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A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia

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Keywords
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Short title: Mortality predictors in acute exacerbation of chronic fibrosing IP

Abstract

Objectives To assess clinical, laboratory, and radiographic findings associated with outcomes and to clarify more practical ways to predict hospital mortality in patients with acute exacerbation (AE) of chronic fibrosing interstitial pneumonia (CFIP).

Design Single-centre retrospective cohort study.

Setting University hospital in Japan.

Participants We identified 51 consecutive patients with AE of idiopathic CFIP through multidisciplinary discussion. Patients who had connective tissue disease, drug-induced lung disease, pneumoconiosis, hypersensitivity pneumonitis, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, and eosinophilic pneumonia were excluded.

Interventions There were no interventions.

Main outcome measures The main outcome was determination of in-hospital mortality predictors. Other outcomes included clinical, laboratory, and radiographic differences between nonsurvivors and survivors in patients with AE of CFIP.

Results: The mean age of the patients with AE of CFIP was 71 years. Compared with survivors, nonsurvivors had significantly shorter duration of symptoms before admission, lower prevalence of peripheral distribution of acute pulmonary infiltrates and centrilobular emphysema (CLE) on thin-section CT, lower peripheral lymphocyte count, higher brain natriuretic peptide titre, lower PaO_2/FIO_2 (P/F) ratio, higher prevalence of systemic inflammatory response syndrome (SIRS), and higher SIRS score on admission (p=0.0069, 0.0032, 0.015, 0,040, 0.0098, 0.012, 9.9×10^{-7}, and 5.4×10^{-6}, respectively). Multivariate analysis revealed SIRS (HR=12.7400, p=0.00055), CLE (HR=0.0679, p=0.00011), and serum procalcitonin (PCT) level (HR=2.7860, p=0.022) to be independent predictors of in-hospital mortality. A Kaplan-Meier estimate on the basis of stratification according to the presence or absence of SIRS and CLE demonstrated a distinct survival curve for each subset of patients.

Conclusion Distinct survival curves documented by the stratification according to the presence or the absence of SIRS and CLE may provide basic information for a rational management strategy for patients with AE of CFIP on admission.

ARTICLE SUMMARY

Article focus

- Several independent predictors of mortality in patients with AE of idiopathic pulmonary fibrosis have been identified. However, more practical ways to predict hospital mortality, which may be of use in routine medical care, are required for AE of CFIP.
- This study was undertaken to identify practical mortality predictors in patients with AE of CFIP.

Key messages

- SIRS and CLE, which have not previously been evaluated as factors possibly affecting outcome, were the most significant predictors of in-hospital mortality in patients with AE of CFIP. Stratification according to the presence or the absence of these 2 factors documented distinct prognoses for the subsets of patients, and thus may be helpful for enabling more appropriate management strategies in the future.

Strength and limitations of this study

- This study's strength was the identification of the novel, non-invasive, and easily applicable predictors of in-hospital mortality in patients with AE of CFIP. The major limitation of the study was the single-centre retrospective design.

Introduction

In patients with a pre-existing chronic process of pulmonary fibrosis, such as idiopathic pulmonary fibrosis (IPF), an acute exacerbation (AE) is the development of acute lung injury superimposed on the underlying disease. Although AE was first described in patients with IPF,[1] it has also been reported in underlying diseases other than IPF, such as interstitial pneumonia associated with connective tissue disease,[2, 3] fibrotic nonspecific interstitial pneumonia (NSIP),[2, 3] hypersensitivity pneumonitis,[4] and asbestosis.[5] This suggests that a variety of chronic fibrosing processes of the lung can present a potential risk for AE.

Because a specific treatment for AE has not yet been established, the mortality rate in patients with AE of IPF remains high.[6] Furthermore, patients with secondary usual interstitial pneumonia (UIP) or pathological pattern of NSIP, who generally have favourable prognosis than those with IPF, also show high mortality from AE.[2 3]

Recently, factors predicting the onset of AE have been described in IPF patients. These include high modified medical research council score, high body mass index, a decline in forced vital capacity (FVC) at 6 months from the diagnosis; [7] low FVC.[8] Factors affecting survival in patients with AE of IPF have been also described,[9] and include high-resolution CT (HRCT) patterns (diffuse/multifocal/peripheral) of acute pulmonary infiltrates, degree of CT involvement, and serum lactate dehydrogenase (LDH) titre. Another report has found that the extent of ground-glass attenuation with traction bronchi- or bronchiolectasis and honeycombing on HRCT were the 2 independent prognostic factors in patients with AE of IPF.[10] CT findings directly associated with disease severity may predict the patient survival; however, the exploration of more objective and easily applicable predictors of mortality would be of value for developing rational management strategies, including novel therapeutic appoaches.[11]

In the present study, we retrospectively analysed 51 consecutive patients with AE of idiopathic chronic fibrosing interstitial pneumonia (CFIP) in order to identify novel in-hospital mortality predictors that are present on admission.

Methods

Subjects

Consecutive patients with AE of idiopathic CFIP admitted to our department between January 2009 and May 2012 were retrospectively studied. During that interval, 56 patients were admitted for AE of CFIP. Of those, 19 patients were successfully managed to hospital discharge (survivors) and 37 patients died during hospitalization (nonsurvivors). Of the latter, 5 patients who died from causes other than AE were excluded.

Diagnostic criteria

The following features based on the previously used criteria[12] were used to define an AE event: 1) aggravation of dyspnoe within 1 month; 2) decline of ≥10% in absolute forced vital capacity or decline of ≥10 Torr in PaO_2 or decline of ≥5% in SpO_2; 3) new ground-glass opacities or consolidation on chest radiograph or thin-section CT (TSCT); 4) negative respiratory culture and serologic test results for respiratory pathogens; and 5) no clinical evidence of pulmonary embolism, congestive heart failure, or pneumothorax as a cause of acute decline.

The diagnosis of idiopathic CFIP was firstly based on TSCT results: presence of a diffuse parenchymal lung disease with significant pulmonary fibrosis, defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion and/or traction bronchiectasis or bronchiolectasis.[13] Patients found to have other distinct diseases on the basis of clinical and /or radiographic findings, associated with the development of pulmonary fibrosis, such as connective tissue disease, drug-induced lung disease, pneumoconiosis, hypersensitivity pneumonitis, sarcoidosis, pulmonary histiocytosis, and lymphangioleiomyomatosis were excluded. The diagnosis of IPF was made according to the 2011 ATS/ERS/JRS/ALAT statement on IPF.[14] For this study, we diagnosed patients with IPF when they displayed features that fit the criteria for UIP as assessed by high-resolution CT (HRCT) or met the criteria for UIP after a combination of HRCT and surgical lung biopsy findings.

CT imaging

TSCT was performed for all patients, usually on the day of admission, using a Somatom Sensation 64 (Siemens Medical Solutions, Forchheim, Germany). Images were obtained with 1.5-mm collimation and 1.5-mm slice intervals from pulmonary apex to lung base, reconstructed with a high-spatial-resolution algorithm and small field-of-view. The images were analysed at a window level of -700 HU and a window width of 1,400 HU.

The extent of the TSCT findings characteristics of AE and CFIP were determined; a thoracic radiologist and a pulmonary physician, both of whom were experts in interstitial lung diseases, examined the CT images without knowledge of any of the clinical, functional, and radiographic findings. Ground-glass opacity (GGO) was defined as an area of slightly increased attenuation in which the vessels remained visible. Honeycombing was defined as an accumulation of cystic spaces with thickened walls. The extent of GGO and honeycombing was scored to the nearest 10% at the 6 lung zones: right upper and middle lobes, left upper segment and lingula, bilateral lower lobes. The scores at the 6 lung zones were then averaged out to obtain a mean score.[15] Finally, new infiltrates including GGO at the time of AE were classified as peripheral, multifocal, or diffuse parenchymal patterns, as previously described.[16]

Because concurrent emphysema may affect an accurate CT diagnosis of UIP and NSIP,[17] CT images before admission were also reviewed, especially for distinguishing honeycombing from emphysema with GGO. We could access previous CT images for 40 of the 51 patients. In the remaining 11 patients, serial thoracic CT images were also reviewed in addition to the CT image obtained on admission to verify the diagnosis of CFIP.

Systemic inflammatory response syndrome (SIRS)

The diagnosis of SIRS was determined at the time of admission, according to the previously defined criteria: temperature >38^0C or <36^0C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or $PaCO_2$ <32 Torr; white blood cell count >12,000/μl, <4,000/μl, or >10% band forms. Subjects who met 2 of more of the criteria were diagnosed with SIRS.[18]

Data expression and the statistics analysis

Clinical data are expressed as mean ± SD for continuous variables. Group comparisons were made using the Mann-Whitney *U* test, χ^2 statistics, and Fisher's exact test, as appropriate. Logistic regression analysis was performed to determine the relationships between clinical parameters. A Kaplan–Meier model was generated to evaluate survival. Univariate and multivariate analyses using the Cox proportional hazards regression models were used to identify independent patient characteristics, laboratory data and CT predictors of hospital mortality. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R Commander (version 1.6-3) designed to include statistical functions frequently used in biostatistics.[19] Statistical significance was defined as a p value of <0.05.

Results

Patient profiles and the onset of AE

The flow diagram in figure 1 shows how the patients were identified. We identified 51 patients with AE of idiopathic CFIP (37 males and 14 females) between January 2009 and May 2012. The mean age, male-to-female ratio, smoking history, and the mean smoking index were similar in nonsurvivors and survivors. The mean duration of symptoms (cough or dyspnoea) before admission was significantly shorter in nonsurvivors (P=0.0069, table 1).

Diagnosis of idiopathic CFIP and TSCT findings

In this cohort, 30 patients were diagnosed with IPF according to the 2011 criteria,[14] and the remaining 21 patients were diagnosed with non-IPF. The latter group included 1 patient with upper-lobe dominant pulmonary fibrosis and 2 patients with familiar pulmonary fibrosis. The remaining 18 patients showed findings consistent with fibrotic NSIP on TSCT.[20]

The prevalence of IPF, the extent of GGO and the extent of honeycombing were not significantly different between nonsurvivors and survivors (table 2). Peripheral distribution of new infiltrates and centrilobular emphysema (CLE) were significantly less prevalent in nonsurvivors (p=0.0032 and 0.015, respectively).

Laboratory data and SIRS

The mean peripheral blood lymphocyte count was significantly lower in nonsurvivors (p=0.040, table 3). The mean serum brain natriuretic peptide (BNP) titer was elevated in both groups and significantly higher in nonsurvivors (p=0.0098). The mean white blood cell counts, serum C-reactive protein, serum Krebs von den Lungen-6, serum surfactant protein-D, serum procalcitonin (PCT), and the mean D-dimer titres were elevated in both groups, but were not significantly different between groups. The mean PaO_2/FIO_2 (P/F) ratio on admission was significantly lower in nonsurvivors (p=0.012). On admission, 28 out of 32 nonsurvivors and 4 of 19 survivors fulfilled the criteria for SIRS ($p=9.9 \times 10^{-7}$, table 3). The mean SIRS score was significantly higher in nonsurvivors ($P=5.4 \times 10^{-6}$). The SIRS score and the serum PCT level were positively correlated (p=0.0045, fig 2).

Treatment and the response

Glucocorticoid pulse therapy (methylprednisolone at 1,000mg/day for 3 consecutive days) was performed in 31 of 32 nonsurvivors and all of the 19 survivors (table 4). Immunosuppressants other than glucocorticoids and mechanical ventilation were used at similar rates in the 2 groups. The mean P/F ratio on the day after glucocorticoid pulse therapy was significantly lower in nonsurvivors (p=0.00018).

Prognosis

In nonsurvivors, the median survival time was 33 days. In survivors, 2 patients died from a second AE event after discharge from hospital. The overall survival was 67% at 30 days, 43% at 60 days, and 40% at 90 days after admission. Kaplan-Meier estimate for overall survival revealed that the survival rate reached a plateau of approximately 35% at approximately 180 days from admission (fig 3).

Univariate and multivariable analyses of survival

Univariate analysis (table 5) revealed that the number of days from onset to admission, the extent of honeycombing on CT, the presence of CLE, serum PCT level, P/F ratio on admission, the presence of SIRS, and the SIRS score were significant predictors of mortality. The P/F ratio on the day after glucocorticoid pulse therapy was also significant in univariate analysis. Multivariable analysis revealed that the serum PCT (hazard ratio [HR] per 10%-increase, 2.7860; 95% confidence interval [CI], 1.1620-6.6770; p=0.022), the presence of CLE (HR, 0.0679; 95%CI, 0.0173-0.2658; p=0.00011), and the presence of SIRS (HR, 12.7400; 95%CI, 2.1150-76.7900; P=0.00055) remained significant predictors after adjusting for age, sex, BNP, P/F ratio on admission, and extent of honeycombing (table 6).

On the basis of the results of multivariate analysis, we divided the patients into 4 subgroups according to the presence or absence of CLE and SIRS (group 1: SIRS- and CLE+; group 2: SIRS- and CLE-; group 3: SIRS+ and CLE+; group 4: SIRS+ and CLE-). A Kaplan-Meier estimate according to this subgrouping revealed a clear distinction in the prognoses between the 4 subgroups (fig 4). All patients in group 1

recovered and survived to discharge; although the prognosis for group 1 was not statistically different from that for groups 2, it was significantly better than that for group 3 ($p=0.016$). There was not significant difference in the prognosis between groups 2 and group 3; however, group 2 had a significantly better prognosis than group 4 ($p=1.3 \times 10^{-6}$). The prognosis for group 3 was significantly better than that for group 4 ($p=0.0034$).

Discussion

In the present study, the signs and symptoms of 18 of 21 patients diagnosed with non-IPF were suggestive of fibrotic NSIP on TSCT. [20] There is the possibility that patient with IPF included in the non-IPF group, and vice versa. However, whether a patient had IPF or not was not associated with outcome in our cohort. Furthermore, the prognostic difference between patients with definite UIP, possible UIP, and findings inconsistent with UIP on TSCT was not significant (data not shown). Thus, we considered that there were convincing reasons to place all subjects studied into the CFIP category. There have been a few reports on AE of non-IPF, including a study of patients with idiopathic NSIP (2007 Park, 2007 Silva) [2 3], in which the overall mortality rate was as high as 70%. This suggests that AE, a manifestation of diffuse alveolar damage, may commonly be fatal, irrespective of an individual pattern of CFIP.

Attention should be paid to the differences between survivors and nonsurvivors in clinical, laboratory, and radiographic findings in this cohort. The relatively short symptom duration before admission in nonsurvivors might be dependent on the severity of the lung injury that has not yet been strictly objectified. Radiographically, factors for discriminating between nonsurvivors and survivors were the distribution pattern of acute pulmonary infiltrates and the presence of CLE, but not the presence of paraseptal emphysema. CT patterns have been shown to be associated with the mortality in patients with AE of IPF, [9] however, there may be a degree of subjectivity in the diagnosis of this condition, and interobserver differences must be considered. Among laboratory data, the serum BNP level and the P/F ratio on the day after glucocorticoid pulse therapy, as well as those on admission, were discriminative. We performed echocardiography in every patient with signs and symptoms clinically suggestive of cardiac dysfunction or those with increased serum BNP, and none showed left ventricular dysfunction. The higher P/F ratio after glucocorticoid pulse therapy suggests that this treatment might be effective for a certain subset of patient. The presence of SIRS and the number of SIRS criteria fulfilled were the factors that provided the most significant discrimination between survivors and nonsurvivors.

The univariate analysis revealed that the extent of honeycombing was associated with survival; this was not apparent in the group comparison. On the basis of the results of the univariate analysis, we performed a multivariate analysis of survival, and it revealed some notable results: the most significant factors for predicting in-hospital mortality were the presence of SIRS and the absence of CLE on TSCT; the serum PCT level was also associated with outcome.

The presence of SIRS, first defined in 1992, indicates a systemic inflammatory response to a variety of severe clinical insults, including noninfectious causes such as trauma, burns, or pancreatitis, etc.[18] The definition of SIRS is simple, and thus can be easily applied in routine medical care; however, the clinical significance of SIRS has been controversial. In infected subjects, the number of SIRS criteria fulfilled did not influence patient outcome, despite the fact that the presence of organ dysfunction or shock showed prognostic significance.[21] In our study, SIRS was significantly more prevalent in nonsurvivors, and was one of the most significant predictors of hospital mortality. The influence of SIRS on mortality in patients with AE of CFIP has not yet been examined, probably because that the disease process has been recognized as a disorder compartmentalized to the lung. Compared with stable IPF patients, patients with AE of IPF has been reported to show increases in serum biomarkers associated with endothelial cell injury, such as thrombomodulin or plasminogen activator inhibitor-1 (PAI-1).[22] In addition, increases in levels of proinflammatory cytokines such as interleukin-6 or interleukin-8 are well-known biomarkers for the severity of the disease in patients with acute lung injury/acute respiratory distress syndrome.[23] These data suggests a possibility that acute lung injury mediates systemic inflammation via certain circulating molecules, as in the case of AE of CFIP. The significance of SIRS as a mortality predictor should be confirmed in future studies. Investigations to determine the mechanisms of SIRS development in patients with AE of CFIP may be essential to allow the development of more specific treatments.

PCT, a prohormone of calcitonin, is produced in the medullary C-cells of the thyroid gland. It was described as an infection parameter in the early 1990's[24] and is now considered to be a useful serum biomarker for early diagnosis of bacterial infections.[25] On the other hand, increase of serum PCT levels caused by noninfectious processes have also been reported. In a retrospective analysis of

patients who underwent cardiopulmonary bypass surgery but who did not have postoperative infection, Hensel et al. described a significant increase in PCT in patients with both SIRS and acute lung injury, compared with those with SIRS alone [26] In their cohort, PCT levels were also elevated in patients without SIRS as well as in patients with SIRS alone, and the levels were statistically similar; this indicates that acute lung injury might play a critical role in the facilitated generation of PCT. Rapid increases of PCT levels in patients with nonbacterial pneumonitis caused by inhalational burn have also been reported.[27] In our cases of AE, serum PCT levels were of prognostic significance, and were also positively correlated with the number of SIRS criteria. The measurement of PCT has 2 key implications in our cohort. First, PCT was useful for excluding the possibility of respiratory infections, because most of the patients had PCT levels of < 0.25 ng/ml (data not shown), which is below the level suggestive of severe pneumonia and/or bacteremia.[28] Second, in the absence of overt respiratory infection, a relatively slight but significant elevation of PCT should not be ignored. PCT was proved to be associated with hospital mortality in both the univariate and multivariate analyses. Although the source of PCT in patients with AE of CFIP has not been confirmed, pulmonary neuroendocrine cells are possible candidates, because an abundance of calcitonin per unit weight of lung tissue has been described.[27 29] The serum PCT level was positively correlated with the number of SIRS criteria, suggesting that PCT could be a novel candidate biomarker for AE of CFIP.

One report has indicated that the absence of smoking history might positively influence the onset of AE in patients with IPF;[8] however, CLE has not been evaluated as a mortality predictor. There are a few possible reasons why the presence of CLE was associated with outcome. First, in some subjects with both CFIP and CLE, diffuse alveolar damage, a histopathological hallmark of AE of CFIP, was not present. Second, the pathogenesis of CLE itself antagonizes that of on-going diffuse alveolar damage. Finally, glucocoticoids are more effective for subjects who have background CLE. As mentioned above, we ruled out the possibility of obvious cardiac dysfunction by echocardiography in the patients studied. Six out of 11 survivors with CLE underwent bronchoalveolar lavage soon after the admission (data not shown), and none showed overt alveolar haemorrhage. Although AE in patients with combined pulmonary fibrosis and emphysema (CPFE) has recently been reported,[30] its curability has not been described. In patients with chronic obstructive pulmonary disease (COPD), gene expression analysis and immunohistochemistry showed that urokinase plasminogen activator (PLAU) and urokinase plasminogen activator receptor (PLAUR) were found to be overexpressed in alveolar macrophages and bronchial epithelium.[31] In infant respiratory distress syndrome, a condition characterized by intraalveolar fibrin deposition, the ratio of PAI-1 to PLAU in tracheal aspirates was higher than that in control subjects,[32] suggesting a role for PLAU in intraalveolar fibrinolysis. Lung-specific overexpression of PLAU in mice was shown to reduce the accumulation of collagen in the lung and reduced mortality after bleomycin-induced lung injury.[33] Thus, constitutive activation of the PLAU-PLAUR system in subjects with CLE, a histological hallmark of COPD, may antagonize the activation of PAI-1, a possible biomarker of AE of CFIP. Generally, COPD itself has been demonstrated to show glucocorticoid resistance.[34] It remains to be determined whether there are any differences in the histological patterns of AE and the efficacy of glucocorticoids between in patients with CFIP alone and those with both CFIP and CLE. The histological patterns could be unraveled by analysis of surgical lung biopsy specimens, and the efficacy of glucocorticoids could be clarified with the accumulation of data from future clinical cases.

The Kaplan-Meier estimate for survival according to the subgrouping by the presence or the absence of SIRS and CLE clearly divided the patients into 4 subgroups. Every patient in group 1 (SIRS-CLE+) was successfully treated with glucocorticoids and discharged. Although an effective pharmaceutical therapy has not been established for patients with AE of IPF, [12] the present study is the first to document a subgroup of CFIP patients who derive a possible benefit from glucocorticoid therapy during AE. Five of the 7 cases in group 1 were of IPF. By contrast, all 22 patients in group 4 (SIRS+CLE-) died due to respiratory failure secondary to AE. In this subgroup, any treatment option, such as polymyxin B-immobilized fibre column treatment[11], should be considered. An indication for the use of glucocorticoids should be also discussed in the future.

The limitations of the present study are as follows. First, the analysis was retrospective. However, we consecutively enrolled every subject admitted with AE of CFIP from January 2009, and collected the hospitalization medical records as completely as possible. Second, this study was undertaken in a single medical institution, and therefore the number of patients studied was limited. Third, the diagnosis of CFIP and the classifications were somewhat dependent on TSCT findings. Because most of

the patients were in moderate to severe respiratory failure (two-thirds of the patients studied had a P/F ratio of ≦ 200, data not shown), surgical lung biopsies on admission were difficult to perform. Half of the patients studied had been referred, and among those, none had undergone surgical lung biopsy. Consequently, 5 patients underwent surgical lung biopsy in this study. We tried, as much as possible, to rule out known entities associated with the development of pulmonary fibrosis. Finally, most of the referred subjects had not undergone pulmonary function tests before admission. Therefore, we could not evaluate pulmonary function test results as mortality predictors.

Several mortality predictors have been identified in patients with AE of IPF. However, it is unclear how those factors could be contribute to the management of this possibly fatal disorder in routine medical practice. We expect that the prognostic significance of CLE and SIRS, factors by which patients could be sub-grouped on admission, could contribute to the rational management of patients with AE of CFIP. The utility of these prognostic factors should be prospectively investigated in future cohorts.

Contributorship
YU conceived and designed the study. YU, AK, FS, AS, KK, KH and MK were involved in the acquisition, analysis, and interpretation of the data and in writing the article before submission.

Data sharing
There are no additional data available.

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Competing Interests
None

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Tables and figures

Table 1 Clinical characteristics of the patients studied

	Nonsurvivors	Survivors	p Value
Age	72 ± 10	69 ± 5	0.22
Male / Female	23 / 9	14 / 5	0.91
Smoking history, +/-	23 / 9	15 / 4	0.48
Smoking index, pack-years	28 ± 25	45 ± 37	0.071
Days from the onset to admission	7 ± 4	14 ± 9	0.0069

Table 2 Classification of CFIP and TSCT findings

	Nonsurvivors	Survivors	p Value
IPF/non-IPF	19/13	11/ 8	0.94
Extent of Honeycombing, %	17 ± 13	11 ± 10	0.12
Extent of GGO, %	56 ± 15	49 ± 15	0.10
Distribution of new infiltrates: diffuse/multifocal/peripheral	29/1/2	12/1/6	0.0032
CLE, +/-	7 / 25	11 / 8	0.015
PSE, +/-	15 / 17	12 / 7	0.39

CFIP, chronic fibrosing interstitial pneumonia; TSCT, thin-section computed tomography; IPF, idiopathic pulmonary fibrosis; GGO, ground-glass opacity; CLE, centrilobular emphysema; PSE, paraseptal emphysema.

Table 3 Laboratory data and SIRS on admission

	Nonsurvivors	Survivors	p Value
WBC, /μl	12,041 ± 6,450	9,712 ± 3,315	0.26
Lymphocyte, /μl	1,182 ±780	1,447 ± 570	0.040
CRP, mg/dl	9.7 ± 6.0	10.4 ± 8.7	0.90
KL-6, U/ml	1,513 ± 687	1,535 ± 1,013	0.63
SP-D, ng/ml	427 ± 321	360 ± 262	0.54
BNP, pg/ml	168 ± 164	93 ± 171	0.0098
D-dimer, mg/ml	4.1 ± 4.6	6.2 ± 10.5	0.35
PCT, ng/ml	0.33 ± 0.60	0.13 ± 0.12	0.17
PaO_2/FIO_2 ratio	157 ± 53	213 ± 81	0.012
SIRS, +/-	28/4	4/15	9.9×10^{-7}
SIRS score	2.5 ± 0.9	1.1 ± 1.0	5.4×10^{-6}

WBC, white blood cell; CRP, C-reactive protein; SP-D, surfactant protein D; KL-6, Krebs von den Lungen-6; BNP, brain natriuretic peptide; PCT, procalcitonin; SIRS, systemic inflammatory response syndrome.

Table 4 Treatment and the response

	Nonsurvivors	Survivors	p Value
Glucocorticoid pulse therapy, +/-	31/1	19/0	1.0
Immunosuppressants other than glucocorticoids, +/-	11/21	2/17	0.096
Mechanical ventilation, +/-	12/20	3/16	0.12
PaO_2/FIO_2 ratio on the day after glucocorticoid pulse therapy	147 ± 67	267 ± 108	0.00014

Table 5 Univariate analysis of survival

	HR	95% CI	p Value
Age, year	1.018	0.973-1.065	0.35
Male sex	1.083	0.50-2.345	0.84
Days from the onset to admission	0.893	0.824-0.969	0.0066
Smoking index, pack-years	0.9995	0.9989-1.0001	0.14
IPF/non-IPF	1.024	0.501-2.091	0.95
Extent of ground-glass opacity, %	1.014	0.990-1.039	0.23
Extent of honeycombing, %	1.031	1.004-1.06	0.023
CLE, +/-	0.356	0.153-0.829	0.017
PSE, +/-	0.785	0.392-1.574	0.50
Lymphocyte, /μl	0.9996	0.9990-1.0002	0.22
CRP, mg/dl	0.9929	0.947-1.041	0.77
KL-6, U/ml	1.000	0.9996-1.0004	0.88
SP-D, ng/ml	1.0005	0.9992-1.0019	0.43
BNP, pg/ml	1.001	0.9992-1.0028	0.27
D-dimer, mg/ml	0.976	0.921-1.045	0.49
PCT, ng/ml	1.889	1.063-3.545	0.030
PaO_2/FIO_2 ratio on admission	0.992	0.987-0.997	0.0038
PaO_2/FIO_2 ratio on the day after glucocorticoid pulse therapy	0.989	0.984-0.994	1.75×10^{-5}
SIRS, +/-	11.85	3.551-39.54	5.78×10^{-5}
Number of SIRS criteria	1.98	1.448-2.707	1.87×10^{-5}

IPF, idiopathic pulmonary fibrosis; CLE, centrilobular emphysema; PSE, paraseptal emphysema; CRP, C-reactive protein; SP-D, surfactant protein D; KL-6, Krebs von den Lungen-6; BNP, brain natriuretic peptide; PCT, procalcitonin; SIRS, systemic inflammatory response syndrome.

Table 6 Multivariate analysis of survival

	Hazard ratio	95% confidence interval	p Value
Age, years	1.0400	0.9845-1.0980	0.16
Male sex	2.2430	0.7999-6.2910	0.13
BNP, pg/ml	0.9988	0.9963-1.0010	0.36
PCT, ng/ml	2.7860	1.1620-6.6770	0.022
PaO_2/FIO_2 ratio on admission	0.9948	0.9825-1.0070	0.41
Extent of honeycombing, %	1.0230	0.9882-1.0580	0.20
CLE, +/-	0.0679	0.0173-0.2658	0.00011
SIRS, +/-	12.7400	2.1150-76.7900	0.00055

BNP, brain natriuretic peptide; PCT, procalcitonin; CLE, centrilobular emphysema; SIRS, systemic inflammatory response syndrome.

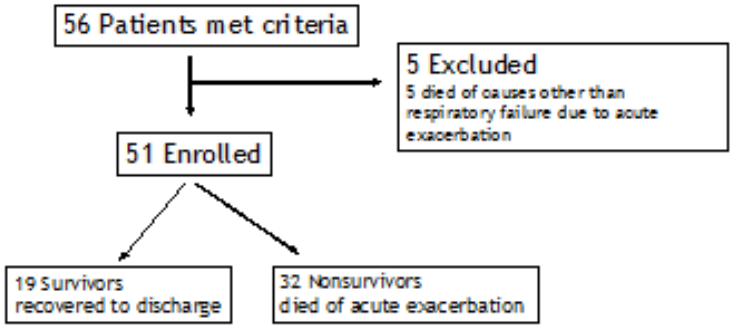

Figure 1 Flow diagram in patients with AE of CFIP

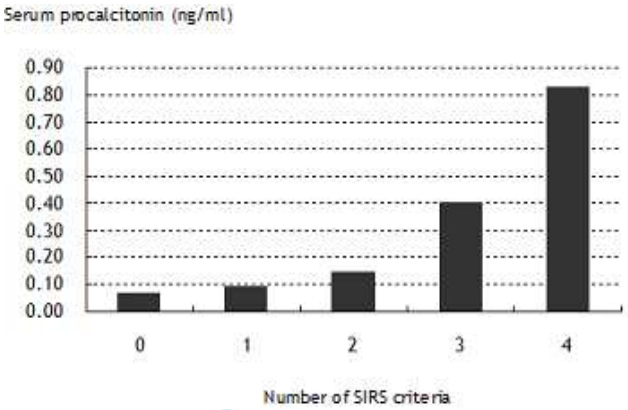

Figure 2 The number of SIRS criteria was positively correlated with the serum procalcitonin concentration (p=0.045). The number of subjects was as follows: 7 (SIRS score 0); 12 (score 1); 11 (score 2); 13 (score 3); 4 (score 4), respectively.

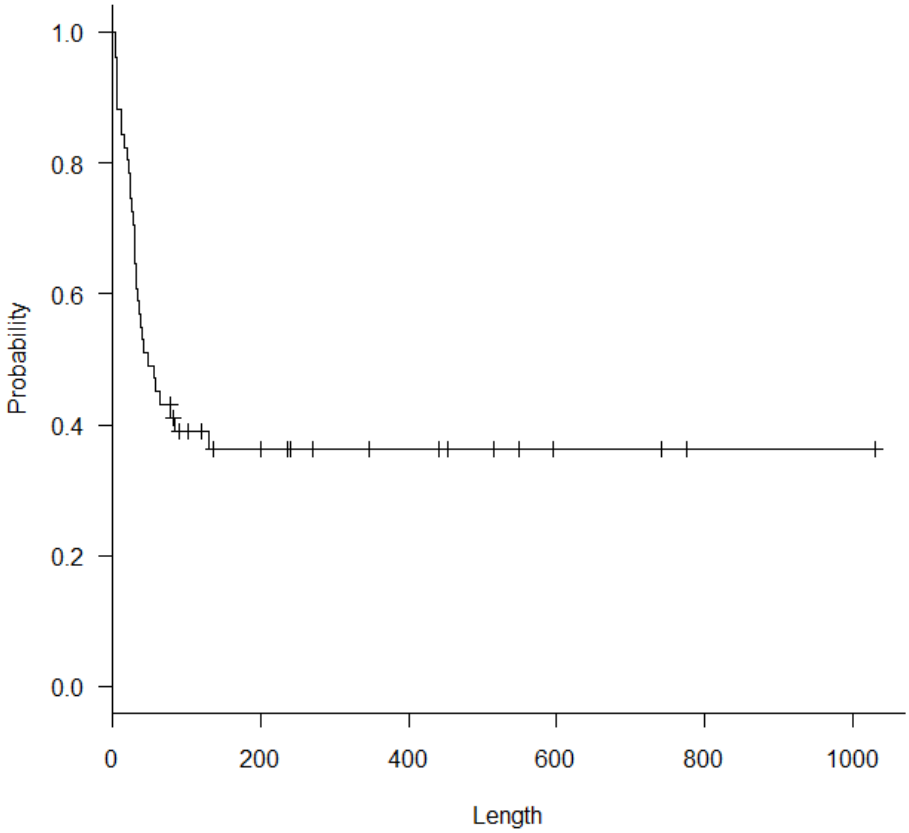

Figure 3 A Kaplan-Meier estimate for overall survival. An x-axis indicates days after admission.

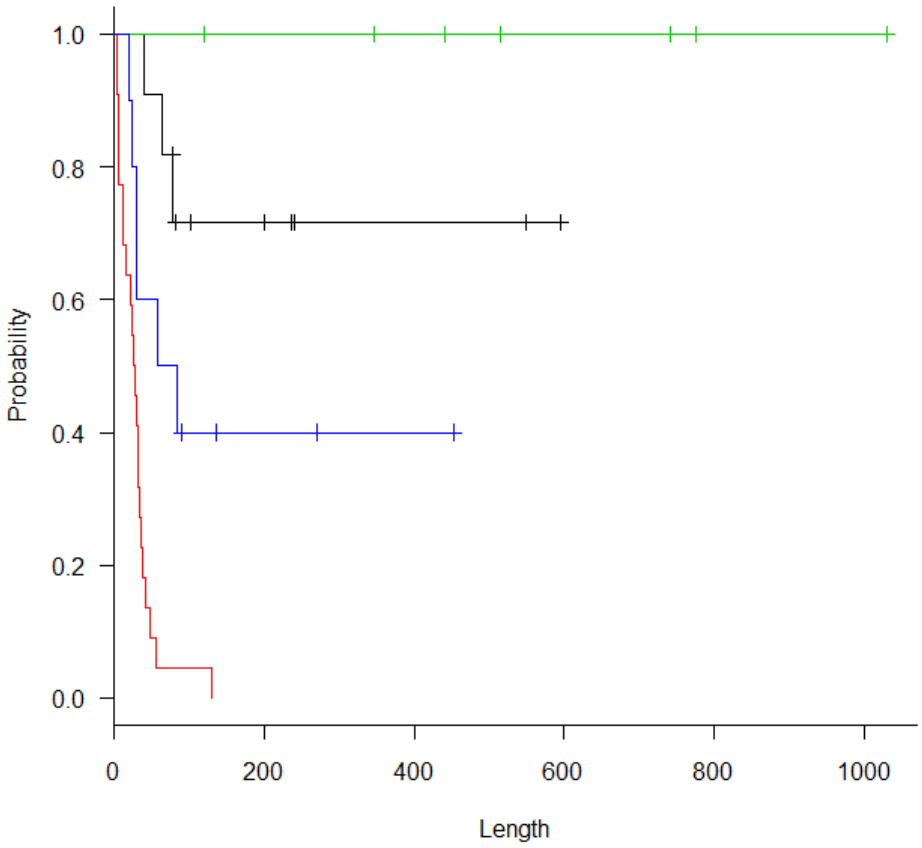

Figure 4 The stratification according to the presence or the absence of CLE and SIRS revealed distinct survival curves of the four groups. Group 1 (green): SIRS-CLE+ (n=7); group 2 (black): SIRS-CLE- (n=11); group 3 (blue): SIRS+CLE+ (n=10); group 4 (red): SIRS+CLE- (n=22). An x-axis indicates days after admission.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia

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Keywords:	Idiopathic pulmonary fibrosis, Centrilobular emphysema, Systemic inflammatory response syndrome

A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia

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Keywords
Idiopathic pulmonary fibrosis; systemic inflammatory response syndrome; centrilobular emphysema; survival

Word count: 4,186

Short title: Mortality predictors in acute exacerbation of chronic fibrosing IP

Abstract

Objectives To assess clinical, laboratory, and radiographic findings associated with outcomes and to clarify more practical ways to predict hospital mortality in patients with acute exacerbation (AE) of chronic fibrosing interstitial pneumonia (CFIP).

Design Single-centre retrospective cohort study.

Setting University hospital in Japan.

Participants We identified 51 consecutive patients with AE of idiopathic CFIP through multidisciplinary discussion. Patients who had connective tissue disease, drug-induced lung disease, pneumoconiosis, hypersensitivity pneumonitis, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, and eosinophilic pneumonia were excluded.

Interventions There were no interventions.

Main outcome measures The main outcome was determination of in-hospital mortality predictors. Other outcomes included clinical, laboratory, and radiographic differences between nonsurvivors and survivors in patients with AE of CFIP.

Results: The mean age of the patients with AE of CFIP was 71 years. Compared with survivors, nonsurvivors had significantly shorter duration of symptoms before admission, lower prevalence of peripheral distribution of ground-glass opacity and centrilobular emphysema (CLE) on thin-section CT, lower peripheral lymphocyte count, higher brain natriuretic peptide titre, lower PaO_2/FIO_2 (P/F) ratio, higher prevalence of systemic inflammatory response syndrome (SIRS), and higher SIRS score on admission (p=0.0069, 0.0032, 0.015, 0,040, 0.0098, 0.012, 9.9×10^{-7}, and 5.4×10^{-6}, respectively). Multivariate analysis revealed SIRS (HR=6.2810, p=0.015), CLE (HR=0.0606, $p=3.6 \times 10^{-5}$), and serum procalcitonin (PCT) level (HR=2.7110, p=0.022) to be independent predictors of in-hospital mortality. A Kaplan-Meier estimate on the basis of stratification according to the presence or absence of SIRS and CLE demonstrated a distinct survival curve for each subset of patients.

Conclusion Distinct survival curves documented by the stratification according to the presence or the absence of SIRS and CLE may provide basic information for a rational management strategy for patients with AE of CFIP on admission.

ARTICLE SUMMARY

Article focus

- Several independent predictors of mortality in patients with AE of IPF have been identified. However, more practical ways to predict hospital mortality, which may be of use in routine medical care, are required for AE of CFIP.
- This study was undertaken to identify practical mortality predictors in patients with AE of CFIP.

Key messages

- SIRS and CLE, which have not previously been evaluated as factors possibly affecting outcome, were the most significant predictors of in-hospital mortality in patients with AE of CFIP. Stratification according to the presence or the absence of these 2 factors documented distinct prognoses for the subsets of patients, and thus may be helpful for enabling more appropriate management strategies in the future.

Strength and limitations of this study

- This study's strength was the identification of the novel, non-invasive, and easily applicable predictors of in-hospital mortality in patients with AE of CFIP. The major limitation of the study was the single-centre retrospective design.

Introduction

In patients with a pre-existing chronic process of pulmonary fibrosis, such as idiopathic pulmonary fibrosis (IPF), an acute exacerbation (AE) is the development of acute lung injury superimposed on the underlying disease. Although AE was first described in patients with IPF,[1] it has also been reported in underlying diseases other than IPF, such as interstitial pneumonia associated with connective tissue disease,[2, 3] fibrotic nonspecific interstitial pneumonia (NSIP),[2, 3] hypersensitivity pneumonitis,[4] and asbestosis.[5] This suggests that a variety of chronic fibrosing processes of the lung can present a potential risk for AE.

Because a specific treatment for AE has not yet been established, the mortality rate in patients with AE of IPF remains high.[6] Furthermore, patients with secondary usual interstitial pneumonia (UIP) or pathological pattern of NSIP, who generally have favourable prognosis than those with IPF, also show high mortality from AE.[2 3]

Recently, factors predicting the onset of AE have been described in IPF patients. These include high modified medical research council score, high body mass index, a decline in forced vital capacity (FVC) at 6 months from the diagnosis; [7] low FVC.[8] Factors affecting survival in patients with AE of IPF have been also described,[9] and include high-resolution CT (HRCT) patterns (diffuse/multifocal/peripheral) of acute pulmonary infiltrates, degree of CT involvement, and serum lactate dehydrogenase (LDH) titre. Another report has found that the extent of ground-glass attenuation with traction bronchi- or bronchiolectasis and honeycombing on HRCT were the 2 independent prognostic factors in patients with AE of IPF.[10] CT findings directly associated with disease severity may predict the patient survival; however, the exploration of more objective and easily applicable predictors of mortality would be of value for developing rational management strategies, including novel therapeutic appoaches.[11]

In the present study, we retrospectively analysed 51 consecutive patients with AE of idiopathic chronic fibrosing interstitial pneumonia (CFIP) in order to identify novel in-hospital mortality predictors that are present on admission.

Methods

Subjects

Consecutive patients with AE of idiopathic CFIP admitted to our department between January 2009 and May 2012 were retrospectively studied. During that interval, 56 patients were admitted for AE of CFIP. Of those, 19 patients were successfully managed to hospital discharge (survivors) and 37 patients died during hospitalization (nonsurvivors). Of the latter, 5 patients who died from causes other than AE were excluded: two acute myocardial infarction (both of the patients had past medical history of old myocardial infarction); one rupture of aortic aneurysm after the graft replacement performed three month ago; two advanced lung cancer (AE was improving or did not progressively worsened by glucocorticoids). Eight patients with suspected AE but were diagnosed with lower respiratory tract infection by bacterial culture of specimens from lower respiratory tract (four patients), bacterial antigens in the urine (two patients), an elevated serum beta-D glucan (two patients) had been excluded in advance.

During the study period, 218 patients with idiopathic CFIP had been under management of our department and of them, 116 patients had been diagnosed with IPF. Of 51 patients studied, 26 had been outpatients of our department and the remaining 25 patients were referred ones. The mean interval between diagnosis of CFIP and admission was 42.3 months, although the data excluded three patients who had not been previously diagnosed with CFIP. 11 of 51 patients had been treated with immunosuppressants: glucocorticoids, eight patients and glucocorticoids and cyclosporin, three patients.

Diagnostic criteria

The following features based on the previously used criteria[12] were used to define an AE event: 1) aggravation of dyspnoe within 1 month; 2) decline of ≥10% in absolute forced vital capacity or decline of ≥10 Torr in PaO_2 or decline of ≥5% in SpO_2; 3) new ground-glass opacities or consolidation on chest radiograph or thin-section CT (TSCT); 4) negative respiratory culture and serologic test results for respiratory pathogens; and 5) no clinical evidence of pulmonary embolism, congestive heart failure, or pneumothorax as a cause of acute decline.

Significant decline in oxygenation was confirmed by previous PaO_2 or SpO_2 in every patient. In five of 26 referred patients, previous chest radiographs had not been obtained, however, all of them evidently showed honeycombing on TSCT on admission. Extensive ground-glass opacity (GGO) was compatible with acute onset of respiratory distress. Cultures of sputum or tracheobronchial aspirate for common bacteria, mycobacteria, and fungi, urinary antigens for *streptococcus pneumoniae* and *legionella pneumophilia* serotype 1, antigens for influenza A and B viruses by pharyngeal swab, antigenemia for cytomegalovirus, serum antigen and antibody for aspergillus, and a titer of serum beta-D glucan were examined in every patient studied and those disclosed negative results. Bronchoalveolar lavage was performed in 17 patients and all bronchoalveolar lavage fluids were negative for routine microbiological culture. Of those, PCR detection for genomes of certain microorganisms (common bacteria, mycobacteria, aspergillus, and *pneumocystis jirovecii*) was also performed in seven patients and gave negative results.

The diagnosis of idiopathic CFIP was firstly based on TSCT results: presence of a diffuse parenchymal lung disease with significant pulmonary fibrosis, defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion and/or traction bronchiectasis or bronchiolectasis.[13] Patients found to have other distinct diseases on the basis of clinical and /or radiographic findings, associated with the development of pulmonary fibrosis, such as connective tissue disease, drug-induced lung disease, pneumoconiosis, hypersensitivity pneumonitis, sarcoidosis, pulmonary histiocytosis, and lymphangioleiomyomatosis were excluded. The diagnosis of IPF was made according to the 2011 ATS/ERS/JRS/ALAT statement on IPF.[14] For this study, we diagnosed patients with IPF when they displayed features that fit the criteria for UIP as assessed by high-resolution CT (HRCT) or met the criteria for UIP after a combination of HRCT and surgical lung biopsy findings.

CT imaging

TSCT was performed for all patients, usually on the day of admission, using a Somatom Sensation 64 (Siemens Medical Solutions, Forchheim, Germany). Images were obtained with 1.5-mm collimation

and 1.5-mm slice intervals from pulmonary apex to lung base, reconstructed with a high-spatial-resolution algorithm and small field-of-view. The images were analysed at a window level of -700 HU and a window width of 1,400 HU.

The extent of the TSCT findings characteristics of AE and CFIP were determined; a thoracic radiologist and a pulmonary physician, both of whom were experts in interstitial lung diseases, examined the CT images without knowledge of any of the clinical, functional, and radiographic findings. GGO was defined as an area of slightly increased attenuation in which the vessels remained visible. Honeycombing was defined as an accumulation of cystic spaces with thickened walls. Emphysema was defined as well-demarcated areas of decreased attenuation in comparison with contiguous normal lung and marginated by a very thin (<1 mm) or no wall with upper zone predominance. The extent of GGO and honeycombing was scored to the nearest 10% at the 6 lung zones: right upper and middle lobes, left upper segment and lingula, bilateral lower lobes. The scores at the 6 lung zones were then averaged out to obtain a mean score.[15] The results by the two readers were correlated well (GGO: $r=0.88$, $p=2.27 \times 10^{-17}$ and honeycombing: $r= 0.92$, $p=2.15 \times 10^{-20}$). Finally, GGO at the time of AE were classified as peripheral, multifocal, or diffuse parenchymal patterns, as previously described.[16]

Because concurrent emphysema may affect an accurate CT diagnosis of UIP and NSIP,[17] CT images before admission were also reviewed, especially for distinguishing honeycombing from emphysema with GGO. We could access previous CT images for 40 of the 51 patients. In the remaining 11 patients, serial thoracic CT images were also reviewed in addition to the CT image obtained on admission not to misdiagnose emphysema with GGO as honeycombing.

Systemic inflammatory response syndrome (SIRS)

The diagnosis of SIRS was determined at the time of admission, according to the previously defined criteria: temperature >38^0C or <36^0C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or $PaCO_2$ <32 Torr; white blood cell count >12,000/μl, <4,000/μl, or >10% band forms. Subjects who met 2 or more of the criteria were diagnosed with SIRS.[18]

Data expression and the statistics analysis

Clinical data are expressed as mean ± SD for continuous variables. Group comparisons were made using the Mann-Whitney *U* test for continuous variables. Chi-squared and Fisher's exact tests were used for categorical variables. Logistic regression analysis was performed to determine the relationships between clinical parameters. A Kaplan–Meier model was generated to evaluate survival. Univariate and multivariate analyses using the Cox proportional hazards regression models were used to identify independent patient characteristics, laboratory data and CT predictors of hospital mortality. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R Commander (version 1.6-3) designed to include statistical functions frequently used in biostatistics.[19] Statistical significance was defined as a p value of <0.05.

Results

Patient profiles and the symptom duration

The flow diagram in figure 1 shows how the patients were identified. We finally identified 51 patients with AE of idiopathic CFIP (37 males and 14 females) between January 2009 and May 2012. The mean age, male-to-female ratio, smoking history, and the mean smoking index were similar in nonsurvivors and survivors. The mean duration of symptoms (cough or dyspnoea) previous to admission was significantly shorter in nonsurvivors (P=0.0069, table 1). The mean durations of hospitalization were 33 days in nonsurvivors and 72 days in survivors.

Diagnosis of idiopathic CFIP and TSCT findings

In this cohort, 30 patients were diagnosed with IPF according to the 2011 criteria,[14] and the remaining 21 patients were diagnosed with non-IPF. The latter group included 1 patient with upper-lobe dominant pulmonary fibrosis and 2 patients with familiar pulmonary fibrosis. The remaining 18 patients showed findings consistent with fibrotic NSIP on TSCT.[20]

The prevalence of IPF, the extent of GGO and the extent of honeycombing were not significantly different between nonsurvivors and survivors (table 2). Peripheral distribution of GGO and centrilobular emphysema (CLE) were significantly less prevalent in nonsurvivors (p=0.0032 and 0.015, respectively).

Laboratory data and SIRS

The mean peripheral blood lymphocyte count was significantly lower in nonsurvivors (p=0.040, table 3). The mean serum brain natriuretic peptide (BNP) titer was elevated in both groups and significantly higher in nonsurvivors (p=0.0098). The mean white blood cell counts, serum C-reactive protein, serum Krebs von den Lungen-6, serum surfactant protein-D, serum procalcitonin (PCT), and the mean D-dimer titres were elevated in both groups, but were not significantly different between groups. The mean PaO_2/FIO_2 (P/F) ratio on admission was significantly lower in nonsurvivors (p=0.012). On admission, 28 out of 32 nonsurvivors and 4 of 19 survivors fulfilled the criteria for SIRS ($p=9.9 \times 10^{-7}$, table 3). The mean SIRS score was significantly higher in nonsurvivors ($P=5.4 \times 10^{-6}$). The SIRS score and the serum PCT level were positively correlated (p=0.0045, fig 2).

Treatment and the response

Glucocorticoid pulse therapy (methylprednisolone at 1,000mg/day for 3 consecutive days) was performed in 31 of 32 nonsurvivors and all of the 19 survivors (table 4). Immunosuppressants other than glucocorticoids and mechanical ventilation were used at similar rates in the 2 groups. The mean P/F ratio on the day after glucocorticoid pulse therapy was significantly lower in nonsurvivors (p=0.00018).

Prognosis

In nonsurvivors, the median survival time was 33 days. In survivors, 2 patients died from a second AE event after discharge from hospital. The overall survival was 67% at 30 days, 43% at 60 days, and 40% at 90 days after admission. Kaplan-Meier estimate for overall survival revealed that the survival rate reached a plateau of approximately 35% at approximately 180 days from admission (fig 3). In this cohort, TSCT classification (definite UIP pattern, possible UIP pattern, and inconsistent with UIP pattern) did not reveal significant difference in survival by the Kaplan-Meier estimate (fig. 4, p=0.51).

Univariate and multivariable analyses of survival

Univariate analysis (table 5) revealed that symptom duration previous to admission, the extent of honeycombing on CT, the presence of CLE, serum PCT level, P/F ratio on admission, the presence of SIRS, and the SIRS score were significant predictors of mortality. The P/F ratio on the day after glucocorticoid pulse therapy was also significant in univariate analysis. Multivariable analysis revealed that the serum PCT (hazard ratio [HR] per 10%-increase, 2.7110; 95% confidence interval [CI], 1.1770-6.4890; p=0.022), the presence of CLE (HR, 0.0606; 95%CI, 0.0161-0.2290; $p=3.6 \times 10^{-5}$), and the presence of SIRS (HR, 6.2810; 95%CI, 1.4220-27.7500; P=0.015) remained significant predictors after adjusting for age, sex, P/F ratio on admission, and extent of honeycombing (table 6). When five patients in whom cause of death was other than AE were included in the multivariate analysis, PCT (HR, 2.3980; 95% CI, 1.1000-5.2240; p=0.028), CLE (HR, 0.1752; 95% CI, 0.06269-0.4894; p=0.00089), and SIRS (HR, 5.2600; 95% CI, 1.4950-18.5100; p=0.0097) were remained to be significant and in

addition, age also showed significance (HR, 1.0440 ; 95% CI, 1.0020-1.0870; p=0.039).

On the basis of the results of multivariate analysis, we divided 51 patients into 4 subgroups according to the presence or absence of CLE and SIRS (group 1: SIRS- and CLE+; group 2: SIRS- and CLE-; group 3: SIRS+ and CLE+; group 4: SIRS+ and CLE-). A Kaplan-Meier estimate according to this subgrouping revealed a clear distinction in the prognoses between the 4 subgroups (fig 5, p=0.0025). All patients in group 1 recovered and survived to discharge, by contrast, all patients in group 4 died of AE.

Discussion

In the present study, the signs and symptoms of 18 of 21 patients diagnosed with non-IPF were suggestive of fibrotic NSIP on TSCT. [20] There is the possibility that patient with IPF included in the non-IPF group, and vice versa. However, whether a patient had IPF or not was not associated with outcome in our cohort. Furthermore, the prognostic difference between patients with definite UIP, possible UIP, and findings inconsistent with UIP on TSCT was not significant. Thus, we considered that there were convincing reasons to place all subjects studied into the CFIP category. There have been a few reports on AE of non-IPF, including a study of patients with idiopathic NSIP (2007 Park, 2007 Silva) [2 3], in which the overall mortality rate was as high as 50%. This suggests that AE, a manifestation of diffuse alveolar damage, may commonly be fatal, irrespective of an individual pattern of CFIP.

Attention should be paid to the differences between survivors and nonsurvivors in clinical, laboratory, and radiographic findings in this cohort. The relatively short symptom duration before admission in nonsurvivors might be dependent on the severity of the lung injury that has not yet been strictly objectified. Radiographically, factors for discriminating between nonsurvivors and survivors were the distribution pattern of acute pulmonary infiltrates and the presence of CLE, but not the presence of paraseptal emphysema. CT patterns have been shown to be associated with the mortality in patients with AE of IPF, [9] however, there may be a degree of subjectivity in the diagnosis of this condition, and interobserver differences must be considered. Among laboratory data, the serum BNP level and the P/F ratio on the day after glucocorticoid pulse therapy, as well as those on admission, were discriminative. We performed echocardiography in every patient with signs and symptoms clinically suggestive of cardiac dysfunction or those with increased serum BNP, and none showed left ventricular dysfunction. The higher P/F ratio after glucocorticoid pulse therapy suggests that this treatment might be effective for a certain subset of patient. The presence of SIRS and the number of SIRS criteria fulfilled were the factors that provided the most significant discrimination between survivors and nonsurvivors.

The univariate analysis revealed that the extent of honeycombing was associated with survival; this was not apparent in the group comparison. On the basis of the results of the univariate analysis, we performed a multivariate analysis of survival, and it revealed some notable results: the most significant factors for predicting in-hospital mortality were the presence of SIRS and the absence of CLE on TSCT; the serum PCT level was also associated with outcome.

The presence of SIRS, first defined in 1992, indicates a systemic inflammatory response to a variety of severe clinical insults, including noninfectious causes such as trauma, burns, or pancreatitis, etc.[18] The definition of SIRS is simple, and thus can be easily applied in routine medical care; however, the clinical significance of SIRS has been controversial. In infected subjects, the number of SIRS criteria fulfilled did not influence patient outcome, despite the fact that the presence of organ dysfunction or shock showed prognostic significance.[21] In our study, SIRS was significantly more prevalent in nonsurvivors, and was one of the most significant predictors of hospital mortality. The influence of SIRS on mortality in patients with AE of CFIP has not yet been examined, probably because that the disease process has been recognized as a disorder compartmentalized to the lung. Compared with stable IPF patients, patients with AE of IPF has been reported to show increases in serum biomarkers associated with endothelial cell injury, such as thrombomodulin or plasminogen activator inhibitor-1 (PAI-1).[22] In addition, increases in levels of interleukin-8 or intracellular adhesion molecule 1, known as molecules related to neutrophil recruitment to the lung, were reported to be independent mortality predictors in patients with acute lung injury/acute respiratory distress syndrome.[23] In our cohorts, the mean ratio of bronchoalveolar neutrophils in 17 patients underwent bronchoalveolar lavage was 20.0% (data not shown). These data suggests a possibility that acute lung injury mediates systemic inflammation via certain circulating molecules, as in the case of AE of CFIP. The significance of SIRS as a mortality predictor should be confirmed in future studies. Investigations to determine the mechanisms of SIRS development in patients with AE of CFIP may be essential to allow the development of more specific treatments.

PCT, a prohormone of calcitonin, is produced in the medullary C-cells of the thyroid gland. It was described as an infection parameter in the early 1990's[24] and is now considered to be a useful serum biomarker for early diagnosis of bacterial infections.[25] On the other hand, increase of serum PCT

levels caused by noninfectious processes have also been reported. In a retrospective analysis of patients who underwent cardiopulmonary bypass surgery but who did not have postoperative infection, Hensel et al. described a significant increase in PCT in patients with both SIRS and acute lung injury, compared with those with SIRS alone [26] In their cohort, PCT levels were also elevated in patients without SIRS as well as in patients with SIRS alone, and the levels were statistically similar; this indicates that acute lung injury might play a critical role in the facilitated generation of PCT. Rapid increases of PCT levels in patients with nonbacterial pneumonitis caused by inhalational burn have also been reported.[27] In our cases of AE, serum PCT levels were of prognostic significance, and were also positively correlated with the number of SIRS criteria. The measurement of PCT has 2 key implications in our cohort. First, PCT was useful for excluding the possibility of respiratory infections, because most of the patients had PCT levels of < 0.25 ng/ml (data not shown), which is below the level suggestive of severe pneumonia and/or bacteremia.[28] Second, in the absence of overt respiratory infection, a relatively slight but significant elevation of PCT should not be ignored. PCT was proved to be associated with hospital mortality in both the univariate and multivariate analyses. Although the source of PCT in patients with AE of CFIP has not been confirmed, pulmonary neuroendocrine cells are possible candidates, because an abundance of calcitonin per unit weight of lung tissue has been described.[27 29] The serum PCT level was positively correlated with the number of SIRS criteria, suggesting that PCT could be a novel candidate biomarker for AE of CFIP.

One report has indicated that the absence of smoking history might positively influence the onset of AE in patients with IPF;[8] however, CLE has not been evaluated as a mortality predictor. There are a few possible reasons why the presence of CLE was associated with outcome. First, in some subjects with both CFIP and CLE, diffuse alveolar damage, a histopathological hallmark of AE of CFIP, was not present. Second, the pathogenesis of CLE itself antagonizes that of on-going diffuse alveolar damage. Finally, glucocoticoids are more effective for subjects who have background CLE. As mentioned above, we ruled out the possibility of obvious cardiac dysfunction by echocardiography in the patients studied. Six out of 11 survivors with CLE underwent bronchoalveolar lavage soon after the admission (data not shown), and none showed overt alveolar haemorrhage. Although AE in patients with combined pulmonary fibrosis and emphysema (CPFE) has recently been reported,[30] its curability has not been described. In patients with chronic obstructive pulmonary disease (COPD), gene expression analysis and immunohistochemistry showed that urokinase plasminogen activator (PLAU) and urokinase plasminogen activator receptor (PLAUR) were found to be overexpressed in alveolar macrophages and bronchial epithelium.[31] In infant respiratory distress syndrome, a condition characterized by intraalveolar fibrin deposition, the ratio of PAI-1 to PLAU in tracheal aspirates was higher than that in control subjects,[32] suggesting a role for PLAU in intraalveolar fibrinolysis. Lung-specific overexpression of PLAU in mice was shown to reduce the accumulation of collagen in the lung and reduced mortality after bleomycin-induced lung injury.[33] Thus, constitutive activation of the PLAU-PLAUR system in subjects with CLE, a histological hallmark of COPD, may antagonize the activation of PAI-1, a possible biomarker of AE of CFIP. Generally, COPD itself has been demonstrated to show glucocorticoid resistance.[34] It remains to be determined whether there are any differences in the histological patterns of AE and the efficacy of glucocorticoids between in patients with CFIP alone and those with both CFIP and CLE. The histological patterns could be unraveled by analysis of surgical lung biopsy specimens, and the efficacy of glucocorticoids could be clarified with the accumulation of data from future clinical cases.

The Kaplan-Meier estimate for survival according to the subgrouping by the presence or the absence of SIRS and CLE clearly divided the patients into 4 subgroups. Every patient in group 1 (SIRS-CLE+) was successfully treated with glucocorticoids and discharged. Although an effective pharmaceutical therapy has not been established for patients with AE of IPF, [12] the present study is the first to document a subgroup of CFIP patients who derive a possible benefit from glucocorticoid therapy during AE. Five of the 7 cases in group 1 were of IPF. By contrast, all 22 patients in group 4 (SIRS+CLE-) died due to respiratory failure secondary to AE. In this subgroup, any treatment option, such as polymyxin B-immobilized fibre column treatment[11], should be considered. An indication for the use of glucocorticoids should be also discussed in the future.

The limitations of the present study are as follows. First, the analysis was retrospective. However, we consecutively enrolled every subject admitted with AE of CFIP from January 2009, and collected the hospitalization medical records as completely as possible. Second, this study was undertaken in a single medical institution, and therefore the number of patients studied was limited. Third, the

diagnosis of CFIP and the classifications were somewhat dependent on TSCT findings. Because most of the patients were in moderate to severe respiratory failure (two-thirds of the patients studied had a P/F ratio of ≦ 200, data not shown), surgical lung biopsies on admission were difficult to perform. Half of the patients studied had been referred, and among those, none had undergone surgical lung biopsy. Consequently, 5 patients underwent surgical lung biopsy in this study. We tried, as much as possible, to rule out known entities associated with the development of pulmonary fibrosis. Finally, most of the referred subjects had not undergone pulmonary function tests before admission. Therefore, we could not evaluate pulmonary function test results as mortality predictors.

Several mortality predictors have been identified in patients with AE of IPF. However, it is unclear how those factors could be contributory to the management of this possibly fatal disorder in routine medical practice. We expect that the prognostic significance of CLE and SIRS, factors by which patients could be sub-grouped on admission, could contribute to the rational management of patients with AE of CFIP. The utility of these prognostic factors should be prospectively investigated in future cohorts.

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A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia

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Abstract

Objectives To assess clinical, laboratory, and radiographic findings associated with outcomes and to clarify more practical ways to predict hospital mortality in patients with acute exacerbation (AE) of chronic fibrosing interstitial pneumonia (CFIP).

Design Single-centre retrospective cohort study.

Setting University hospital in Japan.

Participants We identified 51 consecutive patients with AE of idiopathic CFIP through multidisciplinary discussion. Patients who had connective tissue disease, drug-induced lung disease, pneumoconiosis, hypersensitivity pneumonitis, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, and eosinophilic pneumonia were excluded.

Interventions There were no interventions.

Main outcome measures The main outcome was determination of in-hospital mortality predictors. Other outcomes included clinical, laboratory, and radiographic differences between nonsurvivors and survivors in patients with AE of CFIP.

Results: The mean age of the patients with AE of CFIP was 71 years. Compared with survivors, nonsurvivors had significantly shorter duration of symptoms before admission, lower prevalence of peripheral distribution of ground-glass opacity and centrilobular emphysema (CLE) on thin-section CT, lower peripheral lymphocyte count, higher brain natriuretic peptide titre, lower PaO_2/FIO_2 (P/F) ratio, higher prevalence of systemic inflammatory response syndrome (SIRS), and higher SIRS score on admission (p=0.0069, 0.0032, 0.015, 0,040, 0.0098, 0.012, 9.9×10^{-7}, and 5.4×10^{-6}, respectively). Multivariate analysis revealed SIRS (HR=6.2810, p=0.015), CLE (HR=0.0606, p=3.6×10^{-5}), and serum procalcitonin (PCT) level (HR=2.7110, p=0.022) to be independent predictors of in-hospital mortality. A Kaplan-Meier estimate on the basis of stratification according to the presence or absence of SIRS and CLE demonstrated a distinct survival curve for each subset of patients.

Conclusion Distinct survival curves documented by the stratification according to the presence or the absence of SIRS and CLE may provide basic information for a rational management strategy for patients with AE of CFIP on admission.

ARTICLE SUMMARY

Article focus

- Several independent predictors of mortality in patients with AE of IPF have been identified. However, more practical ways to predict hospital mortality, which may be of use in routine medical care, are required for AE of CFIP.
- This study was undertaken to identify practical mortality predictors in patients with AE of CFIP.

Key messages

- SIRS and CLE, which have not previously been evaluated as factors possibly affecting outcome, were the most significant predictors of in-hospital mortality in patients with AE of CFIP. Stratification according to the presence or the absence of these 2 factors documented distinct prognoses for the subsets of patients, and thus may be helpful for enabling more appropriate management strategies in the future.

Strength and limitations of this study

- This study's strength was the identification of the novel, non-invasive, and easily applicable predictors of in-hospital mortality in patients with AE of CFIP. The major limitation of the study was the single-centre retrospective design.

Introduction

In patients with a pre-existing chronic process of pulmonary fibrosis, such as idiopathic pulmonary fibrosis (IPF), an acute exacerbation (AE) is the development of acute lung injury superimposed on the underlying disease. Although AE was first described in patients with IPF,[1] it has also been reported in underlying diseases other than IPF, such as interstitial pneumonia associated with connective tissue disease,[2, 3] fibrotic nonspecific interstitial pneumonia (NSIP),[2, 3] hypersensitivity pneumonitis,[4] and asbestosis.[5] This suggests that a variety of chronic fibrosing processes of the lung can present a potential risk for AE.

Because a specific treatment for AE has not yet been established, the mortality rate in patients with AE of IPF remains high.[6] Furthermore, patients with secondary usual interstitial pneumonia (UIP) or pathological pattern of NSIP, who generally have favourable prognosis than those with IPF, also show high mortality from AE.[2 3]

Recently, factors predicting the onset of AE have been described in IPF patients. These include high modified medical research council score, high body mass index, a decline in forced vital capacity (FVC) at 6 months from the diagnosis; [7] low FVC.[8] Factors affecting survival in patients with AE of IPF have been also described,[9] and include high-resolution CT (HRCT) patterns (diffuse/multifocal/peripheral) of acute pulmonary infiltrates, degree of CT involvement, and serum lactate dehydrogenase (LDH) titre. Another report has found that the extent of ground-glass attenuation with traction bronchi- or bronchiolectasis and honeycombing on HRCT were the 2 independent prognostic factors in patients with AE of IPF.[10] CT findings directly associated with disease severity may predict the patient survival; however, the exploration of more objective and easily applicable predictors of mortality would be of value for developing rational management strategies, including novel therapeutic appoaches.[11]

In the present study, we retrospectively analysed 51 consecutive patients with AE of idiopathic chronic fibrosing interstitial pneumonia (CFIP) in order to identify novel in-hospital mortality predictors that are present on admission.

Methods

Subjects

Consecutive patients with AE of idiopathic CFIP admitted to our department between January 2009 and May 2012 were retrospectively studied. During that interval, 56 patients were admitted for AE of CFIP. Of those, 19 patients were successfully managed to hospital discharge (survivors) and 37 patients died during hospitalization (nonsurvivors). Of the latter, 5 patients who died from causes other than AE were excluded: two acute myocardial infarction (both of the patients had past medical history of old myocardial infarction); one rupture of aortic aneurysm after the graft replacement performed three month ago; two advanced lung cancer (AE was improving or did not progressively worsened by glucocorticoids). Eight patients with suspected AE but were diagnosed with lower respiratory tract infection by bacterial culture of specimens from lower respiratory tract (four patients), bacterial antigens in the urine (two patients), an elevated serum beta-D glucan (two patients) had been excluded in advance.

During the study period, 218 patients with idiopathic CFIP had been under management of our department and of them, 116 patients had been diagnosed with IPF. Of 51 patients studied, 26 had been outpatients of our department and the remaining 25 patients were referred ones. The mean interval between diagnosis of CFIP and admission was 42.3 months, although the data excluded three patients who had not been previously diagnosed with CFIP. 11 of 51 patients had been treated with immunosuppressants: glucocorticoids, eight patients and glucocorticoids and cyclosporin, three patients.

Diagnostic criteria

The following features based on the previously used criteria[12] were used to define an AE event: 1) aggravation of dyspnoe within 1 month; 2) decline of ≥10% in absolute forced vital capacity or decline of ≥10 Torr in PaO_2 or decline of ≥5% in SpO_2; 3) new ground-glass opacities or consolidation on chest radiograph or thin-section CT (TSCT); 4) negative respiratory culture and serologic test results for respiratory pathogens; and 5) no clinical evidence of pulmonary embolism, congestive heart failure, or pneumothorax as a cause of acute decline.

Significant decline in oxygenation was confirmed by previous PaO_2 or SpO_2 in every patient. In five of 26 referred patients, previous chest radiographs had not been obtained, however, all of them evidently showed honeycombing on TSCT on admission. Extensive ground-glass opacity (GGO) was compatible with acute onset of respiratory distress. Cultures of sputum or tracheobronchial aspirate for common bacteria, mycobacteria, and fungi, urinary antigens for *streptococcus pneumoniae* and *legionella pneumophilia* serotype 1, antigens for influenza A and B viruses by pharyngeal swab, antigenemia for cytomegalovirus, serum antigen and antibody for aspergillus, and a titer of serum beta-D glucan were examined in every patient studied and those disclosed negative results. Bronchoalveolar lavage was performed in 17 patients and all bronchoalveolar lavage fluids were negative for routine microbiological culture. Of those, PCR detection for genomes of certain microorganisms (common bacteria, mycobacteria, aspergillus, and *pneumocystis jirovecii*) was also performed in seven patients and gave negative results.

The diagnosis of idiopathic CFIP was firstly based on TSCT results: presence of a diffuse parenchymal lung disease with significant pulmonary fibrosis, defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion and/or traction bronchiectasis or bronchiolectasis.[13] Patients found to have other distinct diseases on the basis of clinical and /or radiographic findings, associated with the development of pulmonary fibrosis, such as connective tissue disease, drug-induced lung disease, pneumoconiosis, hypersensitivity pneumonitis, sarcoidosis, pulmonary histiocytosis, and lymphangioleiomyomatosis were excluded. The diagnosis of IPF was made according to the 2011 ATS/ERS/JRS/ALAT statement on IPF.[14] For this study, we diagnosed patients with IPF when they displayed features that fit the criteria for UIP as assessed by high-resolution CT (HRCT) or met the criteria for UIP after a combination of HRCT and surgical lung biopsy findings.

CT imaging

TSCT was performed for all patients, usually on the day of admission, using a Somatom Sensation 64 (Siemens Medical Solutions, Forchheim, Germany). Images were obtained with 1.5-mm collimation

and 1.5-mm slice intervals from pulmonary apex to lung base, reconstructed with a high-spatial-resolution algorithm and small field-of-view. The images were analysed at a window level of -700 HU and a window width of 1,400 HU.

The extent of the TSCT findings characteristics of AE and CFIP were determined; a thoracic radiologist and a pulmonary physician, both of whom were experts in interstitial lung diseases, examined the CT images without knowledge of any of the clinical, functional, and radiographic findings. GGO was defined as an area of slightly increased attenuation in which the vessels remained visible. Honeycombing was defined as an accumulation of cystic spaces with thickened walls. Emphysema was defined as well-demarcated areas of decreased attenuation in comparison with contiguous normal lung and marginated by a very thin (<1 mm) or no wall with upper zone predominance. The extent of GGO and honeycombing was scored to the nearest 10% at the 6 lung zones: right upper and middle lobes, left upper segment and lingula, bilateral lower lobes. The scores at the 6 lung zones were then averaged out to obtain a mean score.[15] The results by the two readers were correlated well (GGO: $r=0.88$, $p=2.27 \times 10^{-17}$ and honeycombing: $r= 0.92$, $p=2.15 \times 10^{-20}$). Finally, GGO at the time of AE were classified as peripheral, multifocal, or diffuse parenchymal patterns, as previously described.[16]

Because concurrent emphysema may affect an accurate CT diagnosis of UIP and NSIP,[17] CT images before admission were also reviewed, especially for distinguishing honeycombing from emphysema with GGO. We could access previous CT images for 40 of the 51 patients. In the remaining 11 patients, serial thoracic CT images were also reviewed in addition to the CT image obtained on admission not to misdiagnose emphysema with GGO as honeycombing.

Systemic inflammatory response syndrome (SIRS)

The diagnosis of SIRS was determined at the time of admission, according to the previously defined criteria: temperature >38^{0}C or <36^{0}C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or $PaCO_2$ <32 Torr; white blood cell count >12,000/μl, <4,000/μl, or >10% band forms. Subjects who met 2 or more of the criteria were diagnosed with SIRS.[18]

Data expression and the statistics analysis

Clinical data are expressed as mean ± SD for continuous variables. Group comparisons were made using the Mann-Whitney *U* test for continuous variables. Chi-squared and Fisher's exact tests were used for categorical variables. Logistic regression analysis was performed to determine the relationships between clinical parameters. A Kaplan–Meier model was generated to evaluate survival. Univariate and multivariate analyses using the Cox proportional hazards regression models were used to identify independent patient characteristics, laboratory data and CT predictors of hospital mortality. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R Commander (version 1.6-3) designed to include statistical functions frequently used in biostatistics.[19] Statistical significance was defined as a p value of <0.05.

Results

Patient profiles and the symptom duration

The flow diagram in figure 1 shows how the patients were identified. We finally identified 51 patients with AE of idiopathic CFIP (37 males and 14 females) between January 2009 and May 2012. The mean age, male-to-female ratio, smoking history, and the mean smoking index were similar in nonsurvivors and survivors. The mean duration of symptoms (cough or dyspnoea) previous to admission was significantly shorter in nonsurvivors (P=0.0069, table 1). The mean durations of hospitalization were 33 days in nonsurvivors and 72 days in survivors.

Diagnosis of idiopathic CFIP and TSCT findings

In this cohort, 30 patients were diagnosed with IPF according to the 2011 criteria,[14] and the remaining 21 patients were diagnosed with non-IPF. The latter group included 1 patient with upper-lobe dominant pulmonary fibrosis and 2 patients with familiar pulmonary fibrosis. The remaining 18 patients showed findings consistent with fibrotic NSIP on TSCT.[20]

The prevalence of IPF, the extent of GGO and the extent of honeycombing were not significantly different between nonsurvivors and survivors (table 2). Peripheral distribution of GGO and centrilobular emphysema (CLE) were significantly less prevalent in nonsurvivors (p=0.0032 and 0.015, respectively).

Laboratory data and SIRS

The mean peripheral blood lymphocyte count was significantly lower in nonsurvivors (p=0.040, table 3). The mean serum brain natriuretic peptide (BNP) titer was elevated in both groups and significantly higher in nonsurvivors (p=0.0098). The mean white blood cell counts, serum C-reactive protein, serum Krebs von den Lungen-6, serum surfactant protein-D, serum procalcitonin (PCT), and the mean D-dimer titres were elevated in both groups, but were not significantly different between groups. The mean PaO_2/FIO_2 (P/F) ratio on admission was significantly lower in nonsurvivors (p=0.012). On admission, 28 out of 32 nonsurvivors and 4 of 19 survivors fulfilled the criteria for SIRS ($p=9.9 \times 10^{-7}$, table 3). The mean SIRS score was significantly higher in nonsurvivors ($P=5.4 \times 10^{-6}$). The SIRS score and the serum PCT level were positively correlated (p=0.0045, fig 2).

Treatment and the response

Glucocorticoid pulse therapy (methylprednisolone at 1,000mg/day for 3 consecutive days) was performed in 31 of 32 nonsurvivors and all of the 19 survivors (table 4). Immunosuppressants other than glucocorticoids and mechanical ventilation were used at similar rates in the 2 groups. The mean P/F ratio on the day after glucocorticoid pulse therapy was significantly lower in nonsurvivors (p=0.00018).

Prognosis

In nonsurvivors, the median survival time was 33 days. In survivors, 2 patients died from a second AE event after discharge from hospital. The overall survival was 67% at 30 days, 43% at 60 days, and 40% at 90 days after admission. Kaplan-Meier estimate for overall survival revealed that the survival rate reached a plateau of approximately 35% at approximately 180 days from admission (fig 3). In this cohort, TSCT classification (definite UIP pattern, possible UIP pattern, and inconsistent with UIP pattern) did not reveal significant difference in survival by the Kaplan-Meier estimate (fig. 4, p=0.51).

Univariate and multivariable analyses of survival

Univariate analysis (table 5) revealed that symptom duration previous to admission, the extent of honeycombing on CT, the presence of CLE, serum PCT level, P/F ratio on admission, the presence of SIRS, and the SIRS score were significant predictors of mortality. The P/F ratio on the day after glucocorticoid pulse therapy was also significant in univariate analysis. Multivariable analysis revealed that the serum PCT (hazard ratio [HR] per 10%-increase, 2.7110; 95% confidence interval [CI], 1.1770-6.4890; p=0.022), the presence of CLE (HR, 0.0606; 95%CI, 0.0161-0.2290; $p=3.6 \times 10^{-5}$), and the presence of SIRS (HR, 6.2810; 95%CI, 1.4220-27.7500; P=0.015) remained significant predictors after adjusting for age, sex, P/F ratio on admission, and extent of honeycombing (table 6). When five patients in whom cause of death was other than AE were included in the multivariate analysis, PCT (HR, 2.3980; 95% CI, 1.1000-5.2240; p=0.028), CLE (HR, 0.1752; 95% CI, 0.06269-0.4894; p=0.00089), and SIRS (HR, 5.2600; 95% CI, 1.4950-18.5100; p=0.0097) were remained to be significant and in

addition, age also showed significance (HR, 1.0440 ; 95% CI, 1.0020-1.0870; p=0.039).

On the basis of the results of multivariate analysis, we divided 51 patients into 4 subgroups according to the presence or absence of CLE and SIRS (group 1: SIRS- and CLE+; group 2: SIRS- and CLE-; group 3: SIRS+ and CLE+; group 4: SIRS+ and CLE-). A Kaplan-Meier estimate according to this subgrouping revealed a clear distinction in the prognoses between the 4 subgroups (fig 5, p=0.0025). All patients in group 1 recovered and survived to discharge, by contrast, all patients in group 4 died of AE.

Discussion

In the present study, the signs and symptoms of 18 of 21 patients diagnosed with non-IPF were suggestive of fibrotic NSIP on TSCT. [20] There is the possibility that patient with IPF included in the non-IPF group, and vice versa. However, whether a patient had IPF or not was not associated with outcome in our cohort. Furthermore, the prognostic difference between patients with definite UIP, possible UIP, and findings inconsistent with UIP on TSCT was not significant. Thus, we considered that there were convincing reasons to place all subjects studied into the CFIP category. There have been a few reports on AE of non-IPF, including a study of patients with idiopathic NSIP (2007 Park, 2007 Silva) [2 3], in which the overall mortality rate was as high as 50%. This suggests that AE, a manifestation of diffuse alveolar damage, may commonly be fatal, irrespective of an individual pattern of CFIP.

Attention should be paid to the differences between survivors and nonsurvivors in clinical, laboratory, and radiographic findings in this cohort. The relatively short symptom duration before admission in nonsurvivors might be dependent on the severity of the lung injury that has not yet been strictly objectified. Radiographically, factors for discriminating between nonsurvivors and survivors were the distribution pattern of acute pulmonary infiltrates and the presence of CLE, but not the presence of paraseptal emphysema. CT patterns have been shown to be associated with the mortality in patients with AE of IPF, [9] however, there may be a degree of subjectivity in the diagnosis of this condition, and interobserver differences must be considered. Among laboratory data, the serum BNP level and the P/F ratio on the day after glucocorticoid pulse therapy, as well as those on admission, were discriminative. We performed echocardiography in every patient with signs and symptoms clinically suggestive of cardiac dysfunction or those with increased serum BNP, and none showed left ventricular dysfunction. The higher P/F ratio after glucocorticoid pulse therapy suggests that this treatment might be effective for a certain subset of patient. The presence of SIRS and the number of SIRS criteria fulfilled were the factors that provided the most significant discrimination between survivors and nonsurvivors.

The univariate analysis revealed that the extent of honeycombing was associated with survival; this was not apparent in the group comparison. On the basis of the results of the univariate analysis, we performed a multivariate analysis of survival, and it revealed some notable results: the most significant factors for predicting in-hospital mortality were the presence of SIRS and the absence of CLE on TSCT; the serum PCT level was also associated with outcome.

The presence of SIRS, first defined in 1992, indicates a systemic inflammatory response to a variety of severe clinical insults, including noninfectious causes such as trauma, burns, or pancreatitis, etc.[18] The definition of SIRS is simple, and thus can be easily applied in routine medical care; however, the clinical significance of SIRS has been controversial. In infected subjects, the number of SIRS criteria fulfilled did not influence patient outcome, despite the fact that the presence of organ dysfunction or shock showed prognostic significance.[21] In our study, SIRS was significantly more prevalent in nonsurvivors, and was one of the most significant predictors of hospital mortality. The influence of SIRS on mortality in patients with AE of CFIP has not yet been examined, probably because that the disease process has been recognized as a disorder compartmentalized to the lung. Compared with stable IPF patients, patients with AE of IPF has been reported to show increases in serum biomarkers associated with endothelial cell injury, such as thrombomodulin or plasminogen activator inhibitor-1 (PAI-1).[22] In addition, increases in levels of interleukin-8 or intracellular adhesion molecule 1, known as molecules related to neutrophil recruitment to the lung, were reported to be independent mortality predictors in patients with acute lung injury/acute respiratory distress syndrome.[23] In our cohorts, the mean ratio of bronchoalveolar neutrophils in 17 patients underwent bronchoalveolar lavage was 20.0% (data not shown). These data suggests a possibility that acute lung injury mediates systemic inflammation via certain circulating molecules, as in the case of AE of CFIP. The significance of SIRS as a mortality predictor should be confirmed in future studies. Investigations to determine the mechanisms of SIRS development in patients with AE of CFIP may be essential to allow the development of more specific treatments.

PCT, a prohormone of calcitonin, is produced in the medullary C-cells of the thyroid gland. It was described as an infection parameter in the early 1990's[24] and is now considered to be a useful serum biomarker for early diagnosis of bacterial infections.[25] On the other hand, increase of serum PCT

levels caused by noninfectious processes have also been reported. In a retrospective analysis of patients who underwent cardiopulmonary bypass surgery but who did not have postoperative infection, Hensel et al. described a significant increase in PCT in patients with both SIRS and acute lung injury, compared with those with SIRS alone [26] In their cohort, PCT levels were also elevated in patients without SIRS as well as in patients with SIRS alone, and the levels were statistically similar; this indicates that acute lung injury might play a critical role in the facilitated generation of PCT. Rapid increases of PCT levels in patients with nonbacterial pneumonitis caused by inhalational burn have also been reported.[27] In our cases of AE, serum PCT levels were of prognostic significance, and were also positively correlated with the number of SIRS criteria. The measurement of PCT has 2 key implications in our cohort. First, PCT was useful for excluding the possibility of respiratory infections, because most of the patients had PCT levels of < 0.25 ng/ml (data not shown), which is below the level suggestive of severe pneumonia and/or bacteremia.[28] Second, in the absence of overt respiratory infection, a relatively slight but significant elevation of PCT should not be ignored. PCT was proved to be associated with hospital mortality in both the univariate and multivariate analyses. Although the source of PCT in patients with AE of CFIP has not been confirmed, pulmonary neuroendocrine cells are possible candidates, because an abundance of calcitonin per unit weight of lung tissue has been described.[27 29] The serum PCT level was positively correlated with the number of SIRS criteria, suggesting that PCT could be a novel candidate biomarker for AE of CFIP.

One report has indicated that the absence of smoking history might positively influence the onset of AE in patients with IPF;[8] however, CLE has not been evaluated as a mortality predictor. There are a few possible reasons why the presence of CLE was associated with outcome. First, in some subjects with both CFIP and CLE, diffuse alveolar damage, a histopathological hallmark of AE of CFIP, was not present. Second, the pathogenesis of CLE itself antagonizes that of on-going diffuse alveolar damage. Finally, glucocoticoids are more effective for subjects who have background CLE. As mentioned above, we ruled out the possibility of obvious cardiac dysfunction by echocardiography in the patients studied. Six out of 11 survivors with CLE underwent bronchoalveolar lavage soon after the admission (data not shown), and none showed overt alveolar haemorrhage. Although AE in patients with combined pulmonary fibrosis and emphysema (CPFE) has recently been reported,[30] its curability has not been described. In patients with chronic obstructive pulmonary disease (COPD), gene expression analysis and immunohistochemistry showed that urokinase plasminogen activator (PLAU) and urokinase plasminogen activator receptor (PLAUR) were found to be overexpressed in alveolar macrophages and bronchial epithelium.[31] In infant respiratory distress syndrome, a condition characterized by intraalveolar fibrin deposition, the ratio of PAI-1 to PLAU in tracheal aspirates was higher than that in control subjects,[32] suggesting a role for PLAU in intraalveolar fibrinolysis. Lung-specific overexpression of PLAU in mice was shown to reduce the accumulation of collagen in the lung and reduced mortality after bleomycin-induced lung injury.[33] Thus, constitutive activation of the PLAU-PLAUR system in subjects with CLE, a histological hallmark of COPD, may antagonize the activation of PAI-1, a possible biomarker of AE of CFIP. Generally, COPD itself has been demonstrated to show glucocorticoid resistance.[34] It remains to be determined whether there are any differences in the histological patterns of AE and the efficacy of glucocorticoids between in patients with CFIP alone and those with both CFIP and CLE. The histological patterns could be unraveled by analysis of surgical lung biopsy specimens, and the efficacy of glucocorticoids could be clarified with the accumulation of data from future clinical cases.

The Kaplan-Meier estimate for survival according to the subgrouping by the presence or the absence of SIRS and CLE clearly divided the patients into 4 subgroups. Every patient in group 1 (SIRS-CLE+) was successfully treated with glucocorticoids and discharged. Although an effective pharmaceutical therapy has not been established for patients with AE of IPF, [12] the present study is the first to document a subgroup of CFIP patients who derive a possible benefit from glucocorticoid therapy during AE. Five of the 7 cases in group 1 were of IPF. By contrast, all 22 patients in group 4 (SIRS+CLE-) died due to respiratory failure secondary to AE. In this subgroup, any treatment option, such as polymyxin B-immobilized fibre column treatment[11], should be considered. An indication for the use of glucocorticoids should be also discussed in the future.

The limitations of the present study are as follows. First, the analysis was retrospective. However, we consecutively enrolled every subject admitted with AE of CFIP from January 2009, and collected the hospitalization medical records as completely as possible. Second, this study was undertaken in a single medical institution, and therefore the number of patients studied was limited. Third, the

diagnosis of CFIP and the classifications were somewhat dependent on TSCT findings. Because most of the patients were in moderate to severe respiratory failure (two-thirds of the patients studied had a P/F ratio of ≦ 200, data not shown), surgical lung biopsies on admission were difficult to perform. Half of the patients studied had been referred, and among those, none had undergone surgical lung biopsy. Consequently, 5 patients underwent surgical lung biopsy in this study. We tried, as much as possible, to rule out known entities associated with the development of pulmonary fibrosis. Finally, most of the referred subjects had not undergone pulmonary function tests before admission. Therefore, we could not evaluate pulmonary function test results as mortality predictors.

Several mortality predictors have been identified in patients with AE of IPF. However, it is unclear how those factors could be contributory to the management of this possibly fatal disorder in routine medical practice. We expect that the prognostic significance of CLE and SIRS, factors by which patients could be sub-grouped on admission, could contribute to the rational management of patients with AE of CFIP. The utility of these prognostic factors should be prospectively investigated in future cohorts.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

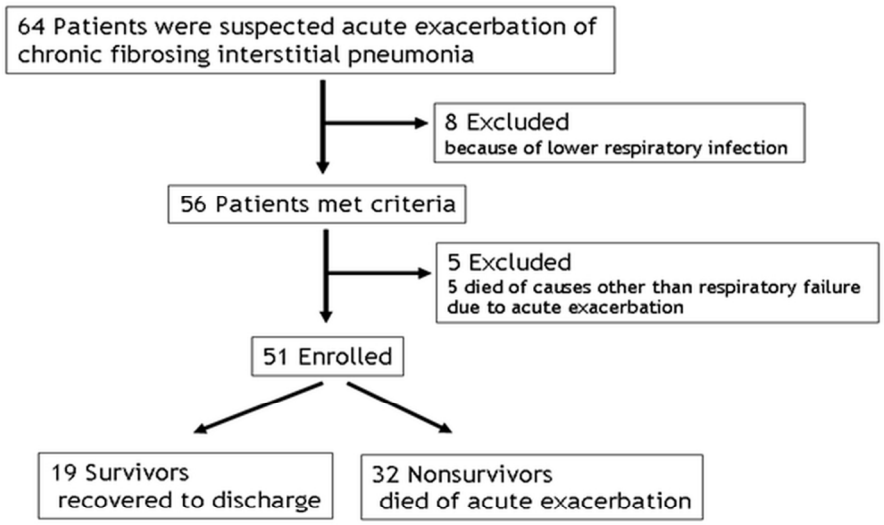

Figure 1 Flow diagram in patients with AE of CFIP

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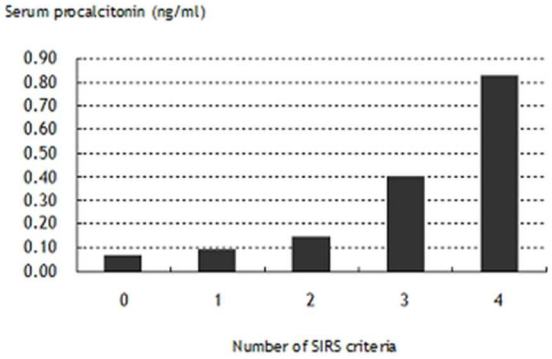

Figure 2 The number of SIRS criteria was positively correlated with the serum procalcitonin concentration (p=0.045). The number of subjects was as follows: 7 (SIRS score 0); 12 (score 1); 11 (score 2); 13 (score 3); 4 (score 4), respectively. Logistic regression analysis was performed for the significance.

158x90mm (300 x 300 DPI)

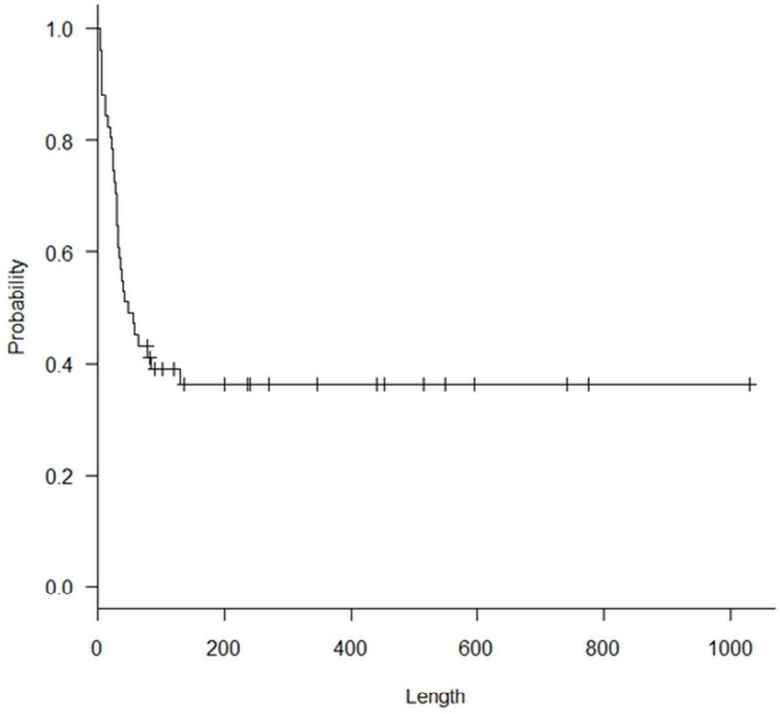

Figure 3 A Kaplan-Meier estimate for overall survival. An x-axis indicates days after admission.

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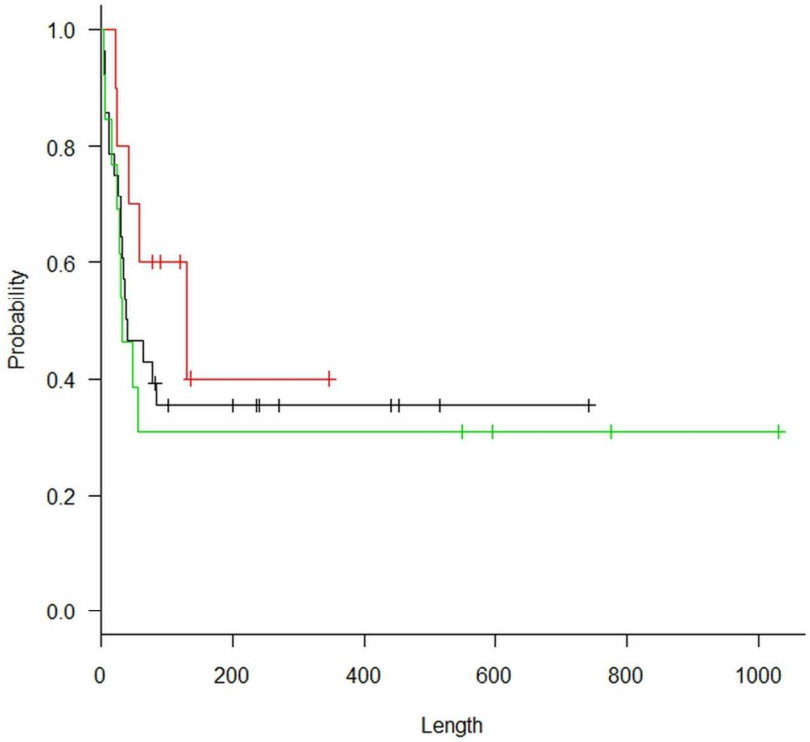

Figure 4 A Kaplan-Meier estimate for survival according to the TSCT classification: definite UIP pattern (black, 28 patients); possible UIP pattern (green, 13 patients); inconsistent with UIP pattern (red, 10 patients). An x-axis indicates days after admission.

96x90mm (300 x 300 DPI)

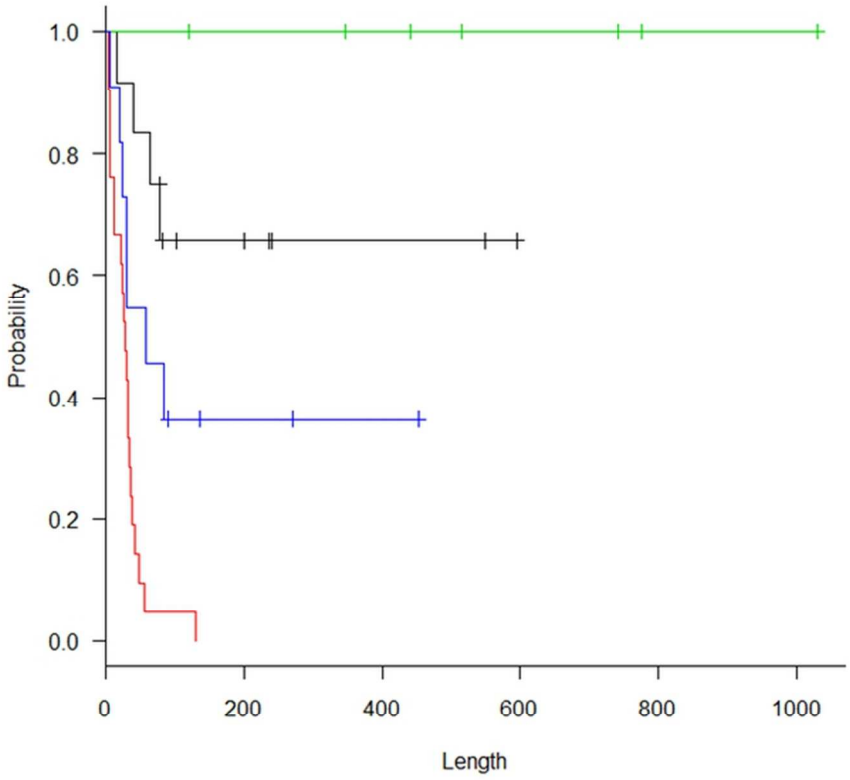

Figure 5 The stratification according to the presence or the absence of CLE and SIRS revealed distinct survival curves of the four groups. Group 1 (green): SIRS-CLE+ (n=7); group 2 (black): SIRS-CLE- (n=12); group 3 (blue): SIRS+CLE+ (n=11); group 4 (red): SIRS+CLE- (n=21). An x-axis indicates days after admission.

90x93mm (300 x 300 DPI)