A Cohort Study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema

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Mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema

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Subject Heading: Mortality predictors in CPFE

Article Focus: Combined pulmonary fibrosis and emphysema (CPFE) has recently been recognized as a new entity. Prognosis is often poor, and pulmonary hypertension is common. There is little information on clinical parameters and predictors of mortality.
What is the most useful clinical predictor of mortality in CPFE?
What is the most informative physiologic predictor of mortality in CPFE?
The aim of the study is to investigate predictor of mortality in CPFE with less invasive way.

Key Messages: Clinical point of view, finger clubbing is useful predictor of mortality in CPFE. In addition, ratio of percent predicted forced expiratory volume in 1 second (%FEV$_1$) and percent forced vital capacity (%FVC) more than 1.2% were independent predictors of mortality in patients with CPFE too. Prediction of prognosis of these patients by minimally invasive methods may be quite useful.

Strengths and Limitations:We investigated all available clinical and physiological data with minimally invasive way.Therefore,most hospitals can refer our result easily. And we compared CPFE with IPF patients. Therefore,our result may be more robust. However, this is single center study. So, our result cannot be generalizable to other hospital's patients. We will require multi-centre study for confirmation.

Abstract
Objectives: Our purpose was to assess the clinical data, predictors of mortality, acute exacerbation of CPFE patients and compared that of idiopathic pulmonary fibrosis (IPF) patients.
Design:Single centre retrospective cohort study.
Setting:Teaching hospital in Japan.

Participants: Ninety-three patients had CPFE and one hundred and fifty-two IPF patients were identified. We identified 93 CPFE patients with high-resolution computed tomographic (HRCT) through multidisciplinary discussion. Patients who had connective tissue disease (CTD), drug-associated ILD, and occupationally related ILD, such as asbestosis and silicosis were excluded.

Interventions: There were no interventions.

Methods: Medical records and HRCT scans from January 2002 through December 2007 were reviewed retrospectively at our hospital. Ninety-three patients had CPFE and one hundred and fifty-two IPF patients were identified during same period.

Results: The mean age of CPFE patients was 74 years. IPF and nonspecific interstitial pneumonia (NSIP) were observed as distinct HRCT patterns. Fourty-two patients showed finger clubbing. Mean serum Krebs von den Lungen-6 (KL-6) and percent predicted forced vital capacity (%FVC) were 1089 IU/L, 63.86% respectively. Twenty-two patients developed acute exacerbation during observation period. Baseline KL-6 was a strong predictor of acute exacerbation. (Odds Ratio = 1.0009, P = 0.027). Finger clubbing (Hazards Ratio = 2.2620, P = 0.015) and percent predicted forced expiratory volume in 1 second (%FEV_1) / %FVC more than 1.2 (Hazards Ratio = 1.9259, P = 0.048) were independent predictors of mortality in CPFE.

Conclusions: Serum KL-6 was a useful predictor of acute exacerbation (cutoff = 1050, ROC: 0.7720), which occurred in 24% (22/93) of the CPFE patients. Finger clubbing and %FEV_1/ %FVC %FVC more than 1.2 were independent predictors of mortality.

Key words: mortality; acute exacerbation; finger clubbing; KL-6 ; %FEV_1/%FVC

There is no additional data available.

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Combined pulmonary fibrosis and emphysema (CPFE) has been recognized as a unique entity that is characterized by upper lobe emphysema and lower lobe fibrosis (1). Emphysema has been associated with heavy smoker's idiopathic pulmonary fibrosis (IPF)(2–3) and usually occurs with elevated lung volume. On the other hand, IPF is associated with a progressive decline in lung volume. In CPFE, lung volume is preserved in many patients, even in those at advanced stages, because supervening fibrosis offsets the effect of emphysema (3–5). CPFE patients also more often have pulmonary arterial hypertension (PAH) (6). PAH has been shown to be a significant prognostic indicator for both IPF (7,8) and chronic obstructive pulmonary disease (COPD) (9). In patients with lung cancer , CPFE is more prevalent than fibrosis (10). Recently, CPFE syndrome has been individualized, partly on the basis of distinct characteristics observed by high-resolution computed tomography (HRCT) of the chest (11).

There is very little information on predictors of mortality for CPFE (1,12). Patients with CPFE often have severe dyspnea and poor cardiopulmonary reserve (13,14), and many patients cannot tolerate invasive procedures such as video-assisted thoracic surgery (VATS).

Thus, the objective of the present study was to determine the predictors of acute exacerbation and mortality in CPFE patients using minimally invasive methods.

Methods

Study Population and HRCT Assessment

This study is retrospective cohort study. We retrospectively investigated our medical records and high-resolution computed tomographic (HRCT) scans from Okinawa Chubu Hospital, Okinawa, Japan from January 1, 2002 through December 31, 2007. During this period we had 319 interstitial lung disease(ILD) patients , among them we had 152 IPF patients. Eligible patients were men and women aged 18 years or older with a proven

diagnosis of IPF or nonspecific interstitial pneumonia (NSIP) according to the American Thoracic Society/ European Respiratory Society (ATS/ERS) statement (15). Among all ILD patients, we identified 93 CPFE patients through multidisciplinary discussion. We excluded patients if; 1) they were without HRCT imaging, 2) had connective tissue disease (CTD), 3) had drug-associated ILD, and 4) had occupationally related ILD, such as asbestosis and silicosis. Demographic and clinical data were obtained, including age, gender, smoking history, dyspnea duration, crackles,clubbing, and Krebs von den Lungen-6 (KL-6) levels. We also checked physiological data including forced expiratory volume in 1 second (FEV_1), $\%FEV_1$, forced vital capacity (FVC), and %FVC. We only included pulmonary function data determined within six months of the date of HRCT.

The HRCT scan imaging patterns were evaluated according to the ATS/ERS criteria (15). We diagnosed IPF patients using the new ATS/ERS and Japanese Respiratory Society /Latin America Thoracic Association criteria (16). Patients who met the following criteria, as described by Cottin et al. (1), were diagnosed as having CPFE: (1) the presence of emphysema on CT, defined as well-demarcated areas of decreased attenuation compared with contiguous normal lung, marginated by a very thin (<1 mm) wall or no wall, and/or multiple bullae (>1 cm) with upper-zone predominance, and (2) the presence of significant pulmonary fibrosis on CT, defined as reticular opacities with peripheral and basal predominance, with or without traction bronchiectasis that occurs with or without honeycombing. The Ethics Committee of Okinawa Chubu Hospital approved this study protocol.

Statistical Methods

Clinical data are presented as means ± SDs or medians (range), depending on distribution. Group comparisons were made using unpaired t-tests, the Wilcoxon rank sum test, Chi-squared statistics, and Fisher's exact test, as appropriate. A Cox proportional hazards model analysis was performed to

determine the relationships between clinical parameters, physiological indices, HRCT imaging patterns and survival. Clinical data analyses were performed using STATA software Version 11.0 (Stata Corp, College Station, TX, USA). Statistical significance was defined as a P value less than 0.05.

Results

Patient Characteristics, Acute Exacerbation (AE), and Clinical Parameters

Ninety-three CPFE patients were (76 men , 17 women) were identified between 2002 and 2007. The mean age was 73 years, and 82 % of the patients were males. The mean time from symptoms to diagnosis was 12.68 months (0–96 months). The mean follow-up period was 30.7 months (0–74.6 months). All patients had histories of smoking (mean: 62 pack-years). The mean modified Medical Research Council (mMRC) breathlessness score was 2.5. During same period we had three hundred nineteen ILD patients, among them we had one hundred and fifty-two IPF patients. Therefore, we compared CPFE clinical parameters with that of IPF patients. Modified MRC scores was similar. (2.6 vs. 2.5 , P = 0.1002). IPF patients showed more longer dyspnea durations compared with those of CPFE patients. (17.04 vs. 12.98 months; P = 0.0002) Bibasilar fine crackles were auscultated in all patients and fourty-two (45 %) had finger clubbing. The baseline percent predicted forced expiratory volume in 1 second (FEV_1) (FEV_1/average %FEV_1 for similar age, sex and body composition) was 70.95%, and the baseline percent predicted forced vital capacity (FVC) was 63.86%. The clinical characteristics of the patients are summarized in Table 1.

The mean partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were 63 mmHg and 43 mmHg, respectively. Fourty-two patients (30%) received home oxygen therapy and 36 (39%) had pulmonary arterial hypertension. The mean systolic pulmonary arterial pressure was 62.76 mmHg. CPFE patients frequently have been reported to have lung cancer,

especially squamous cell carcinoma (10,17). However, in our cohort, only twelve (13 %) patients developed lung cancer.

Among the 93 patients, twenty-two (24%) developed AE, which met the ATS/ERS criteria (15). We performed univariate analysis to determine predictors of AE. Age, mMRC score, dyspnea duration, and serum KL-6 were identified as possible predictors of AE. Multivariate regression analysis was performed for these four factors, serum KL-6 was found to be the strongest predictor of AE in the CPFE patients［Odds Ratio = 1.0009, P = 0.027］. Using receiver operator characteristic curve (ROC) analysis, the useful KL-6 threshold was determined to be 1050 (ROC: 0.7720).

HRCT Imaging and Predictors of Mortality

According to the ATS/ERS criteria (15,16), the patients were divided into those with IPF patterns and those with NSIP patterns. There were 68 patients in the IPF–pattern group and 25 patients in the NSIP–pattern group. The HRCT images also showed patterns indicating that 51 patients had para septal emphysema, 28 had centrilobular emphysema, and 14 had panlobular emphysema. Detailed results are presented in Table 2.

The mean survival of CPFE patients was 30.7 months(0.10–75.63 months). On the other hand, mean survival of IPF patients was 34.5 months (6.79-72.95 months) which was statistically significant(p = 0.0411) (Figure 1). Patients with finger clubbing or increased ratio of $\%FEV_1$ to %FVC showed poor survival in CPFE patients (Figure 2) (Figure 3). Regarding ratio of $\%FEV_1$ to %FVC, we chose 1.2 which was most useful threshold for predictor of mortality with using ROC analysis(ROC: 0.7671). In IPF patients in our cohort, useful cut off value of ratio of $\%FEV_1$ to %FVC was 1.5 (Figure 4)(ROC: 0.8622). Initially, we performed univariate analysis with a cutoff value of 0.1, which showed that KL-6, finger clubbing, PaO_2, and $\%FEV_1$ / % FVC > 1.2 were independent predictors of mortality (Table 3). Cox proportional hazards regression analysis showed that finger clubbing (HR = 2.2620, P = 0.015) and ratio of $\%FEV_1$ to % FVC more than

1.2 (HR = 1.9259, P = 0.048) were the strongest independent predictors of mortality in CPFE patients at our hospital (Table 4).

Discussion

Previous studies have reported a high prevalence of PAH and lung cancer in CPFE patients (1,10). These comorbidities were associated with poor prognosis; the 1-year survival rate for CPFE patients with PAH was only 60% (6,11). Among these patients, high mean pulmonary arterial pressure, high pulmonary vascular resistance, high heart rate, and low diffusing capacity for carbon monoxide (DLco) were significantly associated with poor outcome. In one study, CPFE patients had a five fold higher mortality risk (adjusted HR: 5.10, 95%CI:1.75–14.9) in non-malignant situations (19). In the present study, only twelve of 93 patients had lung cancer in contrast to the number reported in a previous study (10). Our institution is a teaching and community hospital, and the patient population may be different from that of a university hospital.

The pulmonary function indices of the CPFE patients included in the present study were rather different from those in previous reports (1, 20). The CPFE patients in those studies had greater preserved lung volume despite reduced DLco, reduced transfer coefficient for carbon monoxide (Kco), and hypoxemia. Jankowich, et al. reported that CPFE altered physiology but had a mortality rate similar to that of IPF (21). In addition, Peng M, et al. reported similar physiology results for CPFE (22). In our study, the mean percent predicted FVC was 63.86% and that of FEV_1 was 70.95%, which showed more restrictive impairment compared with previous cases. This finding can be explained by the greater volume loss of the lower lung field due to severe fibrosis rather than by the offset effect of emphysema (23). This finding might also be because our cohort had less emphysema area compared with the previously reported cases. Another possibility is that the patients might have been in a different phase of CPFE. Recently, Rogliani, et al. reported the pathology of IPF and

emphysema (24). They evaluated 17 biopsy-proven usual interstitial pneumonia (UIP) patients and found fibroblasts in areas of parenchymal destruction from emphysema/UIP-expressed matrix metalloproteinase (MMP)–2, MMP–9, MMP–7 and membrane type 1 (MT1)–MMP at significantly higher levels when compared with emphysema subjects. On the basis of this result, similar to the findings of the study by Rogliani et al. cited above, interstitial fibroblast activation could be stimulated to a greater degree in the areas of lung destruction in CPFE compared with emphysema alone, as in exaggerated tissue remodeling. Therefore, some of the CPFE patients may have had more intense fibrosis, which contributed to reduced FVC.

In the analysis of the HRCT images, the patients were divided into two groups by IPF pattern and NSIP pattern according to the ATS/ERS criteria (15,16). All of the IPF-pattern patients had honeycombing, and the NSIP-pattern patients more often had consolidation (60% vs. 29%) and ground-glass opacity (34% vs. 100%). These findings were very similar to those from a recent report on HRCT for NSIP (25). In addition, Sumikawa et al. reported that traction bronchiectasis and fibrosis scores were associated with poor prognosis in pathological UIP patients (26). In the present study, HRCT pattern was not an independent prognostic predictor. CPFE patients usually have more severe PAH, low cardiac index (6) and are disabled (27), which we observed in our cohort. Thus, most CPFE patients cannot tolerate invasive procedures such as VATS. Therefore, we cannot compare biopsy-proven UIP with CPFE equally.

Acute exacerbation (AE) is a relentlessly progressive status and is associated with poor outcome (28). Thus, we investigated AE of CPFE. During the observation period (mean: 30.7 months), twenty-two patients (24 %) developed AE. The annual incidence of AE is 9.4%. This finding is similar to that reported in IPF recently (29). Kondoh, et al. reported that high modified MRC score, high body mass index (BMI), and decline in FVC at six months were significant independent risk factors for AE-IPF (30).

KL-6 levels in ILD patients reflect the overall extent of interstitial lesions. Among the many clinical parameters, serum KL-6 was the most powerful predictor of AE in our CPFE patients. ROC analysis showed that the useful threshold was 1050 (ROC = 0.7720).

Finally, we investigated the prognostic predictors of CPFE in our cohort. FVC has been reported robust powerful predictor of mortality in IPF patients (31). DLco often show variable value, so reproducibility is rather poor. In addition when FVC is reduced, DLco cannot be obtained with single breath method. Therefore, we chose %FEV_1 ,% FVC and ratio of these value as important indices out of pulmonary function parameters. Univariate analysis revealed that KL-6, finger clubbing, PaO_2, and ratio of %FEV_1 to % FVC were independent predictors. Regression analysis using a Cox proportional hazards model showed that finger clubbing and ratio of %FEV_1 to % FVC more than 1.2 were the strongest independent predictors of mortality in CPFE at our hospital. On the other hand, ratio of %FEV_1 to % FVC more than 1.5 was useful threshold for mortality in IPF patients. In CPFE patients,lung volume is usually preserved. Therefore, absolute value of FVC or %FVC itself has been reported to be not robust predictor of critical event. However, ratio of %FEV_1 to % FVC may be useful parameter in subgroup of CPFE patients. In terms of different cut-off value of this ratio, CPFE patients tend to have more mild restrictive impairment compared with that of IPF patients. Another interesting finding was that finger clubbing which is associated with poor survival in CPFE patients. Finger clubbing usually shows chronicity in ILD patients. However, it predicted clinical course in CPFE patients at our cohort. So, we insisist on the importance of initial careful evalution of physical findings in CPFE.

Regarding prognosis, CPFE patients showed poor survival compared to that of IPF patients in our cohort. Therefore, even if lung volume is seemingly preserved, we should follow-up these patients carefully with multi-dimentions.

This time, we did not evaluate the treatment in CPFE patients. Currently, there is no consensus on treatment of CPFE with PAH (32,33). This is a vital topic for future study.

There were several limitations in our study. First, this was a single center, uncontrolled design, retrospective study, which means that it is possible that important data was not collected. In addition, the results cannot be generalized to all CPFE patients. Second, we did not measure the exact areas of emphysema and fibrosis. Therefore, our cohort may have been at a different stage compared with previous CPFE patients. Third, most of our patients could not undergo surgical biopsy because of disability and reduced lung function. Thus, we could not evaluate the detailed pathology of our CPFE patients. Fourth, we did not evaluate serial pulmonary function. Recently, Du Bois et al. reported that percent predicted FVC and the 24 week change in FVC were useful predictors of mortality in IPF (34). Therefore, it might be helpful to measure serial FVC as a prognostic predictor in CPFE. Lastly, in keeping with previous reports, our study patients were all heavy smokers. Therefore, we could not distinguish CPFE from smoking-related NSIP (35). However, even considering these limitations, prediction of prognosis using minimally invasive methods in these patients may be quite useful.

In conclusion, our CPFE patients showed poor survival compared to that of IPF patients. CPFE patients often develop AE, for which serum KL-6 was a useful predictor. Finger clubbing and %FEV1 / % FVC more than 1.2 were independent prognostic predictors of mortality in patients with CPFE. A multicenter study of this new entity is warranted for further research.

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Data Sharing

There is no additional data available.

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Figure Legends:

Figure 1; CPFE patients show poor survival compared with that of IPF patients

Figure 2; CPFE patients with clubbing show poor survival compared with that of without clubbing

Figure 3; Ratio of %FEV_1 and %FVC more than 1.2 show poor survival rather than that of less than 1.2 in CPFE patients

Figure 4; Ratio of %FEV_1 and %FVC more than 1.5 show poor survival rather than that of less than 1.5 in IPF patients

TABLE 1. Patient clinical characteristics

	IPF (n= 152)	CPFE (n= 93)	p-value
Age, year (mean)	73.01 ± 3.80 (60-91)	73.83 ± 7.07 (57-90)	0.2361
Male sex, %	83	82	0.8155
Pack-year	49 ± 0.6(15-180)	62 ± 3.1(3-160)	< 0.0001
mMRC scale	2.6 ± 0.04 (1-4)	2.5 ± 0.09 (1-4)	0.1002
Dyspnea duration months	17.04 ± 0.28 (0-56)	12.98 ± 1.30 (0-60)	0.0002
Clubbing, %	53	45	< 0.0001
KL-6, IU/L	1058 ± 12.44 (212-3250)	1089 ± 75.04 (201-4480)	0.5914
Baseline FEV_1,%	78.63 ± 0.32 (41.4-109.3)	70.95 ± 0.89 (37.4-96.7)	< 0.0001

Baseline FVC,%	57.41 ± 0.27 (24.9-82.7)	63.86 ± 0.96 (37.4-99.5)	< 0.0001

Data are presented as mean± SD and mean %predicted ± SD

Definitions of abbreviations: IPF = Idiopathic Pulmonary Fibrosis; NSIP = Non Specific Interstitial Pneumonia; MRC = Medical Research Council; FEV_1= forced expired volume in one second; FVC = forced vital capacity.

Table 2. HRCT Imaging in CPFE patients

	IPF pattern (n=68)	NSIP Pattern (n= 25)	All (n= 93)
Emphysema pattern			
Paraseptal,%	57	48	55
Centrilobular,%	29	32	30
Panlobular,%	14	20	15
Fibrosis pattern			
Traction bronchiectasis, %	96	88	94
Reticulation, %	91	88	90
Honeycombing, %	100	0	73
Ground glass opacity , %	34	100	52
Consolidation, %	29	60	38

Definitions of abbreviations: HRCT = High resolution computed tomography ; IPF = Idiopathic pulmonary fibrosis ; NSIP = Non specific interstitial pneumonia.

Table 3. Results of univariate analysis showing predictors of mortality

	Hazards ratio	95% CI	P-value
KL-6	1.0003	1.00003-1.00063	0.029
Finger clubbing	2.3711	1.2394-4.5362	0.009
PaO_2	0.9477	0.9013-0.9965	0.036
$\%FEV_1/\%FVC$ (> 1.2)	2.6326	1.4855-4.6655	0.001

Definitions of abbreviations: CI = confidence interval ; MRC = Medical research council; FVC = forced vital capacity.

Table 4. Results of the Cox proportional hazards regression analysis

	Hazards ratio	95% CI	P-value
Finger clubbing	2.2620	1.1746-4.3560	0.015
%FEV1/%FVC (> 1.2)	1.9259	1.0057-3.6883	0.048

Definitions of abbreviations: CI = confidence interval ; FVC = forced vital capacity.

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1. Given Name (First Name) 2. Surname (Last Name1. 3. Effective Date

Tomoo Kishaba December 1, 2011

4. Are you the corresponding author? Yes

5. Manuscript Title

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7. **Payment for manuscript preparation**	**No**
8. **Patents (planned, pending or issued)**	No
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Yousuke **Shimaoka** **December 1, 2011**

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Hajime	**Fukuyama**	**December 1, 2011**

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Kyoko **Yoshida** **December 1, 2011**

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Maki	**Noyama**	**December 1, 2011**

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Shin **Yamashiro** **December 1, 2011**

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Hitoshi	**Tamaki**	**December 1, 2011**

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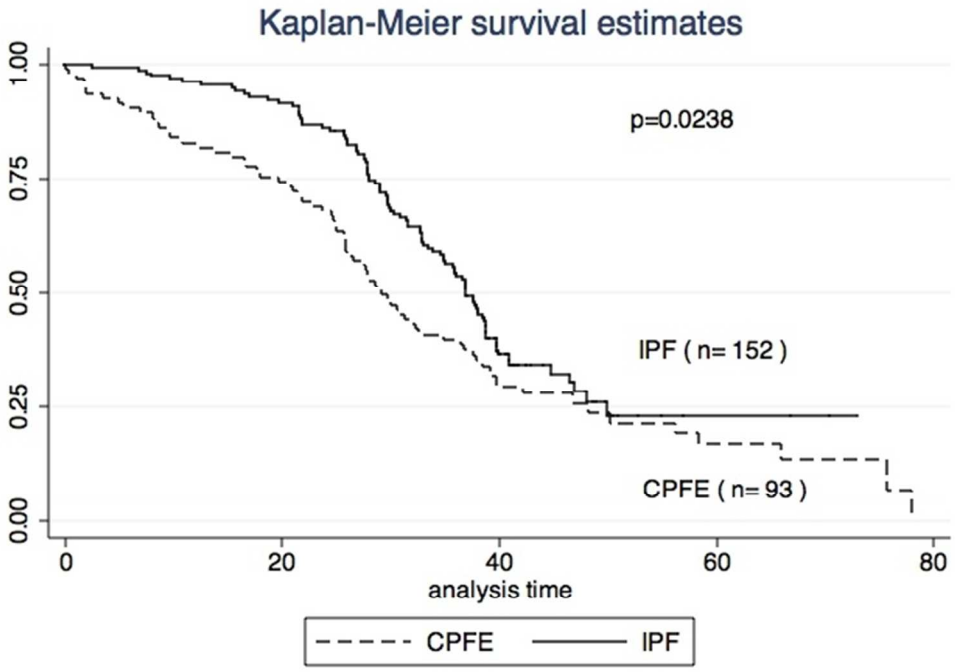

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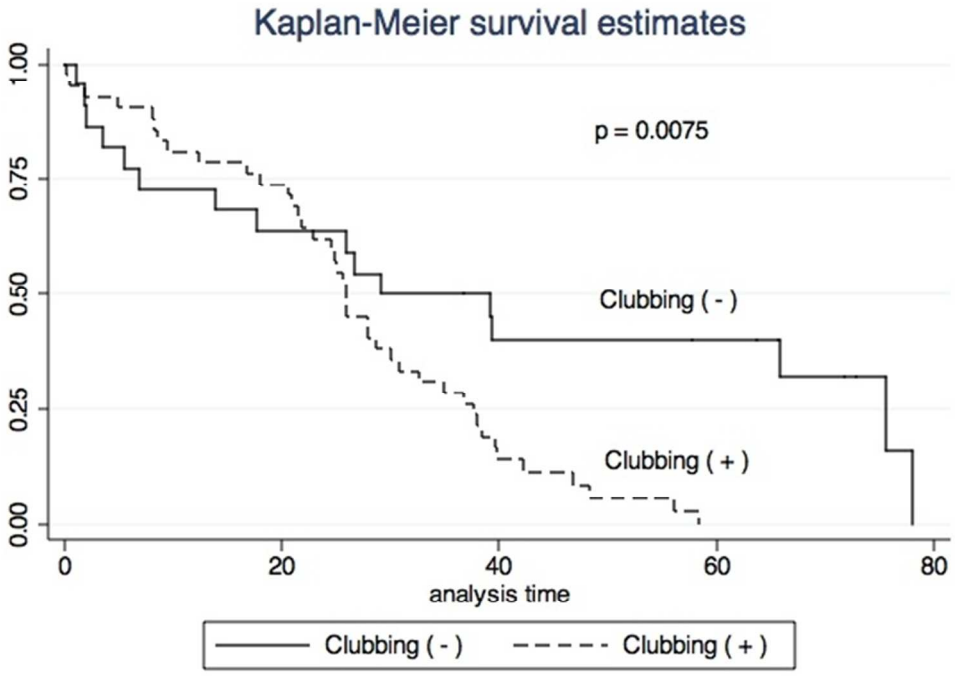

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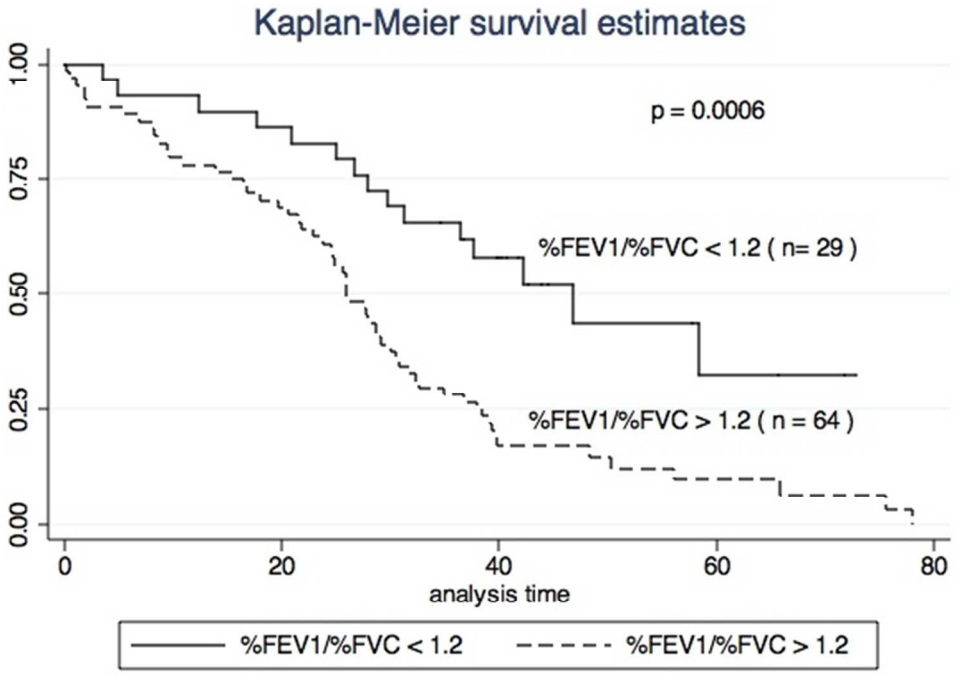

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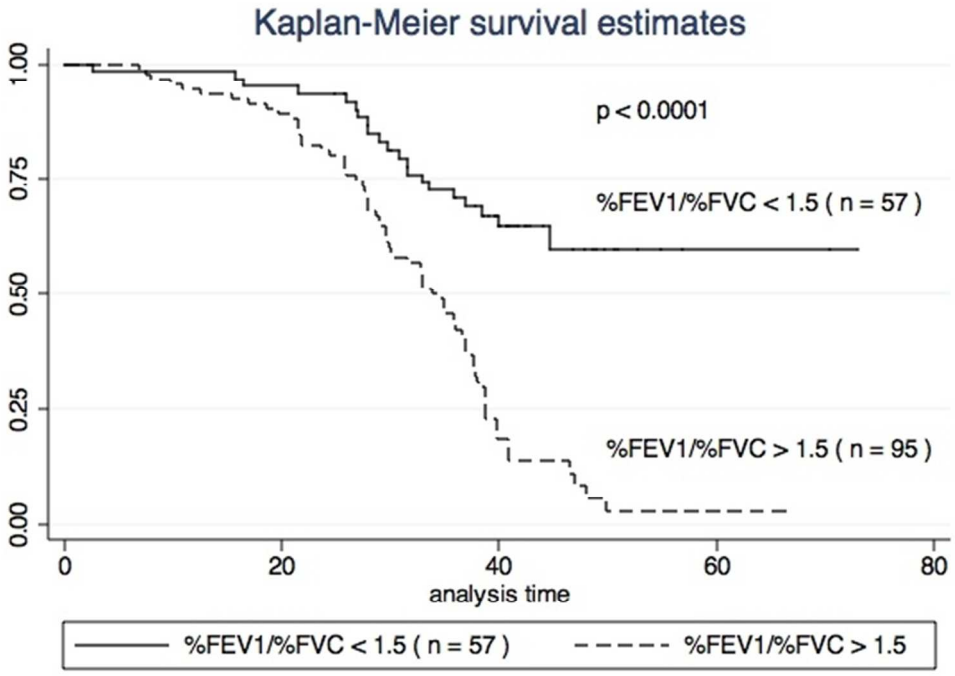

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
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	*2-3*
Bias	9	Describe any efforts to address potential sources of bias	2-3
Study size	10	Explain how the study size was arrived at	2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	2
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	5
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	2.3.6
		(b) Give reasons for non-participation at each stage	4
		(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	6-7
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-7
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	7
		(*b*) Report category boundaries when continuous variables were categorized	6-7
		(*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	6-7
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
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.

A Cohort Study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema

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Primary Subject Heading:	Respiratory medicine
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A Cohort Study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema

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Author Contributions:
T Kishaba, H Tamaki: Study concept and design, acquisition and interpretation of data, and drafting and finalization of the manuscript.
Y Shimaoka, H Fukuyama, K Yoshida, M Tanaka, S Yamashiro: Study design, and acquisition and interpretation of data.

Subject Heading: Mortality predictors in CPFE

Article Focus: Combined pulmonary fibrosis and emphysema (CPFE) has recently been recognized as a new entity. Prognosis is often poor, and pulmonary hypertension is common. There is little information on clinical parameters and predictors of mortality.

What is the most useful clinical predictor of mortality in CPFE?

What is the most informative physiologic predictor of mortality in CPFE?

What is the most sensitive clinical predictor of acute exacerbation in CPFE?

The aim of the study is to investigate predictor of mortality and acute exacerbation in CPFE using less invasive way.

Key Messages: Clinical point of view, finger clubbing is useful predictor of mortality in CPFE. In addition, ratio of percent predicted forced expiratory volume in 1 second (%FEV_1) and percent predicted forced vital capacity (%FVC) more than 1.2% were independent predictors of mortality in patients with CPFE too. Prediction of prognosis of these patients by minimally invasive methods may be quite useful.

Strengths and Limitations: We evaluated clinical and physiological data using minimally invasive way. Therefore, most hospitals can refer our result easily. However, this is single center study. So, our result cannot be generalizable to other hospital's patients.

We will require multi-centre study for confirmation.

Abstract

Objectives: Our purpose was to assess the clinical data, predictors of mortality, acute exacerbation in CPFE patients.

Design: Single centre retrospective cohort study.

Setting: Teaching hospital in Japan.

Participants: Ninety-three patients had CPFE. We identified 93 CPFE patients with high-resolution computed tomographic (HRCT) through multidisciplinary discussion. Patients who had connective tissue disease (CTD), drug-associated ILD, and occupationally related ILD, such as asbestosis and silicosis were excluded.

Interventions: There were no interventions.

Methods: Medical records and HRCT scans from January 2002 through December 2007 were reviewed retrospectively at our hospital. Ninety-three

patients had CPFE.

Results: The mean age of CPFE patients was 74 years. IPF and nonspecific interstitial pneumonia (NSIP) were observed as distinct HRCT patterns. Fourty-two patients showed finger clubbing. Mean serum Krebs von den Lungen-6 (KL-6) and percent predicted forced vital capacity (%FVC) were 1089 IU/L, 63.86% respectively. Twenty-two patients developed acute exacerbation during observation period. Baseline KL-6 was a strong predictor of acute exacerbation. (Odds Ratio = 1.0016, P = 0.009). Finger clubbing (Hazards Ratio = 2.2620, P = 0.015) and percent predicted forced expiratory volume in 1 second (%FEV_1) / % FVC more than 1.2 (Hazards Ratio = 1.9259, P = 0.048) were independent predictors of mortality in CPFE.

Conclusions: Baseline serum KL-6 was a useful predictor of acute exacerbation (cutoff = 1050, ROC: 0.7720), which occurred in 24% (22/93) of the CPFE patients. Finger clubbing and %FEV_1 / %FVC more than 1.2 were independent predictors of mortality.

Key words: mortality; acute exacerbation; finger clubbing; KL-6 ; %FEV_1/%FVC

There is no additional data available

Key words: mortality; acute exacerbation; finger clubbing; KL-6 ; %FEV_1/%FVC

Total Abstract Count: 247

Article summary

Article Focus: Combined pulmonary fibrosis and emphysema (CPFE) has recently been recognized as a new entity. Prognosis is often poor, and pulmonary hypertension is common. There is little information on clinical parameters and predictors of mortality.

What is the most useful clinical predictor of mortality in CPFE?

What is the most informative physiologic predictor of mortality in CPFE?

The aim of the study is to investigate predictor of mortality in CPFE with less invasive way.

Key Messages: Clinical point of view, finger clubbing is useful predictor of mortality in CPFE. In addition, ratio of percent predicted forced expiratory volume in 1 second (%FEV1) and percent forced vital capacity (%FVC) more than 1.2% were independent predictors of mortality in patients with CPFE too. Prediction of prognosis of these patients by minimally invasive methods may be quite useful.

Strengths and Limitations:We investigated clinical and physiological data using minimally invasive way. Therefore,most hospitals can refer our result easily. However, this is single center study. So, our result cannot be generalizable to other hospital's patients.

We will require multi-centre study for confirmation.

Combined pulmonary fibrosis and emphysema (CPFE) has been recognized as a unique entity that is characterized by upper lobe emphysema and lower lobe fibrosis (1). Emphysema is sometimes associated with idiopathic pulmonary fibrosis (IPF)(2–3) and usually occurs with elevated lung volume. On the other hand, IPF is associated with a progressive decline in lung volume. In CPFE, lung volume is preserved in many patients, even in those at advanced stages, because supervening fibrosis offsets the effect of emphysema (3–5). CPFE patients also more often have pulmonary arterial hypertension (PAH) (6). PAH has been shown to be a significant prognostic indicator for both IPF (7,8) and chronic obstructive pulmonary disease (COPD) (9). In patients with lung cancer , CPFE is more prevalent than fibrosis (10). Recently, CPFE syndrome has been individualized, partly on the basis of distinct characteristics observed by high-resolution computed tomography (HRCT) of the chest (11).

There is very little information on predictors of mortality for CPFE (1,12). Patients with CPFE often have severe dyspnea and poor cardiopulmonary reserve (13,14), and many patients cannot tolerate invasive procedures such as video-assisted thoracic surgery (VATS).

Thus, the objective of the present study was to determine the predictors of acute exacerbation and mortality in CPFE patients using minimally invasive methods.

Methods

Study Population and HRCT Assessment

We retrospectively investigated our medical records and high-resolution computed tomographic (HRCT) scans from Okinawa Chubu Hospital, Okinawa, Japan from January 1, 2002 through December 31, 2007. During this period we had 319 interstitial lung disease(ILD) patients Eligible patients were men and women aged 18 years or older with a proven diagnosis of IPF or nonspecific interstitial pneumonia (NSIP) according to

the American Thoracic Society/ European Respiratory Society (ATS/ERS) statement (15). Among all ILD patients, we identified 93 CPFE patients through multidisciplinary discussion including our pulmonologists and radiologists. We excluded patients if; 1) they were without HRCT imaging, 2) had connective tissue disease (CTD), 3) had drug-associated ILD, and 4) had occupationally related ILD, such as asbestosis and silicosis. Demographic and clinical data were obtained, including age, gender, smoking history, dyspnea duration, comorbidity, crackles,clubbing, Krebs von den Lungen-6 (KL-6) levels and Ultrasound Cardiography(UCG)findings. In terms of pulmonary arterial hypertension (PAH), we estimated with UCG .We also checked physiological data including forced expiratory volume in 1 second (FEV_1), $\%FEV_1$, forced vital capacity (FVC), and %FVC. We only included pulmonary function data determined within six months of the date of HRCT.

The HRCT scan imaging patterns were evaluated according to the ATS/ERS criteria (15). We diagnosed IPF patients using the new ATS/ERS and Japanese Respiratory Society /Latin America Thoracic Association criteria (16). Patients who met the following criteria, as described by Cottin et al. (1), were diagnosed as having CPFE: (1) the presence of emphysema on CT, defined as well-demarcated areas of decreased attenuation compared with contiguous normal lung, marginated by a very thin (<1 mm) wall or no wall, and/or multiple bullae (>1 cm) with upper-zone predominance, and (2) the presence of significant pulmonary fibrosis on CT, defined as reticular opacities with peripheral and basal predominance, with or without traction bronchiectasis that occurs with or without honeycombing. Regarding acute exacerbation, we defined by the following criteria (18):(1) sudden deterioration of dyspnea within 30 days (2) new bilateral infiltration on chest radiograph (3)pulmonary infection or other known causes were excluded by bronchoalveolar lavage(BAL). Survival time was defined from the date of HRCT to death or last observation date. The Ethics Committee of Okinawa Chubu Hospital approved this study protocol.

Statistical Methods

Clinical data are presented as means ± SDs or medians (range), depending on distribution. Group comparisons were made using unpaired t-tests, the Wilcoxon rank sum test, Chi-squared statistics, and Fisher's exact test, as appropriate. Logistic regression analysis was performed to determine the relationship between clinical parameters and acute exacerbation. A Cox proportional hazards model analysis was performed to determine the relationships between clinical parameters, physiological indices, HRCT imaging patterns and survival. Clinical data analyses were performed using STATA software Version 11.0 (Stata Corp, College Station, TX, USA). Statistical significance was defined as a P value less than 0.05.

Results

Patient Characteristics, Acute Exacerbation (AE), and Clinical Parameters

The flow diagram in Figure 1 shows how the patients were identified. Ninety-three CPFE patients were (76 men , 17 women) were identified between 2002 and 2007. The mean age was 73 years, and 82 % of the patients were males. The mean time from symptoms to diagnosis was 12.68 months (0–96 months). The mean follow-up period was 30.7 months (0–74.6 months). All patients had histories of smoking (mean: 62 pack-years). The mean modified Medical Research Council (mMRC) breathlessness score was 2.5. Bibasilar fine crackles were auscultated in all patients and fourty-two (45 %) had finger clubbing. The baseline percent predicted forced expiratory volume in 1 second (FEV_1) (FEV_1/average $\%FEV_1$ for similar age, sex and body composition) was 70.95%, and the baseline percent predicted forced vital capacity (FVC) was 63.86%. During observation period, sixty-seven patients (72 %) died. The clinical characteristics of both survivors and non-survivors are summarized in Table 1.

The mean partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were 63 mmHg and 43 mmHg, respectively. Thirty-two patients (34%) received home oxygen therapy and 36 (39%) had pulmonary arterial hypertension. The mean systolic pulmonary arterial pressure was 62 mmHg. CPFE patients frequently have been reported to have lung cancer, especially squamous cell carcinoma (10,17). However, in our cohort, only twelve (13 %) patients developed lung cancer.

Among the 93 patients, twenty-two (24%) developed AE, which met the ATS/ERS criteria (15). We performed univariate analysis to determine predictors of AE. Age, mMRC score, ctpattern, and baseline serum KL-6 were identified as possible predictors of AE. Logistic regression analysis was performed for these four factors, baseline serum KL-6 was found to be the strongest predictor of AE in the CPFE patients［Odds Ratio = 1.0016, P = 0.009］. (Table 2) Using receiver operator characteristic curve (ROC) analysis, the useful KL-6 threshold was determined to be 1050 (ROC: 0.7720).

HRCT Imaging and Predictors of Mortality

According to the ATS/ERS criteria (15,16), the patients were divided into those with UIP patterns and those with NSIP patterns. There were 68 patients in the IPF–pattern group and 25 patients in the NSIP–pattern group. The HRCT images also showed patterns indicating that 51 patients had para septal emphysema, 28 had centrilobular emphysema, and 14 had panlobular emphysema. Detailed results are presented in (Table 3).

The mean survival of CPFE patients was 30.7 months(0.10–75.63 months). (Figure 1). Patients with finger clubbing or increased ratio of $\%FEV_1$ to %FVC showed poor survival in CPFE patients (Figure 2) (Figure 3). Regarding ratio of $\%FEV_1$ to %FVC, we chose 1.2 which was most useful threshold for predictor of mortality with using ROC analysis(ROC: 0.7671). Initially, we performed univariate analysis with a cutoff value of 0.1, which showed that baseline KL-6, finger clubbing, PaO_2, and $\%FEV_1$ / % FVC >

1.2 were independent predictors of mortality. Cox proportional hazards regression analysis showed that finger clubbing (HR = 2.2620, P = 0.015) and ratio of %FEV_1 to % FVC more than 1.2 (HR = 1.9259, P = 0.048) were the strongest independent predictors of mortality in CPFE patients at our hospital (Table 4).

Discussion

Previous studies have reported a high prevalence of PAH and lung cancer in CPFE patients (1,10). These comorbidities were associated with poor prognosis; the 1-year survival rate for CPFE patients with PAH was only 60% (6,11). Among these patients, high mean pulmonary arterial pressure, high pulmonary vascular resistance, high heart rate, and low diffusing capacity for carbon monoxide (DLco) were significantly associated with poor outcome. In one study, CPFE patients had a five fold higher mortality risk (adjusted HR: 5.10, 95%CI:1.75–14.9) in non-malignant situations (19). In the present study, only twelve of 93 patients had lung cancer in contrast to the number reported in a previous study (10). Our institution is a teaching and community hospital, and the patient population may be different from that of a university hospital.

The pulmonary function indices of the CPFE patients included in the present study were rather different from those in previous reports (1, 20). The CPFE patients in those studies had greater preserved lung volume despite reduced DLco, reduced transfer coefficient for carbon monoxide (Kco), and hypoxemia. Jankowich, et al. reported that CPFE altered physiology but had a mortality rate similar to that of IPF (21). In addition, Peng M, et al. reported similar physiology results for CPFE (22). In our study, the mean percent predicted FVC was 63.86% and that of FEV_1 was 70.95%, which showed more restrictive impairment compared with previous cases. This finding can be explained by the greater volume loss of the lower lung field due to severe fibrosis rather than by the offset effect of emphysema (23). This finding might also be because our cohort had

less emphysema area compared with the previously reported cases. Another possibility is that the patients might have been in a different phase of CPFE. Recently, Rogliani, et al. reported the pathology of IPF and emphysema (24). They evaluated 17 biopsy-proven usual interstitial pneumonia (UIP) patients and found fibroblasts in areas of parenchymal destruction from emphysema/UIP-expressed matrix metalloproteinase (MMP)–2, MMP–9, MMP–7 and membrane type 1 (MT1)–MMP at significantly higher levels when compared with emphysema subjects. On the basis of this result, similar to the findings of the study by Rogliani et al. cited above, interstitial fibroblast activation could be stimulated to a greater degree in the areas of lung destruction in CPFE compared with emphysema alone, as in exaggerated tissue remodeling. Therefore, some of the CPFE patients may have had more intense fibrosis, which contributed to reduced FVC.

In the analysis of the HRCT images, the patients were divided into two groups by UIP (usual interstitial pneumonia) pattern and NSIP pattern according to the ATS/ERS criteria (15,16). All of the UIP-pattern patients had honeycombing, and the NSIP-pattern patients more often had consolidation (60% vs. 29%) and ground-glass opacity (100% vs. 34%). These findings were very similar to those from a recent report on HRCT for NSIP (25). In addition, Sumikawa et al. reported that traction bronchiectasis and fibrosis scores were associated with poor prognosis in pathological UIP patients (26). In the present study, HRCT pattern was not an independent prognostic predictor. CPFE patients usually have more severe PAH, low cardiac index (6) and are disabled (27), which we observed in our cohort. Thus, most CPFE patients cannot tolerate invasive procedures such as VATS. Therefore, we cannot compare biopsy-proven UIP with CPFE equally.

Acute exacerbation (AE) is a relentlessly progressive status and is associated with poor outcome (28). Thus, we evaluated AE of CPFE. During the observation period (mean: 30.7 months), twenty-two patients

(24 %) developed AE. The annual incidence of AE is 9.4%. This finding is similar to that reported in IPF recently (29). Kondoh, et al. reported that high modified MRC score, high body mass index (BMI), and decline in FVC at six months were significant independent risk factors for AE-IPF (30). KL-6 levels in ILD patients reflect the overall extent of interstitial lesions. Among the many clinical parameters, baseline serum KL-6 was the most powerful predictor of AE in our CPFE patients. ROC analysis showed that the useful threshold was 1050 (ROC = 0.7720).

Finally, we investigated the prognostic predictors of CPFE in our cohort. FVC has been reported robust powerful predictor of mortality in IPF patients (31). DLco often show variable value, so reproducibility is rather poor. In addition when FVC is reduced, DLco cannot be obtained with single breath method. Therefore, we chose %FEV_1 ,% FVC and ratio of these value as important indices out of pulmonary function parameters. Univariate analysis revealed that KL-6, finger clubbing, PaO_2, and ratio of %FEV_1 to % FVC were independent predictors. Regression analysis using a Cox proportional hazards model showed that finger clubbing and ratio of %FEV_1 to % FVC more than 1.2 were the strongest independent predictors of mortality in CPFE at our hospital. In CPFE patients,lung volume is usually preserved. Therefore, absolute value of FVC or %FVC itself has been reported to be not robust predictor of critical event. However, ratio of %FEV_1 to % FVC may be useful parameter in subgroup of CPFE patients. In terms of different cut-off value of this ratio, CPFE patients tend to have more mild restrictive impairment compared with that of IPF patients. Another interesting finding was that finger clubbing which is associated with poor survival in CPFE patients. Finger clubbing usually shows chronicity in ILD patients. However, it predicted clinical course in CPFE patients at our cohort. So, we insisist on the importance of initial careful evalution of physical findings in CPFE.

Regarding prognosis, CPFE patients showed poor survival similar to that of IPF patients in our cohort. Therefore, even if lung volume is seemingly

preserved, we should follow-up these patients carefully with multi-dimentions.

This time, we did not evaluate the treatment in CPFE patients. Currently, there is no consensus on treatment of CPFE with PAH (32,33). This is a vital topic for future study.

There were several limitations in our study. First, this was a single center, uncontrolled design, retrospective study, which means that it is possible that important data was not collected. In addition, the results cannot be generalized to all CPFE patients. Second, we did not measure the exact areas of emphysema and fibrosis. Therefore, our cohort may have been at a different stage compared with previous CPFE patients. Third, most of our patients could not undergo surgical biopsy because of disability and reduced lung function. Thus, we could not evaluate the detailed pathology of our CPFE patients. Fourth, we did not evaluate serial pulmonary function. Recently, Du Bois et al. reported that percent predicted FVC and the 24 week change in FVC were useful predictors of mortality in IPF (34). Therefore, it might be helpful to measure serial FVC as a prognostic predictor in CPFE. Lastly, in keeping with previous reports, our study patients were all heavy smokers. Therefore, we could not distinguish CPFE from smoking-related NSIP (35). However, even considering these limitations, prediction of prognosis using minimally invasive methods in these patients may be quite useful.

In conclusion, our CPFE patients showed poor survival compared to that of IPF patients. CPFE patients often develop AE, for which baseline serum KL-6 was a useful predictor. Finger clubbing and %FEV1 / % FVC more than 1.2 were independent prognostic predictors of mortality in patients with CPFE. A multicenter study of this new entity is warranted for further research.

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Figure Legends:

Figure 1; Flow diagram in CPFE patients

Figure 2; Survival curve in CPFE patients

Figure 3; CPFE patients with clubbing show poor survival compared with that of without clubbing

Figure 4; Ratio of %FEV1 and %FVC more than 1.2 show poor survival rather than that of less than 1.2 in CPFE patients

TABLE 1. Patient clinical characteristics in CPFE

	Survivors (n= 26)	Non-survivors (n= 67)	p-value

Age, year (mean)	73.19 ± 1.18 (57-84)	73.83 ± 7.07 (56-91)	0.5815
Male sex, %	85	81	0.6570
Pack-year	60 ± 22.0(5-110)	64 ± 31.4 (0-180)	0.5754
mMRC scale	2.6 ± 0.88 (1-4)	2.5 ± 0.93 (1-4)	0.5091
Dyspnea duration months	11.04 ± 5.73 (0-18)	13.07 ± 14.20 (0-96)	0.4821
Clubbing, %	12	55	< 0.0001
KL-6, IU/L	852 ± 278 (505-1200)	1174 ± 725 (201-4250)	0.0413
Systolic PAP, mmHg	28.53 ± 7.01	41.06 ± 11.57	< 0.0001
Baseline FEV_1,%	71.14 ± 8.72 (59.6-103.9)	70.88 ± 9.25 (31.4-106.3)	0.9128
Baseline FVC,%	68.52 ± 9.09 (57-99.7)	61.89 ± 9.48 (24.9-82.3)	0.0058
HOT , %	12	43	0.0035
Paraseptal emphysema, %	19	69	< 0.0001

Acute exacerbation, %	0	31	0.0007
%FEV_1 / %FVC >1.2, %	19	79	< 0.0001
Cancer, %	0	18	0.1068
Cardiovascular, %	27	40	0.2339
Ejection fraction. %	58.2 ± 3.90	56.9 ± 5.19	0.2337
Survival time , months	50.16 ± 17.79 （ 26 – 96 ）	25.68 ± 21.54 （1 – 98 ）	< 0.0001

Data are presented as mean± SD and mean %predicted ± SD

Definitions of abbreviations: IPF = Idiopathic Pulmonary Fibrosis; NSIP = Non Specific Interstitial Pneumonia; mMRC = modified Medical Research Council; FEV_1= forced expired volume in one second; FVC = forced vital capacity.

Table 2. Predictor of acute exacerbation in CPFE patients

	Odds Ratio	95% CI	p-value
Age	0.9691	0.8985-1.0453	0.417
mMRC scale	0.6681	0.3538-1.2616	0.214
Dyspnea duration	0.8967	0.8169-0.9844	0.022

Baseline KL-6	1.0016	1.0003-1.0027	0.009
CT pattern	0.7612	0.2247-2.5779	0.661

Definitions of abbreviations: CI= confidence interval, mMRC = modified Medical Research Council

Table 3. HRCT Imaging in CPFE patients

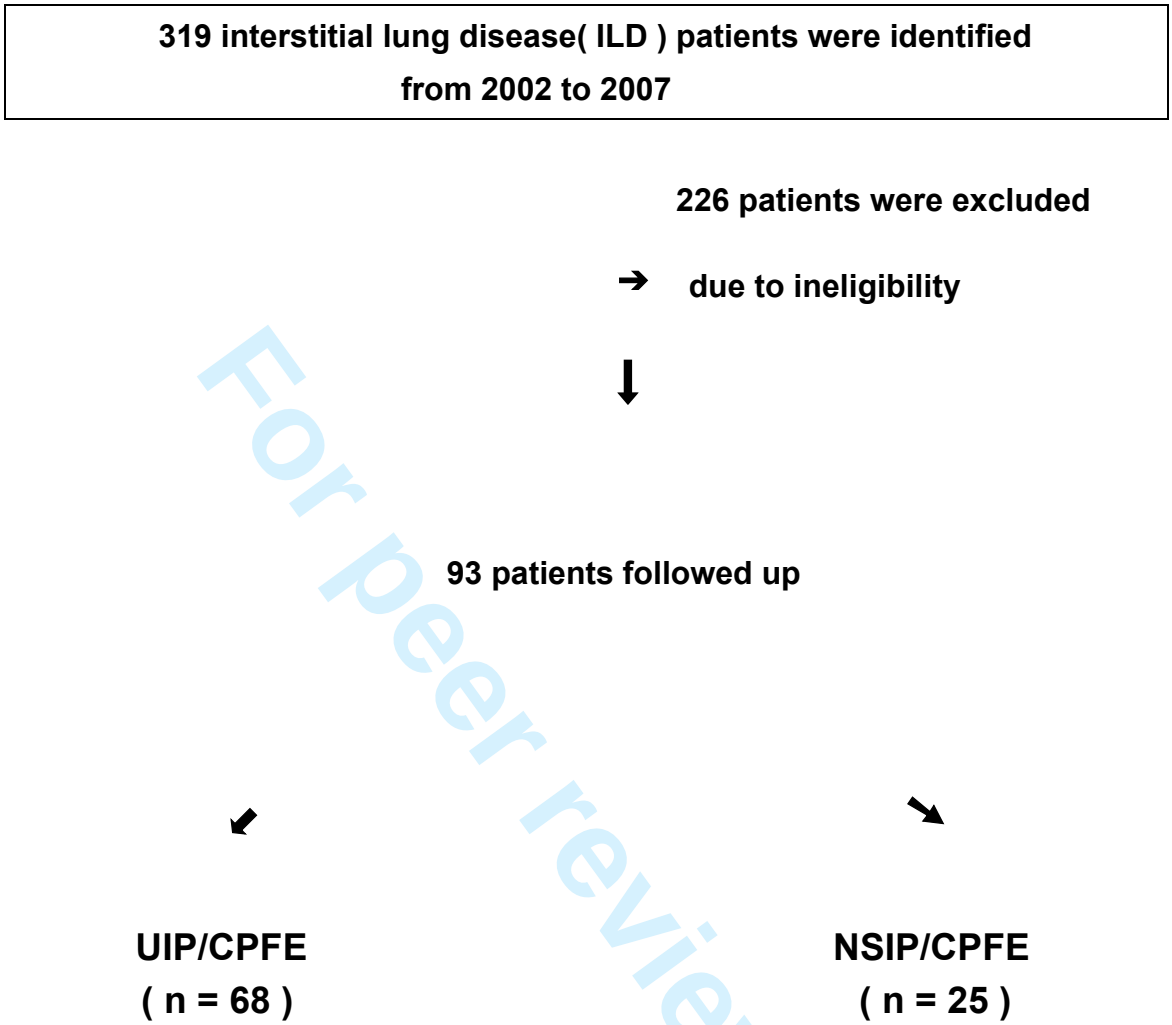
	UIP pattern (n=68)	NSIP Pattern (n= 25)	All (n= 93)
Emphysema pattern			
Paraseptal,%	57	48	55
Centrilobular,%	29	32	30
Panlobular,%	14	20	15
Fibrosis pattern			
Traction bronchiectasis, %	96	88	94
Reticulation, %	91	88	90
Honeycombing, %	100	0	73
Ground glass opacity , %	34	100	52
Consolidation, %	29	60	38

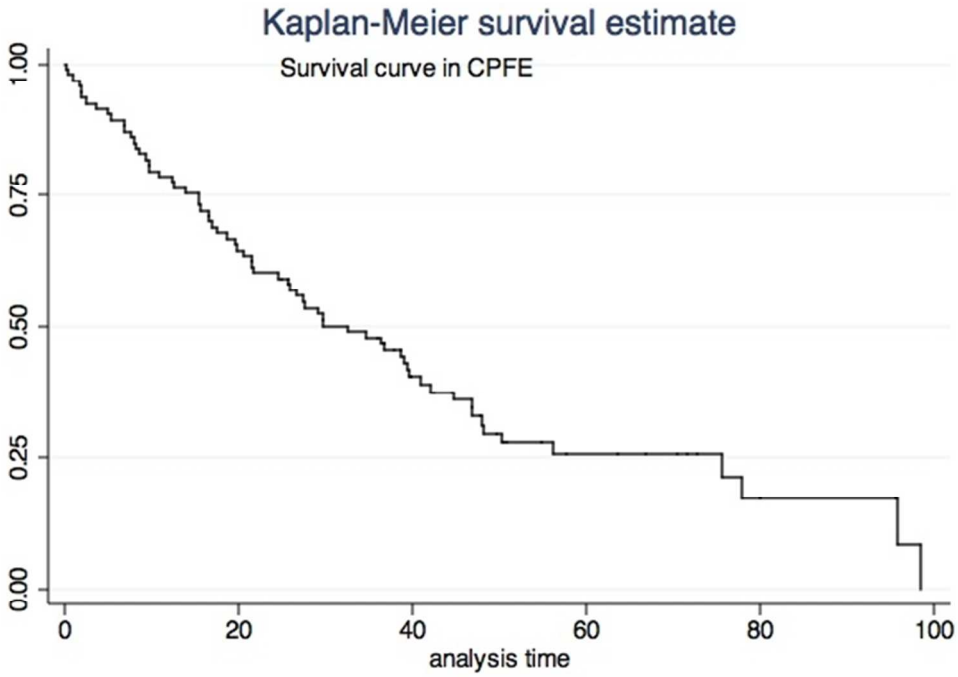
Definitions of abbreviations: HRCT = High resolution computed tomography ; IPF = Idiopathic pulmonary fibrosis ; NSIP = Non specific interstitial pneumonia.

Table 4. Results of the Cox proportional hazards regression analysis of mortality in CPFE patients

	Hazards ratio	95% CI	P-value
Finger clubbing	2.2620	1.1746-4.3560	0.015
%FEV1/%FVC (> 1.2)	1.9259	1.0057-3.6883	0.048

Definitions of abbreviations: CI = confidence interval ; FVC = forced vital capacity.





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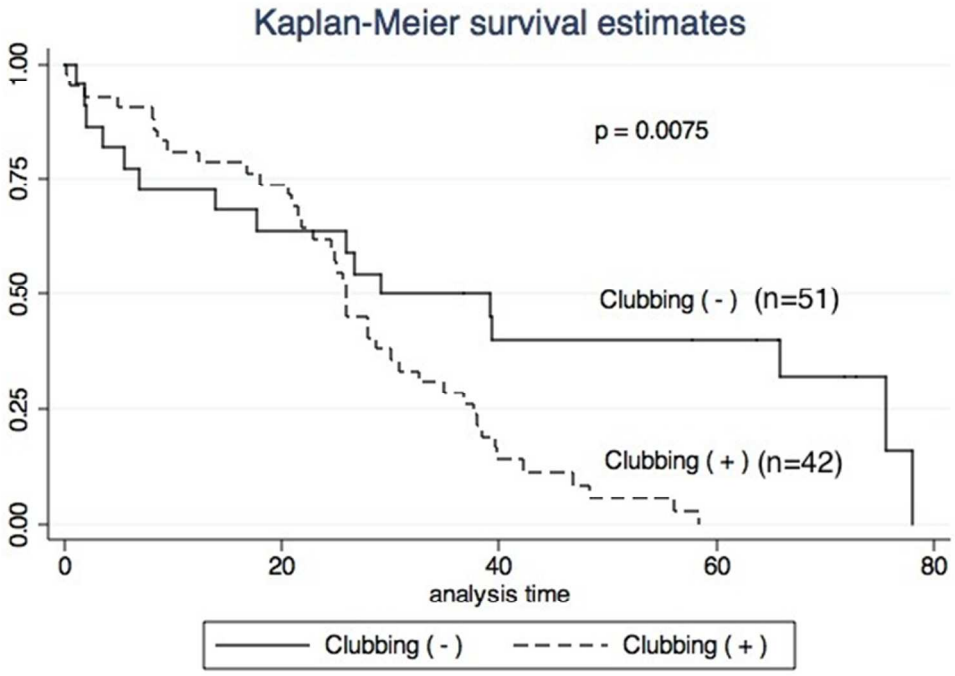

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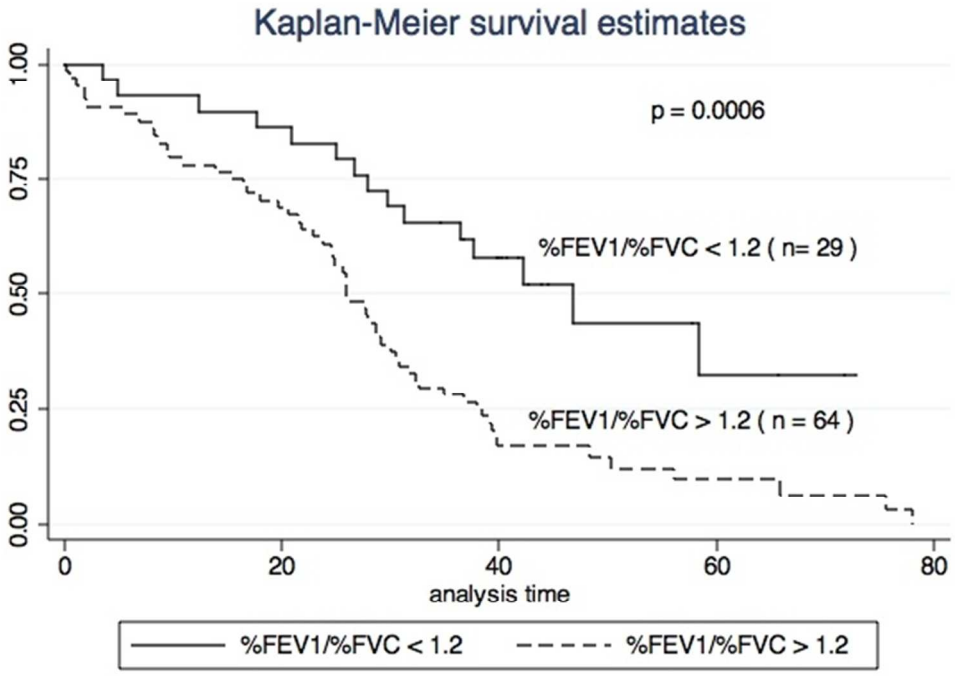

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A Cohort Study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema

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Subject Heading: Mortality predictors in CPFE

Article Focus: Combined pulmonary fibrosis and emphysema (CPFE) has recently been recognized as a new entity. Prognosis is often poor, and pulmonary hypertension is common. There is little information on clinical parameters and predictors of mortality.
What is the most useful clinical predictor of mortality in CPFE?
What is the most informative physiologic predictor of mortality in CPFE?
What is the most sensitive clinical predictor of acute exacerbation in CPFE?
The study aim was to investigate non-invasive predictors of mortality in CPFE.
Key Messages: From a clinical point of view, finger clubbing is useful predictor of mortality in CPFE. In addition, ratio of percent predicted forced expiratory volume in 1 second (%FEV_1) and percent predicted forced vital capacity (%FVC) more than 1.2% were independent predictors of mortality in patients with CPFE too. Prediction of prognosis of these patients by minimally invasive methods may be quite useful.
Strengths and Limitations: This study's strength was the definition of noninvasive, easily obtainable clinical and physiological measures of prognosis in CPFE. The major limitation of the study is the single-center retrospective design.

Abstract

Objectives: Our purpose was to assess the clinical data, predictors of mortality, acute exacerbation in CPFE patients.
Design: Single centre retrospective cohort study.
Setting: Teaching hospital in Japan.
Participants: We identified 93 CPFE patients with high-resolution computed tomographic (HRCT) through multidisciplinary discussion. Patients who had connective tissue disease (CTD),drug-associated ILD, and occupationally related ILD, such as asbestosis and silicosis were excluded.

Interventions: There were no interventions.

Methods: Medical records and HRCT scans from January 2002 through December 2007 were reviewed retrospectively at our hospital. Ninety-three patients had CPFE.

Results: The mean age of CPFE patients was 74 years. IPF and nonspecific interstitial pneumonia (NSIP) were observed as distinct HRCT patterns. Forty two patients showed finger clubbing. Mean serum Krebs von den Lungen-6 (KL-6) and percent predicted forced vital capacity (%FVC) were 1089 IU/L, 63.86% respectively. Twenty-two patients developed acute exacerbation during observation period. Baseline KL-6 was a strong predictor of acute exacerbation. (Odds Ratio = 1.0016, P = 0.009). Finger clubbing (Hazards Ratio = 2.2620, P = 0.015) and percent predicted forced expiratory volume in 1 second (%FEV_1) / % FVC more than 1.2 (Hazards Ratio = 1.9259, P = 0.048) were independent predictors of mortality in CPFE.

Conclusions: Baseline serum KL-6 was a useful predictor of acute exacerbation (cutoff = 1050, ROC: 0.7720), which occurred in 24% (22/93) of the CPFE patients. Finger clubbing and %FEV_1 / %FVC more than 1.2 were independent predictors of mortality.

Key words: mortality; acute exacerbation; finger clubbing; KL-6 ; %FEV_1/%FVC

There is no additional data available

Key words: mortality; acute exacerbation; finger clubbing; KL-6 ; %FEV_1/%FVC

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Combined pulmonary fibrosis and emphysema (CPFE) has been recognized as a unique entity that is characterized by upper lobe emphysema and lower lobe fibrosis (1). Emphysema is sometimes associated with idiopathic pulmonary fibrosis (IPF) and usually occurs with elevated lung volume." should be "Emphysema is sometimes recognized in the setting of idiopathic pulmonary fibrosis (IPF), (2-3) and patients with both emphysema and fibrosis (CPFE) usually have elevated

lung volumes compared to patients with IPF alone. In CPFE, lung volume is preserved in many patients, even in those at advanced stages, because supervening fibrosis offsets the effect of emphysema (3–5). CPFE patients also more often have pulmonary arterial hypertension (PAH) (6). PAH has been shown to be a significant prognostic indicator for both IPF (7,8) and chronic obstructive pulmonary disease (COPD) (9). In patients with lung cancer , CPFE is more prevalent than fibrosis (10). Recently, CPFE syndrome has been individualized, partly on the basis of distinct characteristics observed by high-resolution computed tomography (HRCT) of the chest (11).

There is very little information on predictors of mortality for CPFE (1,12). Patients with CPFE often have severe dyspnea and poor cardiopulmonary reserve (13,14), and many patients cannot tolerate invasive procedures such as video-assisted thoracic surgery (VATS).

Thus, the objective of the present study was to determine the predictors of acute exacerbation and mortality in CPFE patients using noninvasive methods.

Methods

Study Population and HRCT Assessment

We retrospectively investigated our medical records and high-resolution computed tomographic (HRCT) scans from Okinawa Chubu Hospital, Okinawa, Japan from January 1, 2002 through December 31, 2007. During this period we had 319 interstitial lung disease(ILD) patients Eligible patients were men and women aged 18 years or older with a proven diagnosis of IPF or nonspecific interstitial pneumonia (NSIP) according to the American Thoracic Society/ European Respiratory Society (ATS/ERS) statement (15). Among all ILD patients, we identified 93 CPFE patients through multidisciplinary discussion including our pulmonologists and radiologists. We excluded patients if; 1) they were without HRCT imaging, 2) had connective tissue disease (CTD), 3) had drug-associated ILD, and 4)

had occupationally related ILD, such as asbestosis and silicosis. Demographic and clinical data were obtained, including age, gender, smoking history, dyspnea duration, comorbidity, crackles,clubbing, Krebs von den Lungen-6 (KL-6) levels and Ultrasound Cardiography(UCG)findings. In terms of pulmonary arterial hypertension (PAH), we estimated with UCG .We also checked physiological data including forced expiratory volume in 1 second (FEV_1), $\%FEV_1$, forced vital capacity (FVC), and %FVC. We only included pulmonary function data determined within six months of the date of HRCT.

The HRCT scan imaging patterns were evaluated according to the ATS/ERS criteria (15). We diagnosed IPF patients using the new ATS/ERS and Japanese Respiratory Society /Latin America Thoracic Association criteria (16). Patients who met the following criteria, as described by Cottin et al. (1), were diagnosed as having CPFE: (1) the presence of emphysema on CT, defined as well-demarcated areas of decreased attenuation compared with contiguous normal lung, marginated by a very thin (<1 mm) wall or no wall, and/or multiple bullae (>1 cm) with upper-zone predominance, and (2) the presence of significant pulmonary fibrosis on CT, defined as reticular opacities with peripheral and basal predominance, with or without traction bronchiectasis that occurs with or without honeycombing. Regarding acute exacerbation, we defined by the following criteria (18):(1) sudden deterioration of dyspnea within 30 days (2) new bilateral infiltration on chest radiograph (3)pulmonary infection or other known causes were excluded by bronchoalveolar lavage(BAL). Survival time was defined from the date of HRCT to death or last observation date. The Ethics Committee of Okinawa Chubu Hospital approved this study protocol.

Statistical Methods

Clinical data are presented as means ± SDs or medians (range), depending on distribution. Group comparisons were made using unpaired t-tests, the Wilcoxon rank sum test, Chi-squared statistics, and Fisher's exact test, as

appropriate. Logistic regression analysis was performed to determine the relationship between clinical parameters and acute exacerbation. A Cox proportional hazards model analysis was performed to determine the relationships between clinical parameters, physiological indices, HRCT imaging patterns and survival. Clinical data analyses were performed using STATA software Version 11.0 (Stata Corp, College Station, TX, USA). Statistical significance was defined as a P value less than 0.05.

Results

Patient Characteristics, Acute Exacerbation (AE), and Clinical Parameters

The flow diagram in Figure 1 shows how the patients were identified. Ninety-three CPFE patients (76 men , 17 women) were identified between 2002 and 2007. The mean age was 73 years, and 82 % of the patients were males. The mean time from symptoms to diagnosis was 12.68 months (0–96 months). The mean follow-up period was 30.7 months (0–74.6 months). All patients had histories of smoking (mean: 62 pack-years). The mean modified Medical Research Council (mMRC) breathlessness score was 2.5. Bibasilar fine crackles were auscultated in all patients and fourty-two (45 %) had finger clubbing. The baseline percent predicted forced expiratory volume in 1 second (FEV_1) (FEV_1/average $\%FEV_1$ for similar age, sex and body composition) was 70.95%, and the baseline percent predicted forced vital capacity (FVC) was 63.86%. During observation period, sixty-seven patients (72 %) died. The clinical characteristics of both survivors and non-survivors are summarized in Table 1.

The mean partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were 63 mmHg and 43 mmHg, respectively. Thirty-two patients (34%) received home oxygen therapy and 36 (39%) had pulmonary arterial hypertension. The mean systolic pulmonary arterial pressure was 62 mmHg. CPFE patients frequently have been reported to have lung cancer, especially squamous cell carcinoma (10,17). However, in our cohort, only twelve (13 %) patients developed lung cancer.

Among the 93 patients, twenty-two (24%) developed AE, which met the ATS/ERS criteria (15). We performed univariate analysis to determine predictors of AE. Age, mMRC score, ctpattern, and baseline serum KL-6 were identified as possible predictors of AE. Logistic regression analysis was performed for these four factors, baseline serum KL-6 was found to be the strongest predictor of AE in the CPFE patients［Odds Ratio = 1.0016, P = 0.009］. (Table 2) Using receiver operator characteristic curve (ROC) analysis, the useful KL-6 threshold was determined to be 1050 (ROC: 0.7720).

HRCT Imaging and Predictors of Mortality

According to the ATS/ERS criteria (15,16), the patients were divided into those with UIP patterns and those with NSIP patterns. There were 68 patients in the IPF–pattern group and 25 patients in the NSIP–pattern group. The HRCT images also showed patterns indicating that 51 patients had para septal emphysema, 28 had centrilobular emphysema, and 14 had panlobular emphysema. Detailed results are presented in (Table 3).

The mean survival of CPFE patients was 30.7 months(0.10–75.63 months). (Figure 1). Patients with finger clubbing or increased ratio of $\%FEV_1$ to %FVC showed poor survival in CPFE patients (Figure 2) (Figure 3). Regarding ratio of $\%FEV_1$ to %FVC, we chose 1.2 which was most useful threshold for predictor of mortality with using ROC analysis(ROC: 0.7671). Initially, we performed univariate analysis with a cutoff value of 0.1, which showed that baseline KL-6, finger clubbing, PaO_2, and $\%FEV_1$ / % FVC > 1.2 were independent predictors of mortality. Cox proportional hazards regression analysis showed that finger clubbing (HR = 2.2620, P = 0.015) and ratio of $\%FEV_1$ to % FVC more than 1.2 (HR = 1.9259, P = 0.048) were the strongest independent predictors of mortality in CPFE patients at our hospital (Table 4).

Discussion

Previous studies have reported a high prevalence of PAH and lung cancer in CPFE patients (1,10). These comorbidities were associated with poor prognosis; the 1-year survival rate for CPFE patients with PAH was only 60% (6,11). Among these patients, high mean pulmonary arterial pressure, high pulmonary vascular resistance, high heart rate, and low diffusing capacity for carbon monoxide (DLco) were significantly associated with poor outcome. In one study, CPFE patients had a five fold higher mortality risk (adjusted HR: 5.10, 95%CI:1.75–14.9) in non-malignant situations (19). In the present study, only twelve of 93 patients had lung cancer in contrast to the number reported in a previous study (10). Our institution is a teaching and community hospital, and the patient population may be different from that of a university hospital.

The pulmonary function indices of the CPFE patients included in the present study were rather different from those in previous reports (1, 20). The CPFE patients in those studies had greater preserved lung volume despite reduced DLco, reduced transfer coefficient for carbon monoxide (Kco), and hypoxemia. Jankowich, et al. reported that CPFE altered physiology but had a mortality rate similar to that of IPF (21). In addition, Peng M, et al. reported similar physiology results for CPFE (22). In our study, the mean percent predicted FVC was 63.86% and that of FEV_1 was 70.95%, which showed more restrictive impairment compared with previous cases. This finding can be explained by the greater volume loss of the lower lung field due to severe fibrosis rather than by the offset effect of emphysema (23). This finding might also be because our cohort had less emphysema area compared with the previously reported cases. Another possibility is that the patients might have been in a different phase of CPFE. Recently, Rogliani, et al. reported the pathology of IPF and emphysema (24). They evaluated 17 biopsy-proven usual interstitial pneumonia (UIP) patients and found fibroblasts in areas of parenchymal destruction from emphysema/UIP-expressed matrix metalloproteinase (MMP)–2, MMP–9, MMP–7 and membrane type 1 (MT1)–MMP at significantly higher levels when compared with emphysema subjects. On

the basis of this result, similar to the findings of the study by Rogliani et al. cited above, interstitial fibroblast activation could be stimulated to a greater degree in the areas of lung destruction in CPFE compared with emphysema alone, as in exaggerated tissue remodeling. Therefore, some of the CPFE patients may have had more intense fibrosis, which contributed to reduced FVC.

In the analysis of the HRCT images, the patients were divided into two groups by UIP (usual interstitial pneumonia) pattern and NSIP pattern according to the ATS/ERS criteria (15,16). All of the UIP-pattern patients had honeycombing, and the NSIP-pattern patients more often had consolidation (60% vs. 29%) and ground-glass opacity (100% vs. 34%). These findings were very similar to those from a recent report on HRCT for NSIP (25). In addition, Sumikawa et al. reported that traction bronchiectasis and fibrosis scores were associated with poor prognosis in pathological UIP patients (26). In the present study, HRCT pattern was not an independent prognostic predictor. CPFE patients usually have more severe PAH, low cardiac index (6) and are disabled (27), which we observed in our cohort. Thus, most CPFE patients cannot tolerate invasive procedures such as VATS. Therefore, we cannot compare biopsy-proven UIP with CPFE equally.

Acute exacerbation (AE) is a relentlessly progressive status and is associated with poor outcome (28). Thus, we evaluated AE of CPFE. During the observation period (mean: 30.7 months), twenty-two patients (24 %) developed AE. The annual incidence of AE is 9.4%. This finding is similar to that reported in IPF recently (29). Kondoh, et al. reported that high modified MRC score, high body mass index (BMI), and decline in FVC at six months were significant independent risk factors for AE-IPF (30). KL-6 levels in ILD patients reflect the overall extent of interstitial lesions. Among the many clinical parameters, baseline serum KL-6 was the most powerful predictor of AE in our CPFE patients. ROC analysis showed that the useful threshold was 1050 (ROC = 0.7720).

Finally, we investigated the prognostic predictors of CPFE in our cohort. FVC has been reported robust powerful predictor of mortality in IPF patients (31). DLco often show variable value, so reproducibility is rather poor. In addition when FVC is reduced, DLco cannot be obtained with single breath method. Therefore, we chose %FEV_1 ,% FVC and ratio of these value as important indices out of pulmonary function parameters. Univariate analysis revealed that KL-6, finger clubbing, PaO_2, and ratio of %FEV_1 to % FVC were independent predictors. Regression analysis using a Cox proportional hazards model showed that finger clubbing and ratio of %FEV_1 to % FVC more than 1.2 were the strongest independent predictors of mortality in CPFE at our hospital. In CPFE patients,lung volume is usually preserved. Therefore, absolute value of FVC or %FVC itself has been reported to be not robust predictor of critical event. However, ratio of %FEV_1 to % FVC may be useful parameter in subgroup of CPFE patients. In terms of different cut-off value of this ratio, CPFE patients tend to have more mild restrictive impairment compared with that of IPF patients. Another interesting finding was that finger clubbing which is associated with poor survival in CPFE patients. Finger clubbing usually shows chronicity in ILD patients. However, it predicted clinical course in CPFE patients at our cohort. So, we insisist on the importance of initial careful evalution of physical findings in CPFE.

This time, we did not evaluate the treatment in CPFE patients. Currently, there is no consensus on treatment of CPFE with PAH (32,33). This is a vital topic for future study.

There were several limitations in our study. First, this was a single center, uncontrolled design, retrospective study, which means that it is possible that important data was not collected. Second, we did not measure the exact areas of emphysema and fibrosis. Therefore, our cohort may have been at a different stage compared with previous CPFE patients. Third, most of our patients could not undergo surgical biopsy because of disability and reduced lung function. Thus, we could not evaluate the

detailed pathology of our CPFE patients. Fourth, we did not evaluate serial pulmonary function. Recently, Du Bois et al. reported that percent predicted FVC and the 24 week change in FVC were useful predictors of mortality in IPF (34). Therefore, it might be helpful to measure serial FVC as a prognostic predictor in CPFE. Lastly, in keeping with previous reports, our study patients were all heavy smokers. Therefore, we could not distinguish CPFE from smoking-related NSIP (35). However, even considering these limitations, prediction of prognosis using minimally invasive methods in these patients may be quite useful.

In conclusion, CPFE patients showed poor survival in our cohort. CPFE patients often develop AE, for which baseline serum KL-6 was a useful predictor. Finger clubbing and %FEV1 / % FVC more than 1.2 were independent prognostic predictors of mortality in patients with CPFE. A multicenter study of this new entity is warranted for further research.

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Figure Legends:

Figure 1; Flow diagram in CPFE patients

Figure 2; Survival curve in CPFE patients

Figure 3; CPFE patients with clubbing show poor survival compared with that of without clubbing

Figure 4; Ratio of %FEV$_1$ and %FVC more than 1.2 show poor survival rather than that of less than 1.2 in CPFE patients

TABLE 1. Patient clinical characteristics in CPFE

	Survivors (n= 26)	Non-survivors (n= 67)	p-value
Age, year (mean)	73.19 ± 1.18 (57-84)	73.83 ± 7.07 (56-91)	0.5815
Male sex, %	85	81	0.6570
Pack-year	60 ± 22.0(5-110)	64 ± 31.4 (0-180)	0.5754
mMRC scale	2.6 ± 0.88 (1-4)	2.5 ± 0.93 (1-4)	0.5091
Dyspnea duration months	11.04 ± 5.73 (0-18)	13.07 ± 14.20 (0-96)	0.4821
Clubbing, %	12	55	< 0.0001
KL-6, IU/L	852 ± 278 (505-1200)	1174 ± 725 (201-4250)	0.0413

Systolic PAP, mmHg	45	75	< 0.0001
Baseline FEV_1,%	71.14 ± 8.72 (59.6-103.9)	70.88 ± 9.25 (31.4-106.3)	0.9128
Baseline FVC,%	68.52 ± 9.09 (57-99.7)	61.89 ± 9.48 (24.9-82.3)	0.0058
HOT , %	12	43	0.0035
Paraseptal emphysema, %	19	69	< 0.0001
Acute exacerbation, n(%)	0 (0)	22 (32)	0.0007
%FEV_1 / %FVC >1.2, %	19	79	< 0.0001
Cancer, %	0	18	0.1068
Cardiovascular, %	27	40	0.2339
Ejection fraction. %	58.2 ± 3.90	56.9 ± 5.19	0.2337
Survival time , months	50.16 ± 17.79 （ 26 – 96 ）	25.68 ± 21.54 （1 – 98 ）	< 0.0001

Data are presented as mean± SD and mean %predicted ± SD

Definitions of abbreviations: IPF = Idiopathic Pulmonary Fibrosis; NSIP = Non Specific Interstitial Pneumonia; mMRC = modified Medical Research Council; FEV_1= forced expired volume in one second; FVC = forced vital capacity; HOT = Home Oxygen Therapy

Table 2. Predictor of acute exacerbation in CPFE patients

	Odds Ratio	95% CI	p-value
Age	0.9691	0.8985-1.0453	0.417
mMRC scale	0.6681	0.3538-1.2616	0.214
Dyspnea duration	0.8967	0.8169-0.9844	0.022
Baseline KL-6	1.0016	1.0003-1.0027	0.009
CT pattern	0.7612	0.2247-2.5779	0.661

Definitions of abbreviations: CI= confidence interval, mMRC = modified Medical Research Council

Table 3. HRCT Imaging in CPFE patients

	UIP pattern (n=68)	NSIP Pattern (n= 25)	All (n= 93)
Emphysema pattern			
Paraseptal,%	57	48	55

Centrilobular,%	29	32	30
Panlobular,%	14	20	15
Fibrosis pattern			
Traction bronchiectasis, %	96	88	94
Reticulation, %	91	88	90
Honeycombing, %	100	0	73
Ground glass opacity , %	34	100	52
Consolidation, %	29	60	38

Definitions of abbreviations: HRCT = High resolution computed tomography ; IPF = Idiopathic pulmonary fibrosis ; NSIP = Non specific interstitial pneumonia.

Table 4. Results of the Cox proportional hazards regression analysis of mortality in CPFE patients

	Hazards ratio	95% CI	P-value
Finger clubbing	2.2620	1.1746-4.3560	0.015
%FEV1/%FVC (> 1.2)	1.9259	1.0057-3.6883	0.048

Definitions of abbreviations: CI = confidence interval ; FVC = forced vital capacity.

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Y Shimaoka, H Fukuyama, K Yoshida, M Tanaka, S Yamashiro: Study design, and acquisition and interpretation of data.

Subject Heading: Mortality predictors in CPFE

Article Focus: Combined pulmonary fibrosis and emphysema (CPFE) has recently been recognized as a new entity. Prognosis is often poor, and pulmonary hypertension is common. There is little information on clinical parameters and predictors of mortality.

What is the most useful clinical predictor of mortality in CPFE?

What is the most informative physiologic predictor of mortality in CPFE?

What is the most sensitive clinical predictor of acute exacerbation in CPFE?

The study aim was to investigate non-invasive predictors of mortality in CPFE.

Key Messages: From a clinical point of view, finger clubbing is useful predictor of mortality in CPFE. In addition, ratio of percent predicted forced expiratory volume in 1 second (%FEV_1) and percent predicted forced vital capacity (%FVC) more than 1.2% were independent predictors of mortality in patients with CPFE too. Prediction of prognosis of these patients by minimally invasive methods may be quite useful.

Strengths and Limitations: This study's strength was the definition of noninvasive, easily obtainable clinical and physiological measures of prognosis in CPFE. The major limitation of the study is the single-center retrospective design.

Abstract

Objectives: Our purpose was to assess the clinical data, predictors of mortality, acute exacerbation in CPFE patients.

Design: Single centre retrospective cohort study.

Setting: Teaching hospital in Japan.

Participants: We identified 93 CPFE patients with high-resolution computed tomographic (HRCT) through multidisciplinary discussion. Patients who had connective tissue disease (CTD),drug-associated ILD, and occupationally related ILD, such as asbestosis and silicosis were excluded.

Interventions: There were no interventions.

Methods: Medical records and HRCT scans from January 2002 through December 2007 were reviewed retrospectively at our hospital. Ninety-three patients had CPFE.

Results: The mean age of CPFE patients was 74 years. IPF and nonspecific

interstitial pneumonia (NSIP) were observed as distinct HRCT patterns. Forty two patients showed finger clubbing. Mean serum Krebs von den Lungen-6 (KL-6) and percent predicted forced vital capacity (%FVC) were 1089 IU/L, 63.86% respectively. Twenty-two patients developed acute exacerbation during observation period. Baseline KL-6 was a strong predictor of acute exacerbation. (Odds Ratio = 1.0016, P = 0.009). Finger clubbing (Hazards Ratio = 2.2620, P = 0.015) and percent predicted forced expiratory volume in 1 second (%FEV_1) / % FVC more than 1.2 (Hazards Ratio = 1.9259, P = 0.048) were independent predictors of mortality in CPFE. Conclusions: Baseline serum KL-6 was a useful predictor of acute exacerbation (cutoff = 1050, ROC: 0.7720), which occurred in 24% (22/93) of the CPFE patients. Finger clubbing and %FEV_1 / %FVC more than 1.2 were independent predictors of mortality.

Key words: mortality; acute exacerbation; finger clubbing; KL-6 ; %FEV_1/%FVC

There is no additional data available

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Total Abstract Count: 243

Combined pulmonary fibrosis and emphysema (CPFE) has been recognized as a unique entity that is characterized by upper lobe emphysema and lower lobe fibrosis (1). Emphysema is sometimes associated with idiopathic pulmonary fibrosis (IPF) and usually occurs with elevated lung volume." should be "Emphysema is sometimes recognized in the setting of idiopathic pulmonary fibrosis (IPF), (2-3) and patients with both emphysema and fibrosis (CPFE) usually have elevated lung volumes compared to patients with IPF alone. In CPFE, lung volume is preserved in many patients, even in those at advanced stages, because supervening fibrosis offsets the effect of emphysema (3–5). CPFE patients also more often have pulmonary arterial hypertension (PAH) (6). PAH has been shown to be a significant prognostic indicator for both IPF (7,8) and

chronic obstructive pulmonary disease (COPD) (9). In patients with lung cancer , CPFE is more prevalent than fibrosis (10). Recently, CPFE syndrome has been individualized, partly on the basis of distinct characteristics observed by high-resolution computed tomography (HRCT) of the chest (11).

There is very little information on predictors of mortality for CPFE (1,12). Patients with CPFE often have severe dyspnea and poor cardiopulmonary reserve (13,14), and many patients cannot tolerate invasive procedures such as video-assisted thoracic surgery (VATS).

Thus, the objective of the present study was to determine the predictors of acute exacerbation and mortality in CPFE patients using noninvasive methods.

Methods

Study Population and HRCT Assessment

We retrospectively investigated our medical records and high-resolution computed tomographic (HRCT) scans from Okinawa Chubu Hospital, Okinawa, Japan from January 1, 2002 through December 31, 2007. During this period we had 319 interstitial lung disease(ILD) patients Eligible patients were men and women aged 18 years or older with a proven diagnosis of IPF or nonspecific interstitial pneumonia (NSIP) according to the American Thoracic Society/ European Respiratory Society (ATS/ERS) statement (15). Among all ILD patients, we identified 93 CPFE patients through multidisciplinary discussion including our pulmonologists and radiologists. We excluded patients if; 1) they were without HRCT imaging, 2) had connective tissue disease (CTD), 3) had drug-associated ILD, and 4) had occupationally related ILD, such as asbestosis and silicosis. Demographic and clinical data were obtained, including age, gender, smoking history, dyspnea duration, comorbidity, crackles,clubbing, Krebs von den Lungen-6 (KL-6) levels and Ultrasound Cardiography(UCG)findings. In terms of pulmonary arterial hypertension

(PAH), we estimated with UCG .We also checked physiological data including forced expiratory volume in 1 second (FEV_1), $\%FEV_1$, forced vital capacity (FVC), and %FVC. We only included pulmonary function data determined within six months of the date of HRCT.

The HRCT scan imaging patterns were evaluated according to the ATS/ERS criteria (15). We diagnosed IPF patients using the new ATS/ERS and Japanese Respiratory Society /Latin America Thoracic Association criteria (16). Patients who met the following criteria, as described by Cottin et al. (1), were diagnosed as having CPFE: (1) the presence of emphysema on CT, defined as well-demarcated areas of decreased attenuation compared with contiguous normal lung, marginated by a very thin (<1 mm) wall or no wall, and/or multiple bullae (>1 cm) with upper-zone predominance, and (2) the presence of significant pulmonary fibrosis on CT, defined as reticular opacities with peripheral and basal predominance, with or without traction bronchiectasis that occurs with or without honeycombing. Regarding acute exacerbation, we defined by the following criteria (18):(1) sudden deterioration of dyspnea within 30 days (2) new bilateral infiltration on chest radiograph (3)pulmonary infection or other known causes were excluded by bronchoalveolar lavage(BAL). Survival time was defined from the date of HRCT to death or last observation date. The Ethics Committee of Okinawa Chubu Hospital approved this study protocol.

Statistical Methods

Clinical data are presented as means ± SDs or medians (range), depending on distribution. Group comparisons were made using unpaired t-tests, the Wilcoxon rank sum test, Chi-squared statistics, and Fisher's exact test, as appropriate. Logistic regression analysis was performed to determine the relationship between clinical parameters and acute exacerbation. A Cox proportional hazards model analysis was performed to determine the relationships between clinical parameters, physiological indices, HRCT imaging patterns and survival. Clinical data analyses were performed

using STATA software Version 11.0 (Stata Corp, College Station, TX, USA). Statistical significance was defined as a P value less than 0.05.

Results

Patient Characteristics, Acute Exacerbation (AE), and Clinical Parameters

The flow diagram in Figure 1 shows how the patients were identified. Ninety-three CPFE patients (76 men , 17 women) were identified between 2002 and 2007. The mean age was 73 years, and 82 % of the patients were males. The mean time from symptoms to diagnosis was 12.68 months (0–96 months). The mean follow-up period was 30.7 months (0–74.6 months). All patients had histories of smoking (mean: 62 pack-years). The mean modified Medical Research Council (mMRC) breathlessness score was 2.5. Bibasilar fine crackles were auscultated in all patients and fourty-two (45 %) had finger clubbing. The baseline percent predicted forced expiratory volume in 1 second (FEV_1) (FEV_1/average $\%FEV_1$ for similar age, sex and body composition) was 70.95%, and the baseline percent predicted forced vital capacity (FVC) was 63.86%. During observation period, sixty-seven patients (72 %) died. The clinical characteristics of both survivors and non-survivors are summarized in Table 1.

The mean partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were 63 mmHg and 43 mmHg, respectively. Thirty-two patients (34%) received home oxygen therapy and 36 (39%) had pulmonary arterial hypertension. The mean systolic pulmonary arterial pressure was 62 mmHg. CPFE patients frequently have been reported to have lung cancer, especially squamous cell carcinoma (10,17). However, in our cohort, only twelve (13 %) patients developed lung cancer.

Among the 93 patients, twenty-two (24%) developed AE, which met the ATS/ERS criteria (15). We performed univariate analysis to determine predictors of AE. Age, mMRC score, ctpattern, and baseline serum KL-6 were identified as possible predictors of AE. Logistic regression analysis

was performed for these four factors, baseline serum KL-6 was found to be the strongest predictor of AE in the CPFE patients［Odds Ratio = 1.0016, P = 0.009］. (Table 2) Using receiver operator characteristic curve (ROC) analysis, the useful KL-6 threshold was determined to be 1050 (ROC: 0.7720).

HRCT Imaging and Predictors of Mortality

According to the ATS/ERS criteria (15,16), the patients were divided into those with UIP patterns and those with NSIP patterns. There were 68 patients in the IPF–pattern group and 25 patients in the NSIP–pattern group. The HRCT images also showed patterns indicating that 51 patients had para septal emphysema, 28 had centrilobular emphysema, and 14 had panlobular emphysema. Detailed results are presented in (Table 3).

The mean survival of CPFE patients was 30.7 months(0.10–75.63 months). (Figure 1). Patients with finger clubbing or increased ratio of $\%FEV_1$ to %FVC showed poor survival in CPFE patients (Figure 2) (Figure 3). Regarding ratio of $\%FEV_1$ to %FVC, we chose 1.2 which was most useful threshold for predictor of mortality with using ROC analysis(ROC: 0.7671). Initially, we performed univariate analysis with a cutoff value of 0.1, which showed that baseline KL-6, finger clubbing, PaO_2, and $\%FEV_1$ / % FVC > 1.2 were independent predictors of mortality. Cox proportional hazards regression analysis showed that finger clubbing (HR = 2.2620, P = 0.015) and ratio of $\%FEV_1$ to % FVC more than 1.2 (HR = 1.9259, P = 0.048) were the strongest independent predictors of mortality in CPFE patients at our hospital (Table 4).

Discussion

Previous studies have reported a high prevalence of PAH and lung cancer in CPFE patients (1,10). These comorbidities were associated with poor prognosis; the 1-year survival rate for CPFE patients with PAH was only 60% (6,11). Among these patients, high mean pulmonary arterial pressure,

high pulmonary vascular resistance, high heart rate, and low diffusing capacity for carbon monoxide (DLco) were significantly associated with poor outcome. In one study, CPFE patients had a five fold higher mortality risk (adjusted HR: 5.10, 95%CI:1.75–14.9) in non-malignant situations (19). In the present study, only twelve of 93 patients had lung cancer in contrast to the number reported in a previous study (10). Our institution is a teaching and community hospital, and the patient population may be different from that of a university hospital.

The pulmonary function indices of the CPFE patients included in the present study were rather different from those in previous reports (1, 20). The CPFE patients in those studies had greater preserved lung volume despite reduced DLco, reduced transfer coefficient for carbon monoxide (Kco), and hypoxemia. Jankowich, et al. reported that CPFE altered physiology but had a mortality rate similar to that of IPF (21). In addition, Peng M, et al. reported similar physiology results for CPFE (22). In our study, the mean percent predicted FVC was 63.86% and that of FEV_1 was 70.95%, which showed more restrictive impairment compared with previous cases. This finding can be explained by the greater volume loss of the lower lung field due to severe fibrosis rather than by the offset effect of emphysema (23). This finding might also be because our cohort had less emphysema area compared with the previously reported cases. Another possibility is that the patients might have been in a different phase of CPFE. Recently, Rogliani, et al. reported the pathology of IPF and emphysema (24). They evaluated 17 biopsy-proven usual interstitial pneumonia (UIP) patients and found fibroblasts in areas of parenchymal destruction from emphysema/UIP-expressed matrix metalloproteinase (MMP)–2, MMP–9, MMP–7 and membrane type 1 (MT1)–MMP at significantly higher levels when compared with emphysema subjects. On the basis of this result, similar to the findings of the study by Rogliani et al. cited above, interstitial fibroblast activation could be stimulated to a greater degree in the areas of lung destruction in CPFE compared with emphysema alone, as in exaggerated tissue remodeling. Therefore, some

of the CPFE patients may have had more intense fibrosis, which contributed to reduced FVC.

In the analysis of the HRCT images, the patients were divided into two groups by UIP (usual interstitial pneumonia) pattern and NSIP pattern according to the ATS/ERS criteria (15,16). All of the UIP-pattern patients had honeycombing, and the NSIP-pattern patients more often had consolidation (60% vs. 29%) and ground-glass opacity (100% vs. 34%). These findings were very similar to those from a recent report on HRCT for NSIP (25). In addition, Sumikawa et al. reported that traction bronchiectasis and fibrosis scores were associated with poor prognosis in pathological UIP patients (26). In the present study, HRCT pattern was not an independent prognostic predictor. CPFE patients usually have more severe PAH, low cardiac index (6) and are disabled (27), which we observed in our cohort. Thus, most CPFE patients cannot tolerate invasive procedures such as VATS. Therefore, we cannot compare biopsy-proven UIP with CPFE equally.

Acute exacerbation (AE) is a relentlessly progressive status and is associated with poor outcome (28). Thus, we evaluated AE of CPFE. During the observation period (mean: 30.7 months), twenty-two patients (24 %) developed AE. The annual incidence of AE is 9.4%. This finding is similar to that reported in IPF recently (29). Kondoh, et al. reported that high modified MRC score, high body mass index (BMI), and decline in FVC at six months were significant independent risk factors for AE-IPF (30). KL-6 levels in ILD patients reflect the overall extent of interstitial lesions. Among the many clinical parameters, baseline serum KL-6 was the most powerful predictor of AE in our CPFE patients. ROC analysis showed that the useful threshold was 1050 (ROC = 0.7720).

Finally, we investigated the prognostic predictors of CPFE in our cohort. FVC has been reported robust powerful predictor of mortality in IPF patients (31). DLco often show variable value, so reproducibility is rather

poor. In addition when FVC is reduced, DLco cannot be obtained with single breath method. Therefore, we chose %FEV_1 ,% FVC and ratio of these value as important indices out of pulmonary function parameters. Univariate analysis revealed that KL-6, finger clubbing, PaO_2, and ratio of %FEV_1 to % FVC were independent predictors. Regression analysis using a Cox proportional hazards model showed that finger clubbing and ratio of %FEV_1 to % FVC more than 1.2 were the strongest independent predictors of mortality in CPFE at our hospital. In CPFE patients,lung volume is usually preserved. Therefore, absolute value of FVC or %FVC itself has been reported to be not robust predictor of critical event. However, ratio of %FEV_1 to % FVC may be useful parameter in subgroup of CPFE patients. In terms of different cut-off value of this ratio, CPFE patients tend to have more mild restrictive impairment compared with that of IPF patients. Another interesting finding was that finger clubbing which is associated with poor survival in CPFE patients. Finger clubbing usually shows chronicity in ILD patients. However, it predicted clinical course in CPFE patients at our cohort. So, we insisist on the importance of initial careful evalution of physical findings in CPFE.

This time, we did not evaluate the treatment in CPFE patients. Currently, there is no consensus on treatment of CPFE with PAH (32,33). This is a vital topic for future study.

There were several limitations in our study. First, this was a single center, uncontrolled design, retrospective study, which means that it is possible that important data was not collected. Second, we did not measure the exact areas of emphysema and fibrosis. Therefore, our cohort may have been at a different stage compared with previous CPFE patients. Third, most of our patients could not undergo surgical biopsy because of disability and reduced lung function. Thus, we could not evaluate the detailed pathology of our CPFE patients. Fourth, we did not evaluate serial pulmonary function. Recently, Du Bois et al. reported that percent predicted FVC and the 24 week change in FVC were useful predictors of

mortality in IPF (34). Therefore, it might be helpful to measure serial FVC as a prognostic predictor in CPFE. Lastly, in keeping with previous reports, our study patients were all heavy smokers. Therefore, we could not distinguish CPFE from smoking-related NSIP (35). However, even considering these limitations, prediction of prognosis using minimally invasive methods in these patients may be quite useful.

In conclusion, CPFE patients showed poor survival in our cohort. CPFE patients often develop AE, for which baseline serum KL-6 was a useful predictor. Finger clubbing and %FEV1 / % FVC more than 1.2 were independent prognostic predictors of mortality in patients with CPFE. A multicenter study of this new entity is warranted for further research.

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Figure Legends:

Figure 1; Flow diagram in CPFE patients

Figure 2; Survival curve in CPFE patients

Figure 3; CPFE patients with clubbing show poor survival compared with that of without clubbing

Figure 4; Ratio of %FEV1 and %FVC more than 1.2 show poor survival rather than that of less than 1.2 in CPFE patients

TABLE 1. Patient clinical characteristics in CPFE

	Survivors (n= 26)	Non-survivors (n= 67)	p-value
Age, year (mean)	73.19 ± 1.18 (57-84)	73.83 ± 7.07 (56-91)	0.5815
Male sex, %	85	81	0.6570
Pack-year	60 ± 22.0(5-110)	64 ± 31.4 (0-180)	0.5754
mMRC scale	2.6 ± 0.88 (1-4)	2.5 ± 0.93 (1-4)	0.5091
Dyspnea duration months	11.04 ± 5.73 (0-18)	13.07 ± 14.20 (0-96)	0.4821
Clubbing, %	12	55	< 0.0001
KL-6, IU/L	852 ± 278 (505-1200)	1174 ± 725 (201-4250)	0.0413
Systolic PAP, mmHg	45	75	< 0.0001

Baseline FEV_1,%	71.14 ± 8.72 (59.6-103.9)	70.88 ± 9.25 (31.4-106.3)	0.9128
Baseline FVC,%	68.52 ± 9.09 (57-99.7)	61.89 ± 9.48 (24.9-82.3)	0.0058
HOT , %	12	43	0.0035
Paraseptal emphysema, %	19	69	< 0.0001
Acute exacerbation, n(%)	0 (0)	22 (32)	0.0007
%FEV_1 / %FVC >1.2, %	19	79	< 0.0001
Cancer, %	0	18	0.1068
Cardiovascular, %	27	40	0.2339
Ejection fraction. %	58.2 ± 3.90	56.9 ± 5.19	0.2337
Survival time , months	50.16 ± 17.79 (26 – 96)	25.68 ± 21.54 (1 – 98)	< 0.0001

Data are presented as mean± SD and mean %predicted ± SD

Definitions of abbreviations: IPF = Idiopathic Pulmonary Fibrosis; NSIP = Non Specific Interstitial Pneumonia; mMRC = modified Medical Research Council; FEV_1= forced expired volume in one second; FVC = forced vital capacity; HOT = Home Oxygen Therapy

Table 2. Predictor of acute exacerbation in CPFE patients

	Odds Ratio	95% CI	p-value
Age	0.9691	0.8985-1.0453	0.417
mMRC scale	0.6681	0.3538-1.2616	0.214
Dyspnea duration	0.8967	0.8169-0.9844	0.022
Baseline KL-6	1.0016	1.0003-1.0027	0.009
CT pattern	0.7612	0.2247-2.5779	0.661

Definitions of abbreviations: CI= confidence interval, mMRC = modified Medical Research Council

Table 3. HRCT Imaging in CPFE patients

	UIP pattern (n=68)	NSIP Pattern (n= 25)	All (n= 93)
Emphysema pattern			
Paraseptal,%	57	48	55
Centrilobular,%	29	32	30
Panlobular,%	14	20	15
Fibrosis pattern			

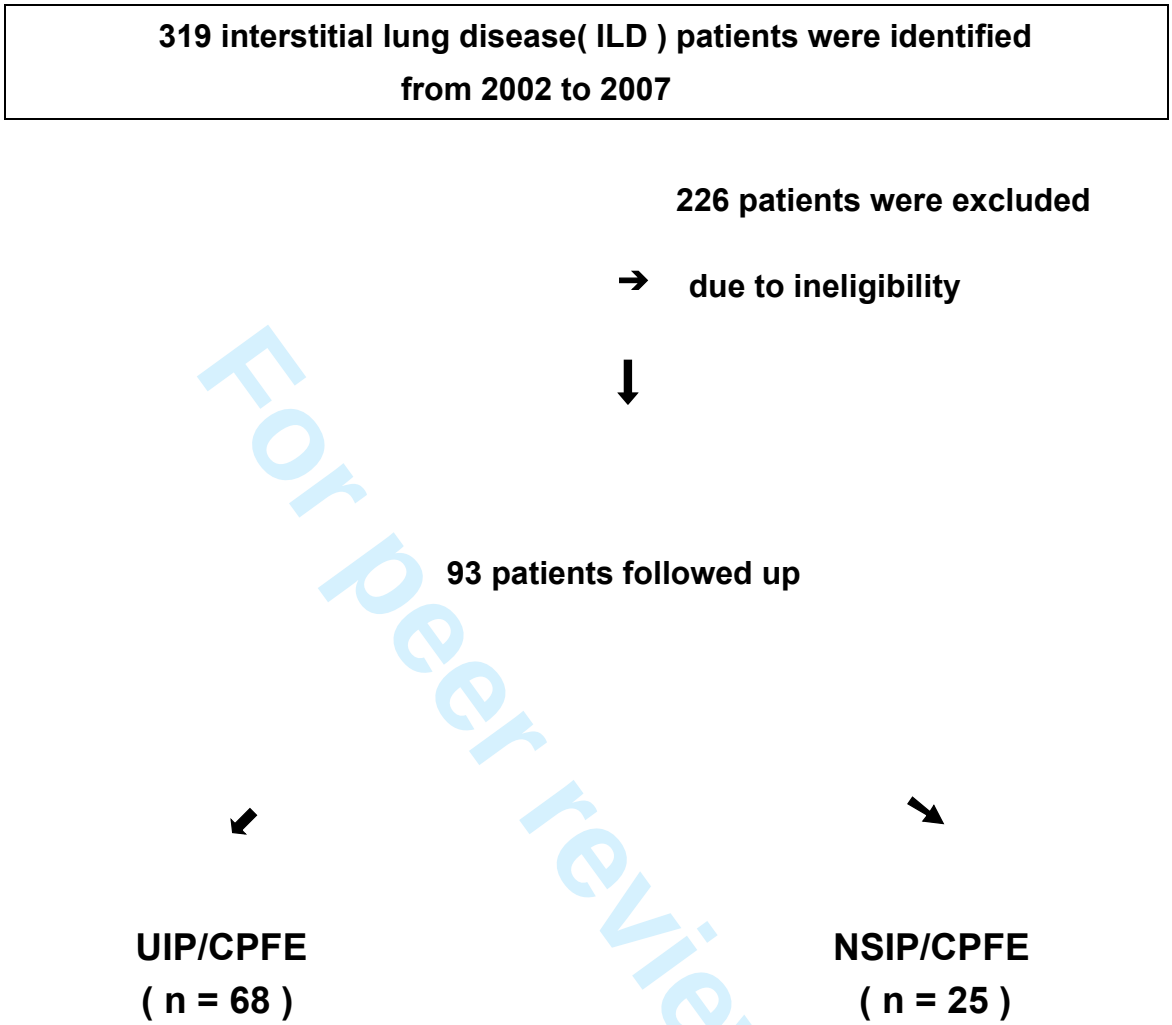
Traction bronchiectasis, %	96	88	94
Reticulation, %	91	88	90
Honeycombing, %	100	0	73
Ground glass opacity , %	34	100	52
Consolidation, %	29	60	38

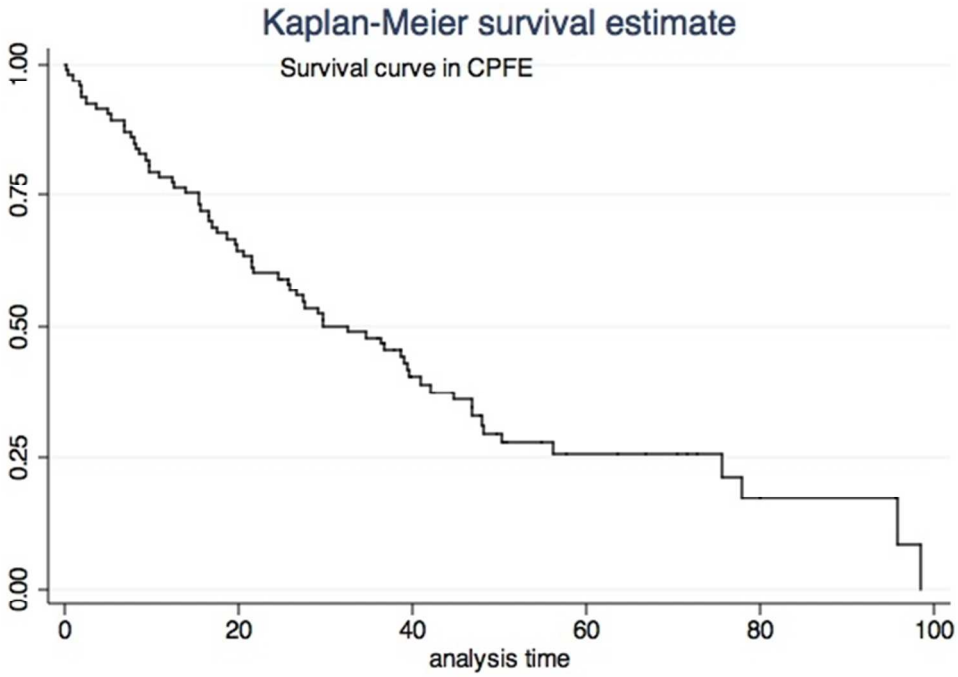
Definitions of abbreviations: HRCT = High resolution computed tomography ; IPF = Idiopathic pulmonary fibrosis ; NSIP = Non specific interstitial pneumonia.

Table 4. Results of the Cox proportional hazards regression analysis of mortality in CPFE patients

	Hazards ratio	95% CI	P-value
Finger clubbing	2.2620	1.1746-4.3560	0.015
%FEV1/%FVC (> 1.2)	1.9259	1.0057-3.6883	0.048

Definitions of abbreviations: CI = confidence interval ; FVC = forced vital capacity.





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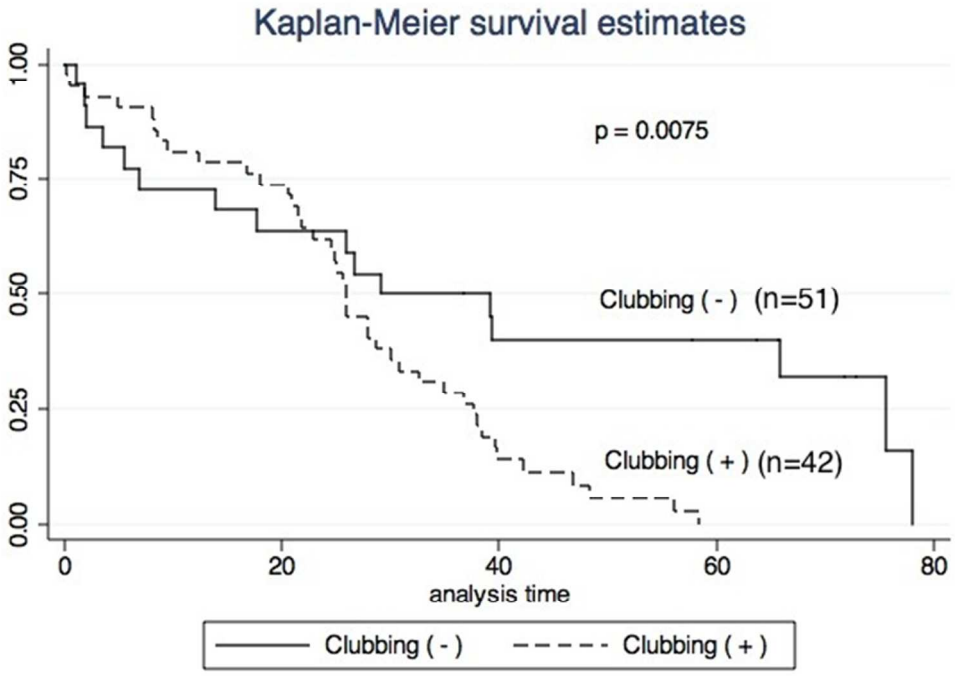

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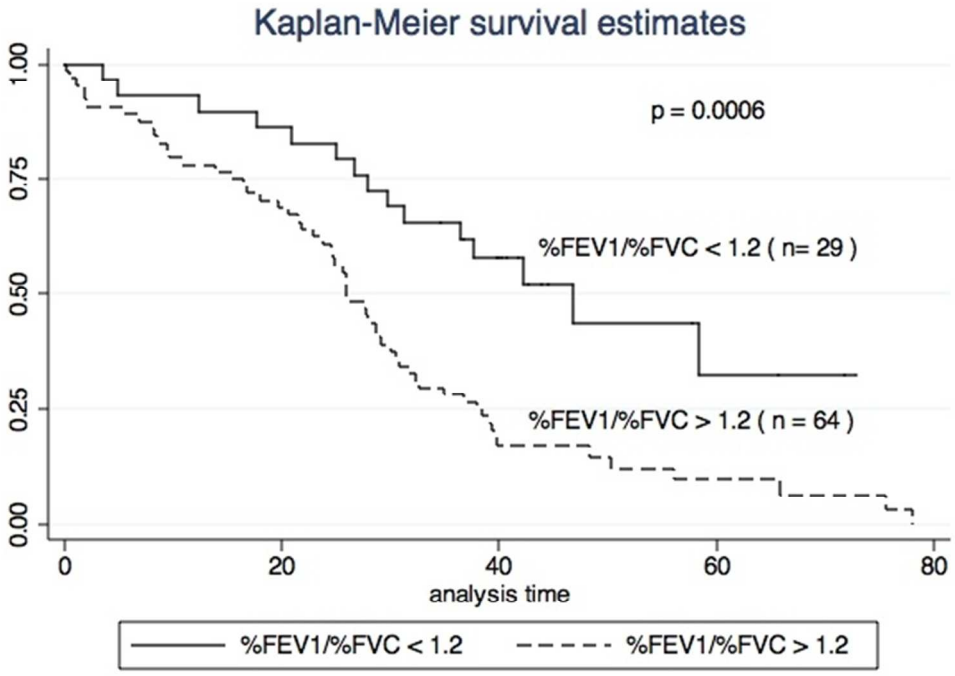

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