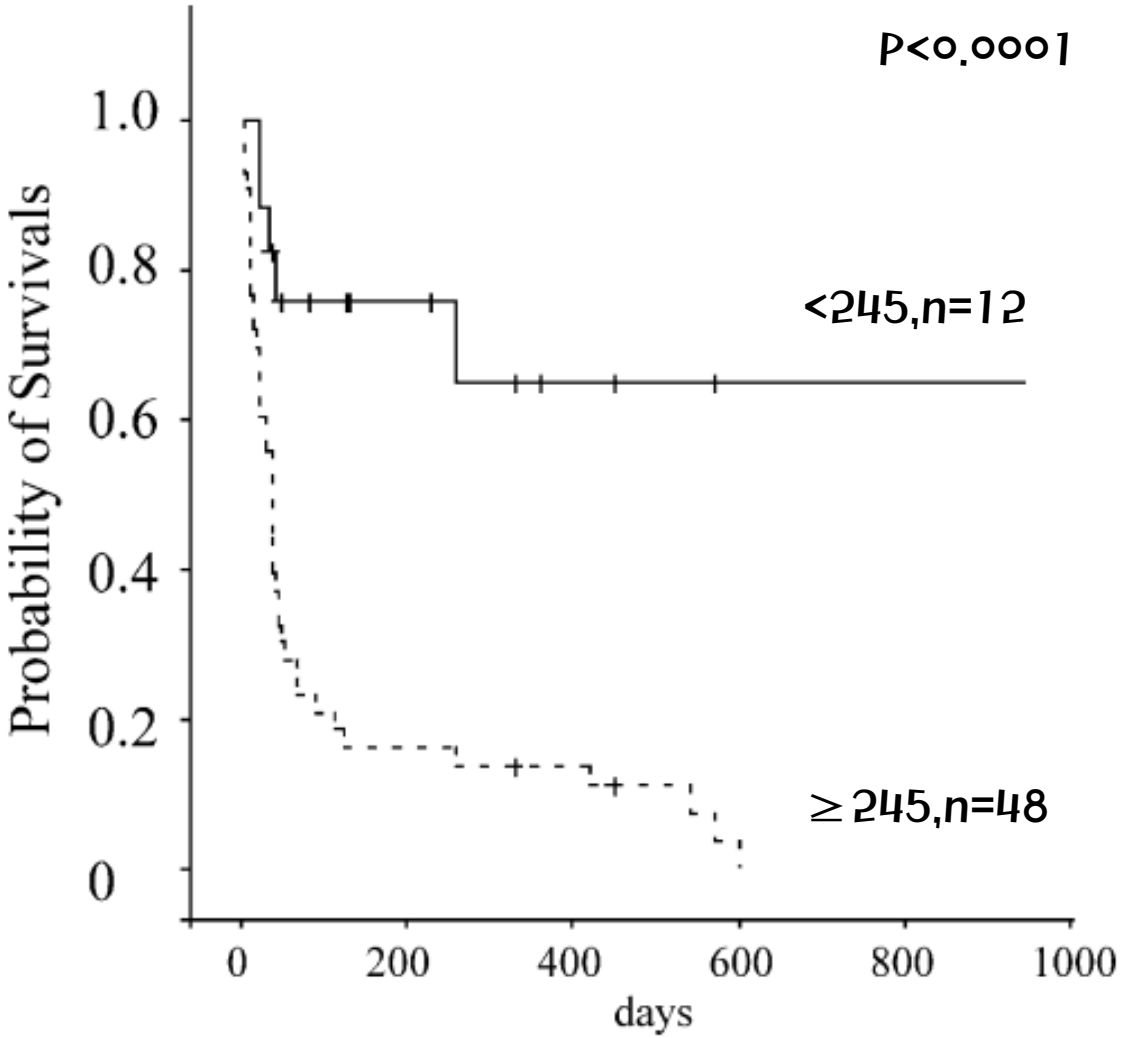
Overall HRCT score (%) = average score of normal attenuation × 1
+ average score of GGAwithout traction bronchiectasis or bronchiolectasis × 2
+ average score of consolidation without traction bronchiectasis or bronchiolectasis × 3
+ average score of GGA with traction bronchiectasis or bronchiolectasis × 4
+ average score of consolidation with tractionbronchiectasis or bronchiolectasis × 5
+ average score of honeycombing × 6.

Table 4 Multivariable analysis with Cox proportional hazards regression models

Variables	Per unit for HR[a]	HR	95%CI[b]	*P* value
(1) $PaCO_2$	1 mmHg	1.17	0.92–1.38	0.2531
(2) KL-6	500 U/mL	1.04	0.91–1.18	0.5859
(3) HRCT score	10%	1.13	1.06–1.19	0.0002

Fujimoto et al. Eur Radiol 2012;22:83-92

HRCT sore and Survival



Fujimoto et al. Eur Radiol 2012;22:83-92

Staging of AE

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

Koihaba et al. Lung 2013

Staging of AE

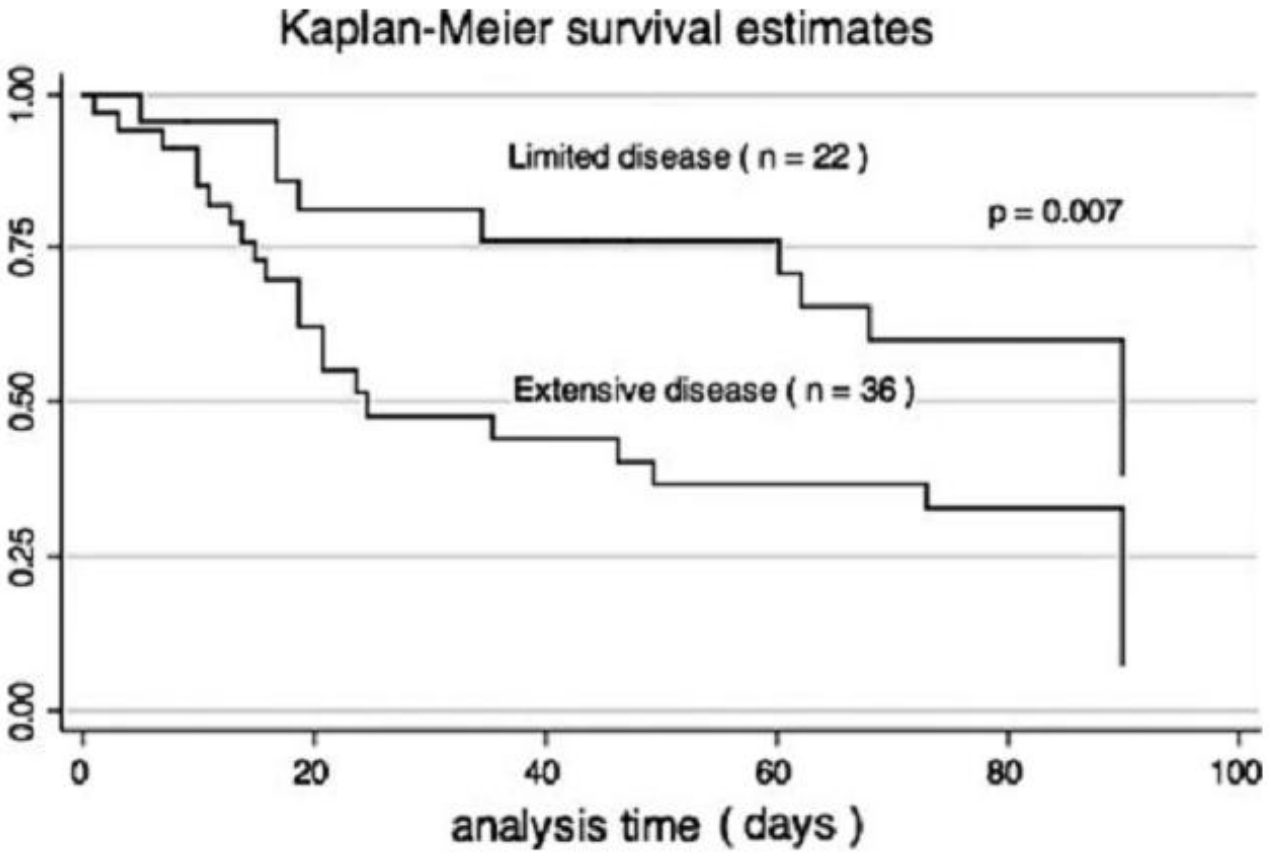


Fig. 3 3-month survival curve according to disease stage. The extensive disease stage group showed high mortality compared with that of the limited disease stage group

Koihaba et al. Lung 2013

Take home messages

- Clinical course of IPF is diverse
- Acute exacerbation is not uncommon
- Diagnosis
  - HRCT : New GGO, consolidation
  - Pathology : DAD, OP
  - Exclude other etiology of deterioration
    : infection, heart failure, pul. embolism
- Treatment : steroid, broad spectrum antibiotics, supportive care
- Prognosis : poor