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Risk factors of acute exacerbation of idiopathic pulmonary fibrosis

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Abstract. *Background:* Although acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) is a well known clinical condition, predicting risk factors remain unknown. We evaluated the frequency, risk factors and impact on survival of AE-IPF. *Methods:* We retrospectively studied patients diagnosed with IPF based on the criteria of the ATS/ERS consensus statement and followed them for periods of more than 3 years except in dead cases. Initial characteristics including the level of dyspnoea, which was assessed with the modified Medical Research Council (MRC) scale, and decline of forced vital capacity (FVC) defined by at least 10% decline at 6 months, were evaluated as possible risk factors for AE. *Results:* Seventy-four patients with IPF were studied. One-year, two-year, and three-year incidence of AE were 8.6%, 12.6%, and 23.9%, respectively. Multivariate analysis revealed that higher body mass index (BMI) [hazard ratio (HR), 1.20; 95% confidence interval (CI), 1.03-1.40], higher modified MRC scale [HR, 2.93; 95% CI, 1.46-5.85], and a decline in FVC at 6 mounths [HR, 0.97-2.60 (per mo); 95% CI, 1.01-7.45] were independent risk factors for AE-IPF. The causes of death were assessed to be AE in 20 of 57 expired patients. A stepwise multivariate Cox regression model evaluating AE-IPF, adjusted for %FVC and decline in FVC, demonstrated a statistically significant impact on overall survival [HR, 2.79; 95% CI, 1.59-4.88; p<0.001]. *Conclusion:* These data suggest that initial high modified MRC scale, high BMI, and decline in FVC at 6 months were significant independent risk factors for AE-IPF. AE was an independent prognostic factor in IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 103-110)*

Key words: idiopathic pulmonary fibrosis, acute exacerbation of idiopathic pulmonary fibrosis, modified Medical Research Council scale, body mass index, risk factor

Abbreviation list
AE: acute exacerbation
BALF: bronchoalveolar lavage fluid
BMI: body-mass index
CI: confidence interval
DLco: diffusing capacity for carbon monoxide
FVC: forced vital capacity
IPF: idiopathic pulmonary fibrosis
mMRC: modified Medical Research Council
MST: median survival time
PFT: pulmonary function testing
SD: standard deviation
SLB: surgical lung biopsy

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Introduction

The clinical course of idiopathic pulmonary fibrosis (IPF) is usually chronic (1), but some patients may experience episodes of acute respiratory worsening (2-6). Although these episodes may occur secondary to common conditions such as pneumonia, pulmonary embolism, pneumothorax or cardiac failure, the term acute exacerbation of IPF (AE-IPF) has been used when a cause cannot be identified for the acute respiratory worsening (2-6).

A number of parameters at the time of diagnosis have been proposed as predictors of survival in IPF (7-17). Demographic factors such as age, gender, degree of dyspnoea, smoking history, and body mass index (BMI) have been shown to be associated with prognosis. In addition, baseline pulmonary function test values, PaO_2, and neutrophilia on BAL have been associated with survival. Although prognosis of AE-IPF is reported to be extremely poor, there has been no study that demonstrates the relationships between AE and baseline known prognostic factors for IPF.

In addition, recent studies revealed that a >10% decrement in FVC over six or twelve months has been significantly associated with decreased survival (13-16). King et al. demonstrated that a >10% decrement in the percentage of predicted FVC represents a valid measure of disease progression (18). Because the pathophysiology of AE-IPF is not known at present, the relationship between disease progression and AE is a matter of interest.

In the present study, we evaluated risk factors for AE-IPF among initial characteristics including above described known prognostic factors for IPF and decline in FVC defined by at least 10% decline at 6 months. In addition, because the impact of AE-IPF on overall survival has not been fully demonstrated until now, the present authors also studied whether impact of AE in overall survival remained after adjusting for other prognostic factors in IPF.

Material and methods

The ethical review board of our institute approved the study. The patients' approval or informed consent was not required for the retrospective review of their records pursuant to the ethical guideline of the Japanese Ministry of Health, Labor and Welfare.

Study subjects

One hundred ten patients were diagnosed with IPF in our hospital between January 2000 and December 2005. The diagnosis of IPF was made based on the criteria of the ATS/ERS consensus statement (1). Patients with a definite pattern of usual interstitial pneumonia (UIP) on high-resolution CT were not required to undergo surgical lung biopsy (n=44). Thirty cases underwent a surgical lung biopsy and the pathologic diagnosis was UIP (Table 1). Patients with underlying connective tissue disease, occupational or environmental exposures, or histopathologic pattern on surgical lung biopsy other than UIP were excluded from the study. Patients whose initial manifestation was AE were excluded.

Patients who were followed with serial pulmonary function tests (PFT) for periods of more than 3 years except in cases of death were included. Serial PFT were performed every 3 to 6 months. Among 110 patients with IPF, 21 patients with insufficient follow-up data and 15 patients without initial BAL evaluation were excluded. The remaining 74 patients comprised the study cohort. All clinical and laboratory data were collected retrospectively from medical records.

Definition of AE-IPF

AE-IPF was defined using the revised Japanese criteria for AE-IPF (19, 20), which states that all of the following three conditions must be satisfied during the course of IPF within a single month: (1) dyspnoea increases, (2) new ground-glass opacities appear on HRCT in addition to previous honeycomb lesions, (3) oxygen partial pressure in resting arterial blood (PaO_2) is lower by more than 10 mmHg than previous measurements. Obvious causes of these changes, such as infection, pneumothorax, cancer, pulmonary embolism or congestive heart failure, need to be excluded.

Incidence and risk factors of AE-IPF

Initial evaluations were made and incidence and risk factors for AE were studied. Initial characteris-

tics including modified Medical Research Council (MMRC), initial cell populations of bronchoalveolar lavage fluid (BALF) and decline in FVC at 6 months, defined by at least 10% decline in the absolute value of the baseline value, were evaluated to determine whether they are risk factors. Patients were treated with varied regimens, including no therapy, prednisone with or without immunosuppressants (cyclophosphamide, azatioprine, or cyclosporin), and experimental protocols. The lack of a prospectively defined treatment regimen, varying lengths of therapy and the overlap of treatment regimens precluded evaluation of the effect of treatment on serial change in pulmonary function, acute exacerbation or survival.

Prognostic factors and impact of acute exacerbation

Survival status in June 2009 was examined from clinical records. Causes of death and impact of AE on survival were studied.

Statistical analysis

Data are expressed as mean ± SD for continuous variables, and percentages for categorical variables. The S-PLUS ver.7.01 (Insightful Corp) was used to select a set of predicting factors for AE and survival by Cox proportion hazards model. Sixteen potential factors were evaluated for the prediction of AE and 17 potential factors (16 factors plus AE) were used for predicting survival. In an effort to determine which of the clinical and physiologic parameters best predicted AE and survival time, stepwise method was calculated on a subset of 70 patients. All predictors with a p-value of less than 0.20 were included and those with a p-value of 0.05 or above were excluded from stepwise selection. We used a forward and backward method in stepwise selection to estimate a more reliable model.

Results

Patients' characteristics and BALF findings at initial evaluation are listed in Table 1.

Diagnosis of acute exacerbation and exclusion of other known causes

During the observation period between January 2000 and June 2009, twenty-three patients were hospitalized and diagnosed with acute exacerbation by JRS criteria for acute exacerbation (19,20).

Table 1. Clinical, pulmonary function, and bronchoalveolar lavage findings in 74 patients with idiopathic pulmonary fibrosis

	Total	AE	None AE	P Value
Number of cases	74	23	51	-
Sex, male	61	20	41	0.721
Age	64.1±7.4	62.9±8.9	64.6±6.7	0.459
Smoking history, N/Ex/C	20/37/17	7/14/2	13/23/15	0.021
BMI	23.5±3.1	24.7±2.9	22.9±3.0	0.019
modified MRC scale, 2 and above	10/33/28/3/0/31	13	18	0.145
PaO_2, mmHg	81.0±11.6	78.7±12.2	82.8±11.0	0.285
FVC, % predicted	77.0±19.2	73.5±20.9	79.1±18.2	0.199
DLco, % predicted	59.3±18.7	57.3±21.6	60.2±17.6	0.554
10% decline in FVC at 6 months, yes	13	8	5	0.018
Time to 10% decline in FVC, mo	18.7±19.2	15.2±12.2	20.4±17.4	0.196
Follow-up time, mo	45.6±26.0	30.2±19.7	52.5±25.6	<0.001
SLB yes	30	10	20	0.928
BAL				
Macrophages, %	90.7±12.1	92.3±7.5	89.9±13.7	0.649
Neutrophils, %	2.0±3.5	1.4±1.5	2.2±4.0	0.981
Lymphocytes, %	5.4±6.7	5.0±6.5	5.5±6.8	0.632
Eosinophils, %	1.0±1.8	1.1±2.3	0.9±1.5	0.585
CD4/8	2.36±2.66	2.65±3.53	2.24±2.12	0.876
Albumin, mg/ml	65±34	60±29	65±37	0.611

Definition of abbreviations: AE = acute exacerbation; N/Ex/C = non-smoker/ex-smoker/current smoker; BMI = body-mass index; MRC = Medical Research Council; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; BAL = bronchoalveolar lavage; SLB = surgical lung biopsy

Among 23 patients with acute exacerbation, microbiological studies of BAL fluid (n=17), sputum (n=23) and blood (n=23) revealed no infectious agents, including bacteria, mycobacteria, viruses, fungi or Pneumocystis jiroveci. Cultures of BALF for various viruses (cytomegalovirus, herpes simplex, varicella zoster virus, measles virus, adenovirus, influenza A, influenza B, parainfluenza 1–3, and respiratory syncytial virus) were evaluated and were negative in all 17 patients. In BAL samples additional stains were used and were negative in 17 patients; Ziehl-Neelsen staining for mycobacteria and Gomori methenamine silver stain for fungi and Pneumocystis jiroveci. Serological studies for atypical pathogens, such as Mycoplasma pneumoniae, Chlamydia pneumoniae, and the viruses listed above, were negative in all 23 patients. All 23 patients underwent a test for urinary antigens of Legionella pneumophila serogroup 1 and Pneumococcus pneumoniae (Binax Now, Binax, Scarborough, ME, USA), which revealed a negative result in all patients. Serum D-dimer, echocardiography and CT (n=23) showed no evidence of heart failure or pulmonary embolism in any patients.

Median time from diagnosis of IPF to acute exacerbation was 26.2 (7.8-92.5) months. Baseline therapies for IPF just before acute exacerbation in these 23 patients were oral corticosteroid and immunosuppressant in 14 (cyslosporin in 13, cyclophosphamide in 1), oral corticosteroid only in 1, and no immunosuppressive therapy in 8.

Incidence and risk factors of acute exacerbation

Comparisons between patients with acute exacerbation (AE group) and those without AE (Non AE group) were shown in Table 1. There was a significant difference in smoking status between AE group and NAE group, however, smoking status was not related to AE with Cox proportional hazard model. BMI was significantly higher in AE than NAE (24.7±2.9 versus 22.9±3.0, p=0.019) (Table 1). Incidences of AE in patients who underwent SLB and those diagnosed with HRCT were not significantly different (10/30 (33.3%) versus 13/44 (29.5%), p = 0.928).

At the 6-month evaluation, thirteen patients showed decline in FVC. There was a significant difference between the AE and NAE groups in the incidence of decline of at least 10% in FVC at 6 months (8/23 vs 5/51, p=0.018) (Table 1).

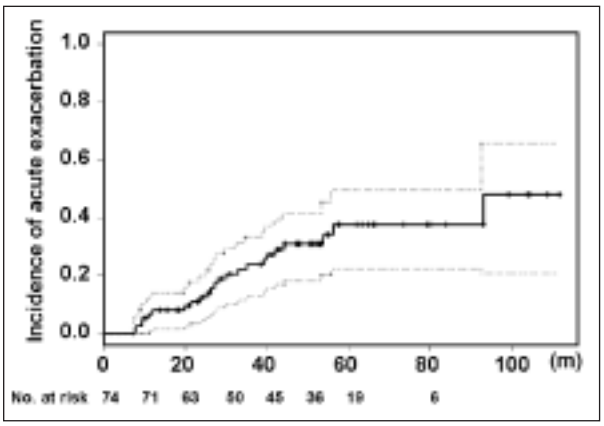

Fig. 1. Incidence of acute exacerbation of idiopathic pulmonary fibrosis Dashed lines indicate 95 percent confidence interval.

The Kaplan Meier curve demonstrated that the one-year, two-year, and three-year incidence of AE-IPF was 8.6% (95% confidence interval (CI), 1.7-12.6%), 12.6% (95% CI, 4.5-20.0%), and 23.9% (95% CI, 12.9-33.5%), respectively (Figure 1).

Univariate analysis with Cox proportional hazards regression models demonstrated that high modified Medical Research Council (MRC) scale and low FVC were significant predictive factors for AE-IPF (Table 2). Stepwise multivariate analysis with Cox proportional hazards regression models demonstrated that high BMI, high modified MRC scale, and decline in FVC at 6 months were significant predictive factors for AE-IPF (Table 3).

Prognostic factors and impact of acute exacerbation

During the follow up, 23 patients (31.1%) were diagnosed with AE-IPF. There was a significant difference in survival between patients with AE [median survival time (MST), 26.4 months] and those without AE (MST, 52.8 months) (log rank test, p=0.0002). Median survival after AE was 22 days.

A total of 57 patients (77.0%) died during the follow-up with MST of 44.4 months from the time of diagnosis of IPF. The causes of death were reported as acute exacerbation in 20 cases (35.1%); chronic respiratory failure due to progressive IPF in 23 cases (40.4%); lung cancer in 6 cases (10.5%); pneumonia in 5 cases (8.8%); and pneumothorax in

Table 2. Univariate analysis with Cox proportional hazards regression models of predictors of acute exacerbation of idiopathic pulmonary fibrosis

Univariate analysis	Hazard Ratio	95% CI	P Value
Sex, male	1.36	0.40-4.61	0.625
Age	0.98	0.92-1.04	0.459
Smoking history	0.85	0.35-2.09	0.218
BMI	1.14	0.99-1.31	0.067
modified MRC scale, 2 and above	2.95	1.28-6.80	0.011
PaO_2, mmHg	0.97	0.95-1.01	0.087
FVC, % predicted, per 10%	0.73	0.57-0.93	0.011
DLco, predicted, per 10%	0.85	0.67-1.07	0.168
10% decline in FVC at 6 months, yes	2.25	0.81-6.25	0.120
SLB yes	1.26	0.55-2.88	0.586
BAL			
Macrophages, %	1.02	0.97-1.07	0.553
Neutrophils, %	0.95	0.77-1.16	0.602
Lymphocytes, %	0.99	0.93-1.05	0.736
Eosinophils, %	1.09	0.90-1.33	0.365
CD4/8	1.05	0.90-1.22	0.574
Albumin, mg/ml	0.97	0.85-1.11	0.663

n=74 except for DLco [71] and BALF CD4/8 [73].
Definition of abbreviations: CI = confidence interval; Sex code is 1 for males and 0 for females; Smoking history, code for never-smoker is 0, code for ex-smoker is 1, and code for current-smoker is 2; SLB code is 1 for yes and 0 for no; disease progression = decline of at least 10% in FVC, ; see Table 1

Table 3. Stepwise multivariate analysis with Cox proportional hazards regression models of predictors of acute exacerbation of idiopathic pulmonary fibrosis

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

n=70, because only patients for whom all data were available were included in the analysis

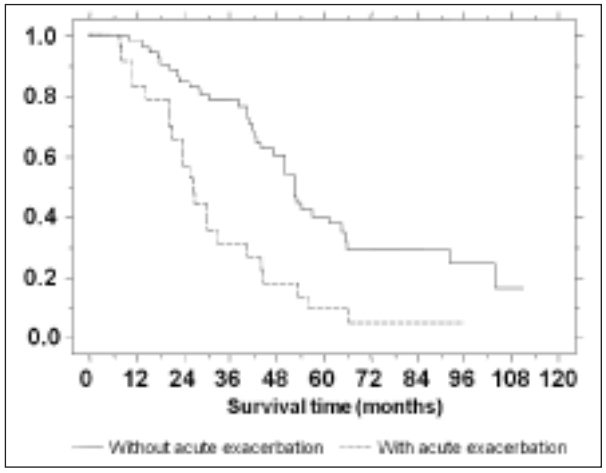

Fig. 2. Kaplan–Meier curves for survival for with or without acute exacerbation. There was a significant difference in survival between patients with AE [median survival time (MST), 26.4 months] and those without AE (MST, 52.8 months) (log rank test, p=0.0002).

1 case (1.8%). A stepwise multivariate Cox regression model evaluating AE-IPF, adjusted for %FVC and at least 10% decline in FVC at 6 months, demonstrated a statistically significant impact on survival [hazard ratio (HR) 2.79 (95% confidence interval (CI) 1.59–4.88); p<0.001; Table 4].

Discussion

This is the first study to show risk factors of AE-IPF. We demonstrated that high BMI, high modified MRC scale and decline in FVC at 6 months were independent risk factors for AE-IPF. We also demonstrated that AE-IPF was a significant prognostic factor for IPF using stepwise multivariate Cox regression model.

In this study, decline of at least 10% in FVC at 6 months was a risk factor for AE-IPF. Recently, se-

Table 4. Univariate and stepwise multivariate analysis with Cox proportional hazards regression models of survival in idiopathic pulmonary fibrosis

	Hazard Ratio	95% CI	P Value
Univariate			
Sex, male	0.694	0.35-1.36	0.286
Age	1.02	0.98-1.06	0.446
BMI	0.97	0.88-1.07	0.590
modified MRC scale, 2 and above	2.54	1.50-4.32	<0.001
Smoking history	0.89	0.61-1.30	0.555
PaO_2, mmHg	0.97	0.95-1.00	0.041
FVC, % predicted, per 10%	0.72	0.62-0.85	<0.001
DLco, % predicted	0.83	0.72-0.96	0.014
10% decline in FVC at 6 months, yes	3.68	1.88-7.19	<0.001
SLB, yes	1.40	0.83-2.35	0.250
Acute exacerbation, yes	2.72	1.58-4.69	<0.001
BAL			
Macrophages, %	1.00	0.97-1.02	0.814
Neutrophils, %	1.06	0.97-1.16	0.170
Lymphocytes, %	0.99	0.95-1.03	0.498
Eosinophils, %	1.05	0.93-1.18	0.418
CD4/8	1.03	0.93-1.14	0.564
Albumin, mg/ml	1.00	0.92-1.08	0.999
Stepwise multivariate analysis			
Acute exacerbation, yes	2.79	1.59-4.88	<0.001
FVC, % predicted, per 10%	0.49	0.33-0.73	<0.001
10% decline in FVC at 6 months, yes	3.37	1.71-6.63	<0.001

Definition of abbreviations: Acute exacerbation (AE) code is 1 for yes and 0 for no; CI = confidence interval; see Table 1

rial FVC changes have been revealed to be a good prognostic factor for IPF (13-16). Although the pathophysiology of AE-IPF is not known at present (6), our finding shows that the initial 6-month progression of the disease defined by FVC decline enhances the risk of subsequent AE-IPF. It has been reported that a subgroup of IPF patients display an accelerated clinical course and have a gene expression pattern that is different from those with slower progression. Further studies of this in rapid decliners need to be done (21).

The present study showed that initial low FVC was a risk factor for AE-IPF. Martinez et al. reported that respiratory hospitalization including that for acute respiratory worsening is more frequent in patients with more severely impaired lung function (FVC≤62%) (22). Miyazaki et al. evaluated the clinical features of patients with AE in chronic HP, and found that UIP pattern and low lung volume at the time of diagnosis may be risk factors for AE (23). Therefore, severe restrictive impairment is a risk factor for acute exacerbation. The reasons high initial modified MRC scale was a risk factor for AE-PF are not known. According to a COPD study, dyspnoea evaluated by modified MRC scale is a risk factor for exacerbation and for mortality (24). Because dyspnoea is a risk factor for acute exacerbation as well as for mortality in IPF, evaluation of initial dyspnoea in IPF is crucial.

Little has been studied about the impact of BMI on IPF. One study showed that higher BMI was associated with better survival in patients with IPF (9); therefore, our result that higher BMI was a significant independent risk factor for AE-IPF is of interest. Because of the clinical and pathologic similarities of acute exacerbations of IPF with acute respiratory distress syndrome (ARDS), a recent cohort study of critically ill patients at risk for ARDS that demonstrated an association between higher BMI and the development of ARDS in a multivariate analysis (25) may support our findings. The hypothesis that obesity itself is associated with a state of inflammation (9) is a possible explanation. Another possible explanation is that gastroesophageal reflux disease (GERD) was responsible for the relation found between AE-IPF and high BMI. Obesity increases the prevalence of GERD (26), and GERD is thought to be a possible risk factor for acute exacer-

bation as well as IPF itself (27). Therefore, high BMI may be a risk for AE because of the increased risk of GERD. Further studies are needed to elucidate the impact of BMI on IPF.

In this study, the one year, two year, and three year incidence of acute exacerbation was 8.6%, 12.6%, and 23.9%, respectively. Kim et al. reported that the 2-yr frequency of acute exacerbation among 147 patients with biopsy-proven IPF was 9.6% after the diagnosis (5). Of 107 patients followed up for 9 months in a double-blind, randomized, placebo-controlled trial of pirfenidone therapy for the treatment of IPF, AE-IPF were manifested in 14% of patients in the placebo group (5 of 35 patients) and in none of the patients in the pirfenidone group (28). Of 56 patients who were followed for approximately 3 years in a randomized controlled trial of anticoagulant therapy in IPF patients, 32 patients (57%) were hospitalized for acute exacerbation (29). In a recent larger phase III study of a pirfenidone trial in Japan, the same criteria for AE-IPF as in the present study was used. The incidence of acute exacerbation during the study (52 weeks) or within 28 days after the termination of the study was 5.6%, 5.5%, and 4.8% in the high-dose, low-dose and placebo groups, respectively (20), which is similar to our one year incidence of 8.6%. Because our results showed that baseline clinical characteristics may affect incidence of AE-IPF, differences in the study populations may have caused the variation in incidences of acute exacerbation.

In the present study, AE-IPF was the most common cause of death in 40.4%, followed by chronic respiratory failure due to progressive IPF in 36.8%, and was a significant overall prognostic factor for IPF. Recently, Daniels et al. reported that the majority of patients with IPF who underwent autopsy died from respiratory causes, and AE-IPF was the most common cause of death (30). AE-IPF seems to be an important cause of death in IPF, and should be included as a crucial endpoint in clinical trials of IPF.

There are some limitations in this study. First, this study included only Japanese patients and is a single-center analysis. Some studies of drug induced lung injury suggest ethnic differences in the susceptibility to AE-IPF (31). Further studies are therefore needed to ascertain whether this result applies equally to other ethnic groups or not. Second, all patients did not undergo endotracheal aspiration or bronchoalveolar lavage, therefore, infectious etiology could not be excluded in some patients with AE-IPF. Third, because the intervals of pulmonary function testing were not strictly controlled, the criticism may be made that the time until a decline of at least 10% in FVC in the present study is inaccurate. Longer intervals of PFT may lead to missing the exact time of a decline of at least 10% in FVC. However, the median interval of PFT before disease progression in this study was 3 months (mean, 3.8±1.5 months; range 1-6 months), which we think is an acceptable interval to evaluate the time to disease progression in IPF. Fourth, a significant number of values are missing because follow-up data were insufficient in 21 patients and initial BAL evaluation was not done in 15 patients. Although this might influence the results of the study, we had to exclude those patients from the evaluation of known prognostic factors, such as BALF and serial FVC change, as risk factors for acute exacerbation.

In conclusion, the findings of this study demonstrate that initial high modified MRC scale, high BMI, and decline of at least 10% in FVC at 6 months are significant independent risk factors for AE-IPF. AE-IPF was rather common in our cohort of patients with IPF and had a significant impact on overall survival. Further exploration of this issue may lead to additional insights into the pathogenesis of not only AE but also IPF itself.

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References

1. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646-64.
2. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest 1993; 103: 1808-12.
3. Akira M, Hamada H, Sakatani M, Kobayashi C, Nishioka M, Yamamoto S. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. AJR 1997; 168: 79-83.

4. Parambil JG, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. Chest 2005; 128: 3310-5.
5. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J 2006; 27: 143-50.
6. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007; 176: 636-43.
7. Flaherty KR, Toews GB, Travis WD, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. Eur Respir J 2002; 19: 275-83.
8. Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005; 128: 2393-9.
9. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. Chest 2007; 131: 1448-53.
10. King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001; 164: 1171-81.
11. Schwartz DA, Helmers RA, Galvin JR, et al. Determinants of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994; 149: 450-4.
12. Nishiyama O, Taniguchi H, Kondoh Y, et al. A simple assessment of dyspnea as a prognostic indicator in idiopathic pulmonary fibrosis. Eur Respir J 2010 Apr 22. [Epub ahead of print].
13. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003; 168: 531-7.
14. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003; 168: 538-42.
15. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003; 168: 543-8.
16. Jegal Y, Kim DS, Shim TS, et al. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005; 171: 639-44.
17. Kinder BW, Brown KK, Schwarz MI, Ix JH, Kervitsky A, King TE Jr. Baseline BAL neutrophilia predicts early mortality in idiopathic pulmonary fibrosis. Chest 2008; 133: 226-32
18. King TE Jr, Safrin S, Starko KM, et al. Analyses of efficacy endpoints in a controlled trial of interferon-γ1b for idiopathic pulmonary fibrosis. Chest 2005; 127: 171-7.
19. Taniguchi H, Kondoh Y. Revised criteria for acute exacerbation of idiopathic pulmonary fibrosis. The Annual Report by Study Group of Ministry of Health and Welfare for Diffuse Lung Disease 2004; 114-9.
20. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35: 821-9.
21. Selman M, Carrillo G, Estrada A, et al. Accelerated variant of idiopathic pulmonary fibrosis: PLoS ONE 2(5): e482.
22. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med 2005; 142 (12 Pt 1): 963-7.
23. Miyazaki Y, Tateishi T, Akashi T, Ohtani Y, Inase N, Yoshizawa Y. Clinical predictors and histologic appearance of acute exacerbations in chronic hypersensitivity pneumonitis. Chest 2008; 134: 1265-70.
24. Ong KC, Earnest A, Lu SJ. A multidimensional grading system (BODE index) as predictor of hospitalization for COPD. Chest 2005; 128: 3810-6.
25. Gong MN, Bajwa EK, Thompson BT, Christiani DC. Body mass index is associated with the development of acute respiratory distress syndrome. Thorax 2010; 65: 44-50
26. El-Serag H. The association between obesity and GERD: a review of the epidemiological evidence. Dig Dis Sci 2008; 53: 2307-12.
27. Tobin RW, Pope CE 2nd, Pellegrini CA, et al. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998; 158: 1804-8.
28. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005; 171: 1040-7.
29. Kubo H, Nakayama K, Yanai M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest 2005; 128: 1475-82.
30. Daniels CE, Yi ES, Ryu JH. Autopsy Findings in 42 consecutive patients with idiopathic pulmonary fibrosis. Eur Respir J 2008; 32: 170-4.
31. Azuma A, Hagiwara A, Kudoh S. Basis of acute exacerbation of idiopathic pulmonary fibrosis in Japanese patients Am J Respir Crit Care Med 2008; 177: 1397-8.