Eur Respir J 2011; 37: 356–363
DOI: 10.1183/09031936.00159709

Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome

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ABSTRACT: Although acute exacerbation of idiopathic pulmonary fibrosis (IPF) has become well recognised, the reported incidence and outcomes are highly variable, and risk factors are unknown. The aim of this study was to estimate the incidence, risk factors and impact of acute exacerbations, and other known causes of rapid deterioration.

This was a retrospective review of 461 patients with IPF (269 cases were biopsy-proven).

The median follow-up period was 22.9 months. Rapid deterioration requiring hospitalisation occurred in 163 (35.4%) patients, with multiple episodes in 42 patients. Acute exacerbation was the most frequent cause (55.2%), followed by infection. The 1- and 3-yr incidences of acute exacerbation were 14.2 and 20.7%, respectively. Never having smoked and low forced vital capacity (FVC) were significant risk factors. The in-hospital mortality rate was 50.0%, and the 1- and 5-yr survival rates from the initial diagnosis were 56.2 and 18.4%, respectively. Acute exacerbation was a significant predictor of poor survival after the initial diagnosis, along with increased age, low FVC and diffusing capacity of the lung for carbon monoxide, and steroid use with or without cytotoxic therapy.

1- and 3-yr incidences of acute exacerbation were 14.2 and 20.7%, respectively. Never having smoked and low FVC were risk factors. Acute exacerbation had a serious impact on the overall survival of the patients with IPF.

KEYWORDS: Acute exacerbation, idiopathic pulmonary fibrosis, incidence, prognostic factors, risk factors, survival

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Received:
Oct 09 2009
Accepted after revision:
June 12 2010
First published online:
July 01 2010

The natural course of idiopathic pulmonary fibrosis (IPF) is not clearly defined, and the clinical course among individual patients is highly variable [1]. Although it has become more evident that acute exacerbation (AE) of IPF, the sudden acceleration of disease process or acute injury superimposed on an already diseased lung, can occur, the incidence, risk factors and outcomes of AE remain unknown. The results of previous reports are variable, probably due to the small numbers of subjects and different definitions for AE. Therefore, COLLARD *et al.* [2] recently proposed diagnostic criteria for AE for future studies. Furthermore, clinically similar rapid deterioration (RD) can be caused by other conditions, such as infection, pulmonary embolism, pneumothorax or heart failure [3]. However, there are no reports about the incidence or outcomes of these events, except as autopsy findings or causes of death. Therefore, the aim of this study was to investigate the incidence, risk factors and outcome not only of AE using the criteria of COLLARD *et al.* [2], but also of RD from other causes.

MATERIALS AND METHODS

Study population

The subjects consisted of 461 patients (269 confirmed by surgical lung biopsy) diagnosed as having IPF according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus classification [4] at the Asan Medical Center, Seoul, South Korea from 1990 to 2009. Most of the biopsied patients were included in our previous reports [5–7].

Methods

RD was defined as an acute (within 30 days) worsening of dyspnoea requiring hospitalisation and the presence of newly developed radiologic

This article has supplementary material available from www.erj.ersjournals.com

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

abnormalities. AE was defined by the criteria of COLLARD *et al.* [2] (supplementary Table E1). Briefly, AE refers to a sudden aggravation of dyspnoea within 30 days with new bilateral lung infiltration in patients with known IPF or high-resolution computed tomography (HRCT) evidence of IPF without evidence of pulmonary infection or other known causes. Cases in which all these criteria were fulfilled were classified as ''definite AE'' and subjects who had not undergone endotracheal aspiration or bronchoalveolar lavage (BAL), but fulfilled all other criteria, were classified as ''suspected AE''. Clinically suspected infections (symptoms such as grossly purulent sputum and rapid resolution of symptoms in response to antibiotics alone) without an identified organism were categorised as ''suspected infection''.

All data were obtained from medical records. Although this was a retrospective study, we had an investigation protocol for suspected AE with new bilateral lung infiltration (supplementary Table E2). All microbiological studies and BAL were attempted in all patients, and echocardiography or embolism HRCT were performed in patients with suspected heart failure (on clinical/serial chest radiographs), or pulmonary thromboembolism, respectively. Survival status was obtained from medical records, the records of the National Health Insurance of Korea, Seoul, South Korea, and/or telephone interviews. Baseline clinical parameters were obtained within 1 month of the initial diagnosis.

Physiological assessments

Spirometry, diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) and total lung capacity (TLC) were measured according to the ATS/ERS recommendation [8–10], and the results were expressed as percentages of the normal predicted values (% pred).

Statistical methods

Data are presented as mean$\pm$SD for continuous variables or percentages for categorical variables. Chi-squared and Fisher's exact tests were used for categorical data, and the unpaired t-test and Mann–Whitney U-test were used for continuous data. A Cox regression analysis was used to identify significant variables capable of predicting AE or acting as prognostic factors. A logistic regression analysis was used to identify discriminating factors between AE and infection or prognostic factors of AE at the time of RD. The incidence of AE was obtained from the Kaplan–Meier survival curve by treating AE as the death variable. Survival was also evaluated using a Kaplan–Meier survival curve and the log rank test. p-values <0.05 were considered statistically significant. All data were analysed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

This study was approved by the Institutional Review Board of the Asan Medical Center.

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.

RESULTS

Incidence of AE

The mean age of all subjects was 63.4 yrs, and 77.7% were male. The median follow-up period was 22.9 months (range 0.1–168.3 months). During follow-up, 163 (35.4%) patients were admitted due to RD, and 42 (25.8%) of those RD patients experienced >1 episode of RD (range 2–4). AE occurred in 96 (20.8%) patients, and 17 (17.7%) of those AE patients experienced multiple episodes of AE (range 2–3 episodes).

The 1- and 3-yr incidences of AE (first event, unless otherwise specified) were 14.2 and 20.7%, respectively (table 1). 14 patients first presented and were diagnosed with IPF at the time of AE. After the exclusion of these cases, the 1- and 3-yr incidences of AE were 11.6 and 18.2%, respectively. The 1- and 3-yr incidences of total RD were 23.0 and 35.4%, respectively.

Aetiologies of RD

Among the 163 patients with RD, 23 (14.1%) patients had a focal lesion, such as pneumothorax or focal pneumonia. The remaining 140 (85.9%) patients had bilateral infiltration (bilateral ground glass attenuation (diffuse, multifocal patchy or subpleural) with or without some area of consolidation on HRCT). AE was the most frequent cause of RD (90 patients, 55.2% of RD), followed by infection (51 patients, 31.3% of RD) (table 2). Among the infections, opportunistic infections comprised 57.1% of documented organisms. They usually developed in the patients treated with steroids, regardless of whether or not cytotoxic agents were used (supplementary Table E3). Heart failure occurred in five patients (3.1% of RD), and pulmonary thromboembolism was observed in two cases (1.2% of RD). One patient satisfying all the criteria of AE had BAL eosinophilia (28% of RD) and rapidly improved after steroid treatment. We searched for various causes of eosinophilic pneumonia, but could not find a source of this disease. Although a biopsy was not performed at the time of RD, this patient was thought to have acute eosinophilic pneumonia, which might be a yet-unreported cause of RD.

Risk factors for AE

The patients with AE had lower forced vital capacity (FVC) and TLC compared to the non-RD group, even after the exclusion of the patients who first presented at the time of RD (table 3). In the univariate Cox analysis, low FVC, $D_{L,CO}$ and TLC, and never having smoked were significant risk factors for AE. In the multivariate analysis, among the parameters with p-values <0.1 in the univariate analysis, low FVC and never having smoked were significant factors (table 4).

Comparison of the clinical features of AE and bilateral infection

In the patients with AE, the frequency of fever, C-reactive protein (CRP) levels, disease duration and the percentage of neutrophils in BAL fluid were all significantly lower compared to those with infection, whereas the duration of dyspnoea and

TABLE 2 Aetiologies of rapid deterioration (RD; first episode)

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 pneumoniae* (2)
		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)

AE: acute exacerbation; PTE: pulmonary thromboembolism; AEP: acute eosinophilic pneumonia; MRSA: methicillin-resistant *Staphylococcus aureus*; CMV: cytomegalovirus; RSV: respiratory syncytial virus. [#]: percentage of total subjects (n=461); [¶]: identified by culture, antigen test (for *S. pneumoniae* and Legionella), or direct fluorescence monoclonal antibody stain (for *P. jiroveci*); [+]: cases in which no organism was identified, but infection was clinically suspected due to symptoms such as grossly purulent sputum and rapid resolution of symptoms in response to antibiotics alone; [§]: cases in which no organism was identified, but the criteria for AE were not completely satisfied due to incomplete study.

the percentage of lymphocytes in BAL fluid were higher in the AE group (table 5). In the multivariate logistic analysis (supplementary Table E4), the percentage of neutrophils in BAL fluid and fever were significant discriminating parameters between AE and infection.

Precipitating factors of AE

In the majority of patients, there were no identifiable precipitating factors of AE. However, 16 patients developed AE after the following procedures: video-assisted thoracoscopic surgery (n=8); lung resection due to lung cancer (n=3); operation for herniated intervertebral discs or spinal stenosis (n=2); BAL (n=1); vertebroplasty (n=1); and transarterial chemoembolisation due to hepatocellular carcinoma (n=1).

Immediate outcome and prognostic factors of AE

The immediate outcome of AE was very poor (fig. 1a and supplementary Table E5); the median survival was 2.2 months from the onset, and a half of the patients died during hospitalisation. About 50% of patients were admitted to an intensive care unit, and ~80% of these patients died. There was no difference in outcome between patients with AE and infection (fig. 1a and supplementary Table E5). The causes of in-hospital death in AE included AE itself (69.6%), infection (23.9%), diffuse alveolar haemorrhage (2.2%) and others (4.3%). The causes in patients with infection were infection (76.2%), disease progression (4.8%), diffuse alveolar haemorrhage (4.8%), cardiovascular disease (4.8%) and others (9.5%).

Among patients with AE, nonsurvivors had shorter durations of dyspnoea, lower arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) ratios, higher CRP levels, and higher percentages of neutrophils and lower percentages of lymphocytes in BAL fluid compared with survivors (supplementary Table E6). However, the multivariate analysis revealed that only CRP was an independent predictor of survival (OR 2.467, 95% CI 1.030–5.911; p=0.043; table 6). High-dose steroids were mostly used for treatment of patients with AE; however, treatment did not affect their outcome (table 7).

Impact of AE on the overall course of IPF

AE exerted a significant impact on the overall course of the disease. After the initial diagnosis, the median survival of patients with AE was much shorter (15.5 months) than that of patients without RD (60.6 months; p<0.001; fig. 1b and supplementary Table E7). The 5-yr rate of survival of patients with AE was 18.4%, whereas 50.0% of patients without RD survived (p<0.001). In the multivariate Cox analysis, AE was a significant predictor (hazard ratio 2.592, 95% CI 1.888–3.560; p<0.001) for poor overall survival in patients with IPF (table 8). In addition to AE, old age, low FVC and $D_{L,CO}$, and, interestingly, immunosuppressive therapy with steroids alone or with cytotoxic agents were independent poor prognostic factors. Not only AE, but also RD of bilateral lesions had a serious impact on the overall survival (fig. 1b and supplementary Table E7). Focal RD had a far weaker impact on survival.

Multiple episodes of RD

42 patients experienced more than one episode of RD, ranging from two (n=32) to four (n=1) episodes (supplementary Table E8). Similar to the overall trends in the first RD episodes, AE was the most frequent cause of second episodes (20 out of 42 patients) (supplementary Table E9) and the majority of patients (n=15) had AE as the cause of their first episode. Infection was the next most common cause of second episodes (n=15); notably, however, in the majority of these cases (n=7), the prior episode had been caused by AE.

DISCUSSION

In this study, we found that one-third (35.4%) of patients with IPF were hospitalised due to RD, and a quarter of these patients had multiple episodes. AE was the most frequent cause of RD, and 20.8% of all subjects experienced AE during

TABLE 3 Comparison of the baseline characteristics between patients with and without acute exacerbation (AE)

Characteristics	Non-RD	AE	p-value	Infection[#]	p-value[¶]
Patients	298	90		37	
Age yrs	63.4±8.1	64.3±8.9	NS	63.7±8.6	NS
Males	228 (76.5)	69 (76.7)	NS	30 (81.1)	NS
Smoking			0.107		NS
Never smoked	76 (25.5)	31 (34.4)		10 (27.0)	
Smokers	222 (74.5)	59 (65.6)		27 (73.0)	
Smoking exposure pack-yrs	34.8±19.2	35.7±20.0	NS	34.0±16.2	NS
PFT % pred[+]					
FVC	77.6±17.0	72.0±15.7	0.005	75.5±18.5	NS
$D_{L,CO}$	66.4±19.0	62.2±19.3	NS	61.2±18.0	0.088
TLC	78.7±14.4	73.8±15.0	0.021	75.9±18.5	NS
FEV_1	88.5±18.0	86.0±18.3	NS	89.0±17.5	NS
BAL %[+]					
Macrophages	71.0±18.4	67.8±16.4	NS	66.9±16.1	NS
Lymphocytes	15.7±12.4	15.7±11.2	NS	18.2±14.2	NS
Neutrophils	9.4±14.1	11.3±13.7	NS	10.8±9.4	NS
Eosinophils	3.2±4.6	3.2±4.4	NS	1.9±2.3	NS
CRP mg·dL^{-1}[+]	0.5±0.7	0.4±0.3	NS	0.7±0.7	0.055
Steroid with/without cytotoxic agent[§]	184 (61.7)	56 (62.2)	NS	20 (54.1)	NS

Data are presented as n, mean±SD or n (%), unless otherwise stated. RD: rapid deterioration; PFT: pulmonary function test; % pred: % predicted; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; TLC: total lung capacity; FEV_1: forced expiratory volume in 1 s; BAL: bronchoalveolar lavage; CRP: C-reactive protein; NS: nonsignificant. [#]: infection with bilateral lesions; [¶]: No-RD *versus* infection; [+]: data from the patients who first presented with RD were excluded; [§]: within 30 days prior to RD.

follow-up. The 1- and 3-yr incidences of AE were 14.2 and 20.7%, respectively. Never having smoked and low FVC were significant risk factors for AE. About a half of the patients died in hospital, and 1- and 5-yr survival rates from the initial diagnosis were 56.2 and 18.4%, respectively. AE, older age, low FVC and $D_{L,CO}$, and immunosuppressive therapy were significant predictors for poor overall prognosis.

Although there are many reports on the cause of death or occurrence of AE in patients with IPF in general [3, 7, 11, 12] and among patients with IPF admitted to an ICU [13–16], few studies have examined the incidence of RD and its impact on the course of IPF. PANOS *et al.* [3] reported that disease progression was the major cause of death in IPF (39%), followed by cardiovascular disease (27%), lung cancer (10%), pulmonary embolism (3%), pulmonary infection (3%) and others (18%). However, reports from Asia showed different trends. Our previous study revealed that IPF progression was the main cause of death (51.4%, including AE in 18.4%), followed by pneumonia (9.7%), lung cancer (4.9%), cardiovascular disease (1%) and others (33%) [7]. JEON *et al.* [11] reported IPF progression in 68% (AE in 46%), followed by infection (14%), lung cancer (8%), pulmonary embolism (2%), cardiovascular disease (2%) and others (6%). NAGAI *et al.* [12] also showed similar results: progression of IPF (72%), lung cancer (13%) and pulmonary infection (8%). The low proportion of cardiovascular disease and pulmonary embolism as a cause of death in Asian IPF patients may reflect ethnic differences, namely, the low prevalence of cardiovascular disease and thromboembolism in the general population of Asia [17–20].

Several retrospective studies on IPF patients admitted to ICUs showed that the majority had no identifiable cause of RD (probably AE), whereas a smaller number of cases were caused by pneumonia, pneumothorax, heart failure or complications of operation [13–16]. KUBO *et al.* [21], in a prospective study of anticoagulation therapy, showed that the major causes of RD were AE (n=32 events), pneumonia (n=8), heart failure (n=2) and sepsis (n=2). Our present study, which comprises a much larger number of patients and includes all categories of RD (not just patients admitted to an ICU or patients who died), confirmed that AE was the most common cause of RD, followed by infection.

The incidence of RD in IPF has not been previously reported, and the reported incidences of AE have varied widely (5% in 9 months and 57% in 3 yrs) [6, 21], probably due to differences in AE definitions and study designs. Therefore, COLLARD *et al.* [2] proposed diagnostic criteria for AE, in the hope of standardising future studies. The present report is one of the first to use the criteria of COLLARD *et al.* [2].

Furthermore, we found that a quarter of our enrolled RD patients had multiple episodes, which was suggested in previous reports [6, 21]. Consecutive episodes of AE or AE followed by infection were most frequent (supplementary Table E8).

There are no previous reports regarding risk factors for the development of AE or RD. In this study, we found that patients with AE had never smoked and had significantly lower lung function compared to non-RD patients (table 3), which may

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

HR: hazard ratio; PFT: pulmonary function test; FVC: forced vital capacity; % pred: % predicted; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; TLC: total lung capacity; BAL: bronchoalveolar lavage; CRP: C-reactive protein; NS: nonsignificant. [#]: within 30 days prior to RD; [¶]: TLC % pred was excluded from the multivariate analysis due to the close correlation between FVC % pred and TLC % pred ($r=0.765$; $p<0.001$).

TABLE 5 Comparison of the clinical features of the patients with acute exacerbation (AE) and the bilateral infection at the time of rapid deterioration (RD)

Characteristics	AE	Infection	p-value
Patients	90	37	
Age yrs	65.3±7.9	66.1±7.6	NS
Males	69 (76.7)	30 (81.1)	NS
Disease duration months	16.5±24.5	29.5±34.7	0.014
Steroid with/without cytotoxic agent use[#]	56 (62.2)	20 (54.1)	NS
Duration[¶] months	3.4±3.8	4.5±5.2	NS
Last dose[¶] mg	18.8±13.2	18.4±15.0	NS
Duration of dyspnoea days	11.2±12.5	6.1±7.4	0.030
Initial symptoms			
Documented fever	18 (20.0)	19 (51.4)	0.001
Sputum production	63 (70.0)	31 (83.8)	NS
CRP mg·dL^{-1}	8.3±6.8	14.7±9.8	<0.001
$P_{a,O_2}/F_{I,O_2}$	253±83	228±91	NS
BAL			
Total cells·mm^{-3}	292±168	349±342	NS
Lymphocytes %	19.7± 19.6	8.1±7.5	0.041
Neutrophils %	22.9±19.9	55.2±28.9	0.001

Data are presented as n, mean±SD or n (%), unless otherwise stated. CRP: C-reactive protein; P_{a,O_2}: arterial oxygen tension; F_{I,O_2}: inspiratory oxygen fraction; BAL: bronchoalveolar lavage; NS: nonsignificant. [#]: within 30 days prior to RD; [¶]: steroid (prednisolone) treatment.

suggest that AE tends to occur in patients with advanced disease (before death).

There was an increased risk of opportunistic infections in patients with IPF, which may be due to prior treatment with steroids with or without cytotoxic agents, although we could not demonstrate this effect clearly in this study (supplementary Table E3) [22–25]. Because the clinical features of infection are similar to AE, infection, particularly opportunistic infection, was the most important and difficult differential diagnosis of AE. In most reports, including the present study, infection was the second most common cause of RD or death. These findings may suggest a possibility that AE may be a masked or undiagnosed infection. Viral infection has also been suggested as a possible cause of AE [26, 27]. Interestingly, CRP levels were elevated in both conditions, although they were much higher in infections than in AE, and CRP levels were a significant prognostic factor of AE (table 6). These findings may suggest that inflammation can be one pathogenic mechanism contributing to AE.

The outcome of AE in earlier reports was invariably very high [13, 16, 28], probably due to the inclusion of only very severe cases. However, more recent studies reported better outcomes (9-month mortality rate 20%) [29, 30]. In the present study, the in-hospital and 90-day mortalities were 50.0 and 60.0%, respectively; however, the mortality of patients requiring mechanical ventilation was 90.0% (supplementary Table E5).

The univariate logistic analysis showed that the duration of dyspnoea, $P_{a,O_2}/F_{I,O_2}$ ratio, CRP level and percentage of lymphocytes in BAL fluid were prognostic factors; however, in the multivariate analysis, only the CRP level was an independent risk factor (table 6). Our study clearly showed that AE exerted a serious impact on the overall survival of patients (fig. 1b and supplementary Table E7). The multivariate Cox analysis revealed that AE was a significant predictor of poor prognosis. Old age, low FVC, low $D_{L,CO}$ and steroids with or without cytotoxic agent treatments were also independent predictors.

Because this was a retrospective study, it has several limitations. 1) Although we tried to perform investigations according to the protocol, not all patients underwent a complete work-up. BAL and/or endotracheal aspiration were performed in 52.8% and echocardiography and/or brain natiuretic peptide (BNP) in 55.2%, although all patients with any suspicion of cardiovascular problems underwent echocardiography and BNP with consultation to cardiology. Similarly, embolism computed tomography was performed in 21%, although the clinical features (including HRCT findings) of nonperformers were inconsistent with pulmonary embolism without predisposition. Therefore, we believe the risk of misclassifying pulmonary embolism or heart failure was not high. The most difficult differential diagnosis was infection, as previously described. 2) Although we tried to obtain information from all of the patients by telephone interviews and tracking to other hospitals, 34 out of 461 patients were still

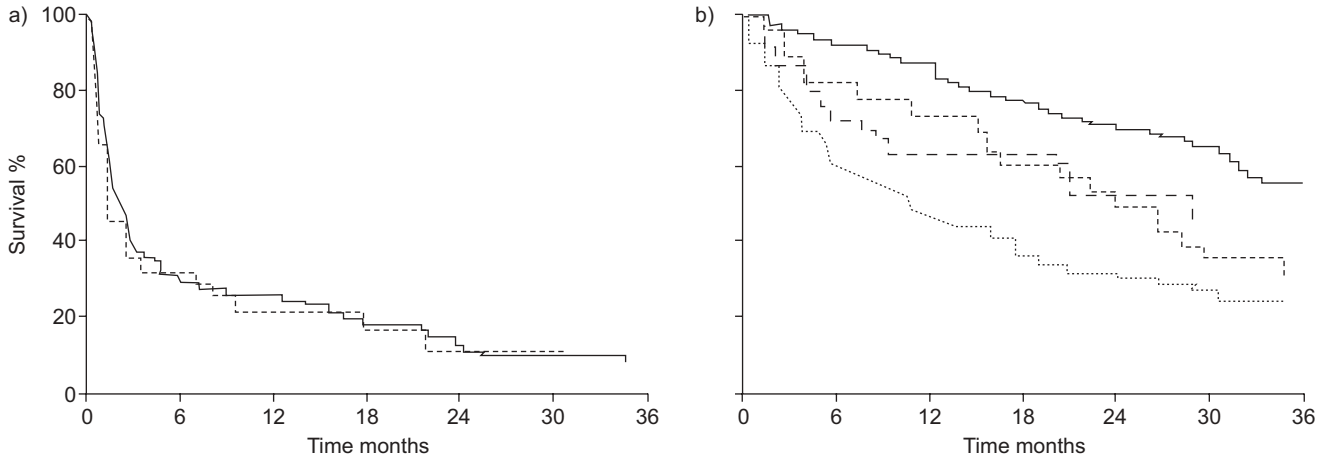

FIGURE 1. a) Comparison of survival curves (from rapid deterioration to death or last follow-up) between patients with acute exacerbation (AE) (—) and infection (---). b) Comparison of survival curves (from initial diagnosis to death or last follow-up) for patients with no rapid deterioration (RD) (—), AE (·····), bilateral infection (----) and focal RD (– – –).

unavailable during follow-up. 3) This study was the result of an analysis of a single tertiary referral center. However, the demographic features and average lung function of our subjects were comparable to other studies. 4) The median follow-up period was relatively short (22.9 months). However, considering the short survival of IPF, this follow-up period was long enough to reveal the incidence, risk factors, prognostic factors and occurrence of multiple episodes of RD. Despite these limitations, this was the largest study evaluating AE and RD and the first study using the criteria of COLLARD *et al.* [2] for AE. The criteria of COLLARD *et al.* [2] may overestimate the occurrence of AE, because negative culture results cannot completely rule out the possibility of infection and ''suspected AE'' was included for those with inadequate work-ups. However, when we reanalysed our data using only the cases with definite AE (data not shown), the results were similar.

In conclusion, we show that RD is relatively common during the course of IPF (one-third of IPF patients) and AE was the most frequent cause of RD, followed by infection. Low FVC and never having smoked were risk factors for AE, and CRP at the time of AE was a prognostic factor. AE exerted a serious impact on the overall survival of patients with IPF, and old age, low FVC and $D_{L,CO}$, and immunosuppressive treatments were other independent predictors of poor prognosis.

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

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

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

TABLE 7 Treatment during acute exacerbation (AE) and in-hospital outcome of patients with AE according to treatment

Treatment regimen	Cases	Survival	p-value
Steroid pulse[#]	13 (14.4)	7 (53.8)	0.933
Steroid pulse[#] plus cytotoxic agent[¶]	8 (8.9)	4 (50.0)	
High-dose steroid[+]	46 (51.1)	19 (41.3)	
High-dose steroid[+] plus cytotoxic agent[¶]	14 (15.6)	11 (78.6)	
Low-dose steroid[§]	6 (6.7)	3 (50.0)	
Low-dose steroid[§] plus cytotoxic agent[¶]	1 (1.1)	1 (100.0)	
No treatment	2 (2.2)	0	
Total	90 (100)	45 (50)	

Data are presented as n (%) unless otherwise stated. [#]: steroid pulse was $\geqslant$500 mg·day^{-1} methylprednisolone for 3 days, followed by high-dose steroid; [¶]: cytotoxic agents were azathioprine, cyclosporine or cyclophosphamide; [+]: high-dose steroid was $\geqslant$0.5 mg·kg^{-1}·day^{-1} prednisolone; [§]: low-dose steroid was $\leqslant$0.5 mg·kg^{-1}·day^{-1} prednisolone.

TABLE 8 Prognostic factors for the overall survival from the initial diagnosis of idiopathic pulmonary fibrosis

Parameters	HR (95% CI)	p-value
Univariate Cox analysis		
Age	1.016 (1.001–1.031)	0.032
Male sex	0.910 (0.685–1.209)	NS
Smoking	0.737 (0.568–0.956)	0.021
PFT % pred		
FVC	0.976 (0.968–0.984)	<0.001
$D_{L,CO}$	0.978 (0.971–0.986)	<0.001
TLC	0.975 (0.965–0.984)	<0.001
BAL		
Macrophages	1.003 (0.993–1.014)	NS
Lymphocytes	0.998 (0.985–1.012)	NS
Neutrophils	0.996 (0.980–1.012)	NS
Eosinophils	0.979 (0.941–1.018)	NS
CRP	1.073 (0.808–1.423)	NS
Steroid with/without cytotoxic agent	1.529 (1.177–1.986)	0.001
Occurrence of AE[#]	2.770 (2.132–3.599)	<0.001
Multivariate Cox analysis[¶]		
Age	1.017 (1.001–1.033)	0.032
PFT % pred		
FVC	0.987 (0.977–0.997)	0.009
$D_{L,CO}$	0.985 (0.976–0.994)	0.001
Steroid with/without cytotoxic agent	1.552 (1.113–2.164)	0.010
Occurrence of AE	2.592 (1.888–3.560)	<0.001

HR: hazard ratio; PFT: pulmonary function test; % pred: % predicted; FVC: forced vital capacity; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; TLC: total lung capacity; BAL: bronchoalveolar lavage; CRP: C-reactive protein; AE: acute exacerbation; NS: not significant. [#]: overall occurrence during follow up; [¶]: TLC % pred was excluded from the multivariate analysis due to the close correlation between FVC and TLC % pred ($r=0.765$; $p<0.001$).

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

The authors thank the excellent statistical support of S-C. Yun (University of Ulsan College of Medicine, Seoul, South Korea).

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