



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

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6 **Mortality predictors and characteristics of patients with combined**
7 **pulmonary fibrosis and emphysema**
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47 **Author Contributions:**
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49 **T Kishaba, H Tamaki: Study concept and design, acquisition and**
50 **interpretation of data, and drafting and finalization of the manuscript.**
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54 **Y Shimaoka, H Fukuyama, K Yoshida, M Tanaka, S Yamashiro: Study**
55 **design, and acquisition and interpretation of data.**
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8 **Subject Heading: Mortality predictors in CPFE**
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11 **Article Focus:** Combined pulmonary fibrosis and emphysema (CPFE) has
12 recently been recognized as a new entity. Prognosis is often poor, and
13 pulmonary hypertension is common. There is little information on clinical
14 parameters and predictors of mortality.
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17 **What is the most useful clinical predictor of mortality in CPFE?**

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

19 **The aim of the study is to investigate predictor of mortality in CPFE with**
20 **less invasive way.**
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25 **Key Messages:** Clinical point of view, finger clubbing is useful predictor of
26 mortality in CPFE. In addition, ratio of percent predicted forced expiratory
27 volume in 1 second (%FEV₁) and percent forced vital capacity (%FVC)
28 more than 1.2% were independent predictors of mortality in patients with
29 CPFE too. Prediction of prognosis of these patients by minimally invasive
30 methods may be quite useful.
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36 **Strengths and Limitations:**We investigated all available clinical and
37 physiological data with minimally invasive way. Therefore, most hospitals
38 can refer our result easily. And we compared CPFE with IPF patients.
39 Therefore, our result may be more robust. However, this is single center
40 study. So, our result cannot be generalizable to other hospital's patients.
41 We will require multi-centre study for confirmation.
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46 **Abstract**
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48 **Objectives:** Our purpose was to assess the clinical data, predictors of
49 mortality, acute exacerbation of CPFE patients and compared that of
50 idiopathic pulmonary fibrosis (IPF) patients.
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52 **Design:**Single centre retrospective cohort study.
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54 **Setting:**Teaching hospital in Japan.
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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. 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 = 1.0009, P = 0.027). Finger clubbing (Hazards Ratio = 2.2620, P = 0.015) and percent predicted forced expiratory volume in 1 second (%FEV₁) / %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 %FEV₁/ %FVC more than 1.2 were independent predictors of mortality.

Key words: mortality; acute exacerbation; finger clubbing; KL-6 ; %FEV₁/ %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

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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 (FEV₁), %FEV₁, 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, margined 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 \pm 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

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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 forty-two (45 %) had finger clubbing. The baseline percent predicted forced expiratory volume in 1 second (FEV₁) (FEV₁/average %FEV₁ 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 (PaO₂) and carbon dioxide (PaCO₂) were 63 mmHg and 43 mmHg, respectively. Forty-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,

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5 especially squamous cell carcinoma (10,17). However, in our cohort, only
6 twelve (13 %) patients developed lung cancer.
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10 Among the 93 patients, twenty-two (24%) developed AE, which met the
11 ATS/ERS criteria (15). We performed univariate analysis to determine
12 predictors of AE. Age, mMRC score, dyspnea duration, and serum KL-6
13 were identified as possible predictors of AE. Multivariate regression
14 analysis was performed for these four factors, serum KL-6 was found to be
15 the strongest predictor of AE in the CPFE patients [Odds Ratio = 1.0009, P
16 = 0.027] . Using receiver operator characteristic curve (ROC) analysis, the
17 useful KL-6 threshold was determined to be 1050 (ROC: 0.7720).
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23 24 HRCT Imaging and Predictors of Mortality

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26 According to the ATS/ERS criteria (15,16), the patients were divided into
27 those with IPF patterns and those with NSIP patterns. There were 68
28 patients in the IPF–pattern group and 25 patients in the NSIP–pattern
29 group. The HRCT images also showed patterns indicating that 51 patients
30 had para septal emphysema, 28 had centrilobular emphysema, and 14 had
31 panlobular emphysema. Detailed results are presented in Table 2.
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37 The mean survival of CPFE patients was 30.7 months(0.10–75.63 months).
38 On the other hand, mean survival of IPF patients was 34.5 months
39 (6.79-72.95 months) which was statistically significant(p = 0.0411)
40 (Figure 1). Patients with finger clubbing or increased ratio of %FEV₁
41 to %FVC showed poor survival in CPFE patients (Figure 2) (Figure 3).
42 Regarding ratio of %FEV₁ to %FVC, we chose 1.2 which was most useful
43 threshold for predictor of mortality with using ROC analysis(ROC: 0.7671).
44 In IPF patients in our cohort, useful cut off value of ratio of %FEV₁ to %FVC
45 was 1.5 (Figure 4)(ROC: 0.8622). Initially, we performed univariate
46 analysis with a cutoff value of 0.1, which showed that KL-6, finger clubbing,
47 PaO₂, and %FEV₁ / % FVC > 1.2 were independent predictors of mortality
48 (Table 3). Cox proportional hazards regression analysis showed that finger
49 clubbing (HR = 2.2620, P = 0.015) and ratio of %FEV₁ to % FVC more than
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5 1.2 (HR = 1.9259, P = 0.048) were the strongest independent predictors of
6 mortality in CPFE patients at our hospital (Table 4).
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9 Discussion

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12 Previous studies have reported a high prevalence of PAH and lung cancer
13 in CPFE patients (1,10). These comorbidities were associated with poor
14 prognosis; the 1-year survival rate for CPFE patients with PAH was only
15 60% (6,11). Among these patients, high mean pulmonary arterial pressure,
16 high pulmonary vascular resistance, high heart rate, and low diffusing
17 capacity for carbon monoxide (DLco) were significantly associated with
18 poor outcome. In one study, CPFE patients had a five fold higher mortality
19 risk (adjusted HR: 5.10, 95%CI:1.75–14.9) in non-malignant situations (19).
20 In the present study, only twelve of 93 patients had lung cancer in contrast
21 to the number reported in a previous study (10). Our institution is a
22 teaching and community hospital, and the patient population may be
23 different from that of a university hospital.
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33 The pulmonary function indices of the CPFE patients included in the
34 present study were rather different from those in previous reports (1, 20).
35 The CPFE patients in those studies had greater preserved lung volume
36 despite reduced DLco, reduced transfer coefficient for carbon monoxide
37 (Kco), and hypoxemia. Jankowich, et al. reported that CPFE altered
38 physiology but had a mortality rate similar to that of IPF (21). In addition,
39 Peng M, et al. reported similar physiology results for CPFE (22). In our
40 study, the mean percent predicted FVC was 63.86% and that of FEV₁ was
41 70.95%, which showed more restrictive impairment compared with
42 previous cases. This finding can be explained by the greater volume loss
43 of the lower lung field due to severe fibrosis rather than by the offset effect
44 of emphysema (23). This finding might also be because our cohort had
45 less emphysema area compared with the previously reported cases.
46 Another possibility is that the patients might have been in a different
47 phase of CPFE. Recently, Rogliani, et al. reported the pathology of IPF and
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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).

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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 %FEV₁ ,% FVC and ratio of these value as important indices out of pulmonary function parameters. Univariate analysis revealed that KL-6, finger clubbing, PaO₂, and ratio of %FEV₁ to % FVC were independent predictors. Regression analysis using a Cox proportional hazards model showed that finger clubbing and ratio of %FEV₁ to % FVC more than 1.2 were the strongest independent predictors of mortality in CPFE at our hospital. On the other hand, ratio of %FEV₁ 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 %FEV₁ 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 evaluation 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-dimentionns.

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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

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18 **Figure Legends:**
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21 **Figure 1; CPFE patients show poor survival compared with that of IPF**
22 **patients**
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26 **Figure 2; CPFE patients with clubbing show poor survival compared with**
27 **that of without clubbing**
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31 **Figure 3; Ratio of %FEV₁ and %FVC more than 1.2 show poor survival**
32 **rather than that of less than 1.2 in CPFE patients**
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36 **Figure 4; Ratio of %FEV₁ and %FVC more than 1.5 show poor survival**
37 **rather than that of less than 1.5 in IPF patients**
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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 FEV1,%	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
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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; FEV₁= 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

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8 **Definitions of abbreviations: HRCT = High resolution computed**
9 **tomography ; IPF = Idiopathic pulmonary fibrosis ; NSIP = Non specific**
10 **interstitial pneumonia.**
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22 **Table 3. Results of univariate analysis showing predictors of mortality**
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	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
PaO₂	0.9477	0.9013-0.9965	0.036
%FEV₁/%FVC (> 1.2)	2.6326	1.4855-4.6655	0.001

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43 **Definitions of abbreviations: CI = confidence interval ; MRC = Medical**
44 **research council; FVC = forced vital capacity.**
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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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6 **Section 4** Other relationships

7 **Are there other relationships or activities that readers could perceive to have influenced, or that**
8 **give the appearance of potentially influencing, what you wrote in the submitted work?**
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10 No other relationships/conditions/circumstances that present a potential conflict of interest
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ICMJE Form for Disclosure of Potential Conflicts of Interest

Identifying Information

Section 1.

1. Given Name (First Name) 2. Surname (Last Name) 3. Effective Date
Shin **Yamashiro** **December 1, 2011**

4. Are you the corresponding author? No

5. Manuscript Title

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

The Work Under Consideration for Publication

Section 2.

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the

"Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration for Publication

1. Grant No
2. Consulting fee or honorarium No
3. **Support for travel to meetings for the study or other purposes** **No**
4. **Fees for participation in review activities such as data monitoring boards, statistical analysis, endpoint committees, and the like** **No**
5. **Payment for writing or reviewing the manuscript** **No**
6. **Provision of writing assistance, medicines, equipment, or administrative support** **No**

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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Type of Relationship (in alphabetical order)

- | | |
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| 1. Board membership | No |
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| 3. Employment | No |
| 4. Expert testimony | No |
| 5. Grants/grants pending | No |
| 6. Payment for lectures including | No |
| 7. Payment for manuscript | No |
| preparation | |
| 8. Patents (planned, pending or | |
| issued) | No |
| 9. Royalties | No |
| 10. Payment for development of | |
| educational presentations | No |
| 11. Stock/stock options | No |
| 12. Travel/accommodations/ | |
| meeting expenses unrelated to | |
| activities listed** | No |
| 13. Other (err on the side of full | |
| disclosure) | No |

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Section 4 Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

No other relationships/conditions/circumstances that present a potential conflict of interest

For peer review only

ICMJE Form for Disclosure of Potential Conflicts of Interest

Identifying Information

Section 1.

1. Given Name (First Name) 2. Surname (Last Name) 3. Effective Date
Hitoshi **Tamaki** **December 1, 2011**

4. Are you the corresponding author? No

5. Manuscript Title

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

The Work Under Consideration for Publication

Section 2.

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

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1. Grant No
2. Consulting fee or honorarium No
3. **Support for travel to meetings for the study or other purposes** **No**
4. **Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like** **No**
5. **Payment for writing or reviewing the manuscript** **No**
6. **Provision of writing assistance, medicines, equipment, or administrative support** **No**

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Relevant financial activities outside the submitted work.

Type of Relationship (in alphabetical order)

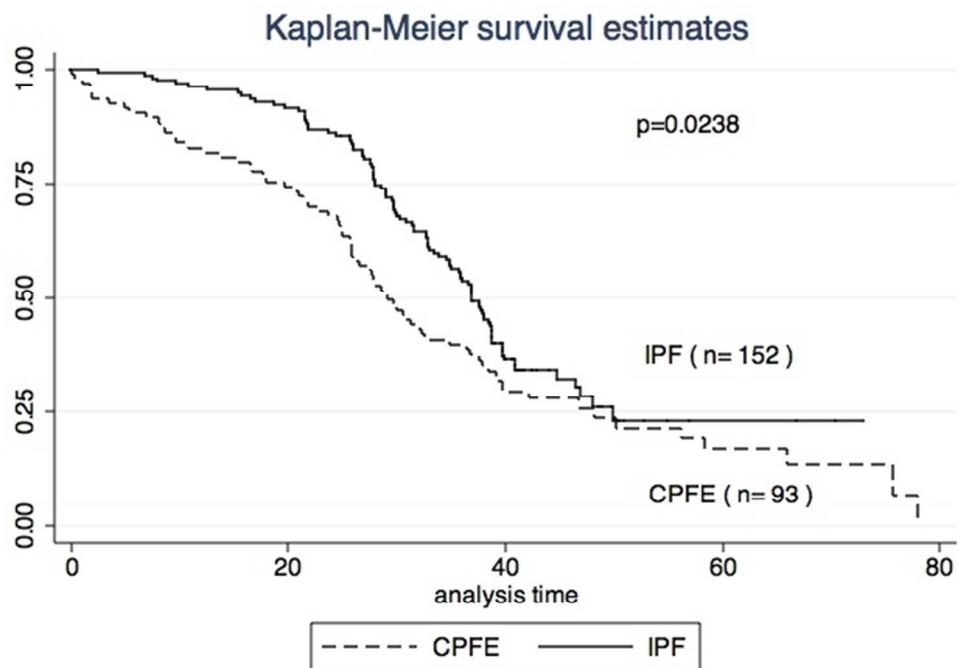
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| 1. Board membership | No |
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| 3. Employment | No |
| 4. Expert testimony | No |
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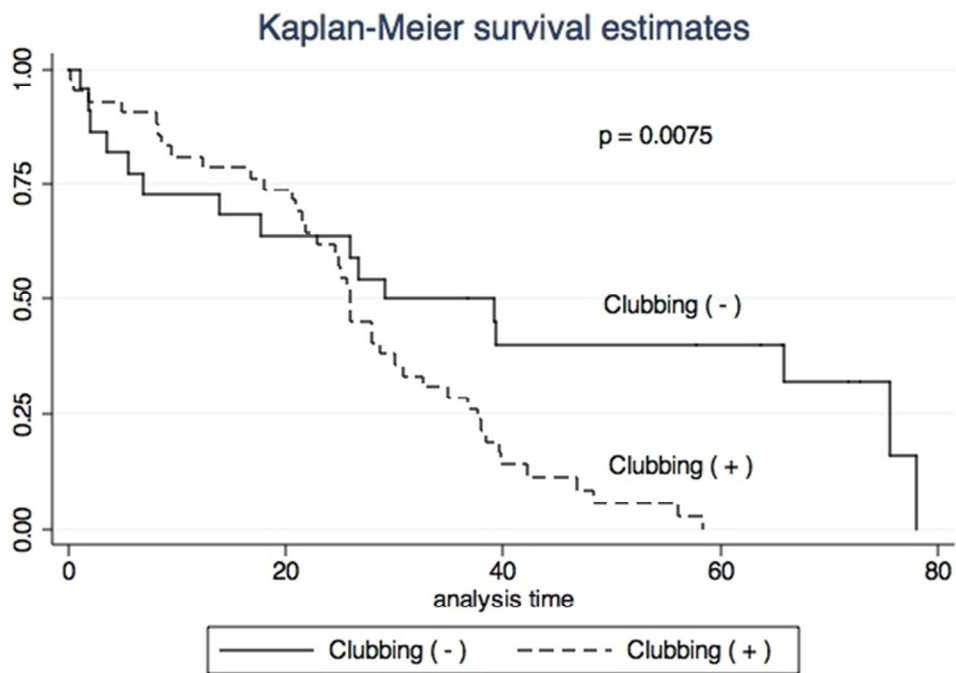
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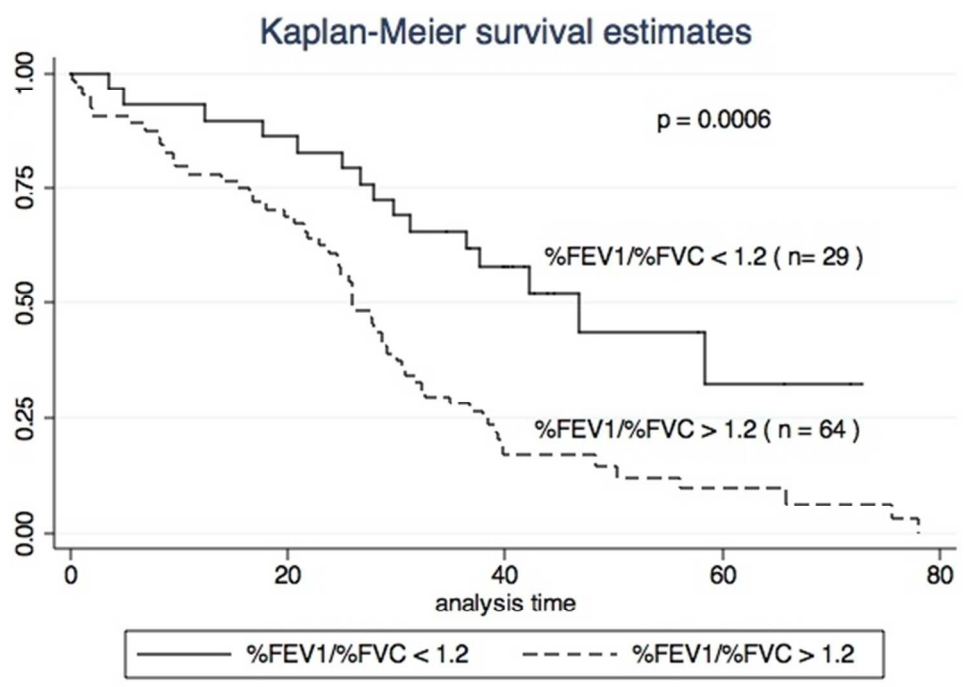
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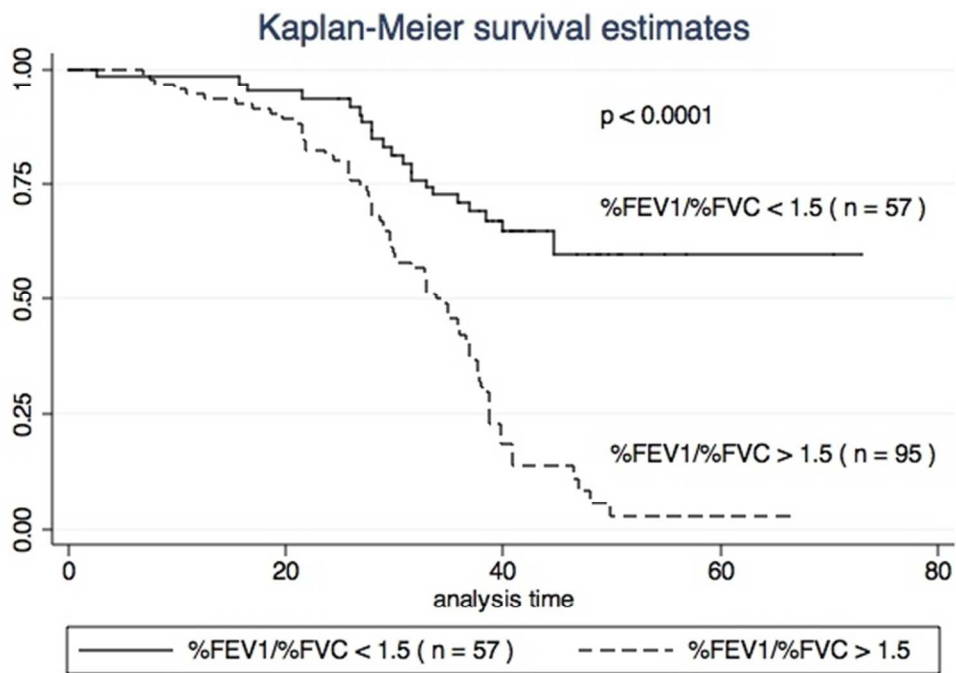
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

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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Manuscript ID:	bmjopen-2012-000988.R1
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Date Submitted by the Author:	26-Mar-2012
Complete List of Authors:	Kishaba, Tomoo; Okinawa Chubu Hospital, Respiratory Medicine Shimaoka, Yousuke; Okinawa Chubu Hospital, Respiratory medicine Fukuyama, Hajime; Okinawa Chubu Hospital, Respiratory medicine Yoshida, Kyoko; Nakamura Clinic, Home care Tanaka, Maki; Kurashiki Central Hospital, Respiratory medicine Yamashiro, Shin; Okinawa Chubu Hospital, Respiratory medicine Tamaki, Hitoshi; Okinawa Chubu Hospital, Respiratory medicine
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	THORACIC MEDICINE, Interstitial lung disease < THORACIC MEDICINE, Respiratory physiology < THORACIC 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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Total Word Count: 2477

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

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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 (%FEV₁) 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

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6 patients had CPFE.

7 **Results:** The mean age of CPFE patients was 74 years. IPF and nonspecific
8 interstitial pneumonia (NSIP) were observed as distinct HRCT patterns.

9
10 **Fourty-two** patients showed finger clubbing. Mean serum Krebs von den
11 Lungen-6 (KL-6) and percent predicted forced vital capacity (%FVC) were
12 1089 IU/L, 63.86% respectively. Twenty-two patients developed acute
13 exacerbation during observation period. Baseline KL-6 was a strong
14 predictor of acute exacerbation. (Odds Ratio = 1.0016, P = 0.009). Finger
15 clubbing (Hazards Ratio = 2.2620, P = 0.015) and percent predicted forced
16 expiratory volume in 1 second (%FEV₁) / % FVC more than 1.2 (Hazards
17 Ratio = 1.9259, P = 0.048) were independent predictors of mortality in CPFE.
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21 **Conclusions:** Baseline serum KL-6 was a useful predictor of acute
22 exacerbation (cutoff = 1050, ROC: 0.7720), which occurred in 24% (22/93) of
23 the CPFE patients. Finger clubbing and %FEV₁ / %FVC more than 1.2 were
24 independent predictors of mortality.
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29 **Key words:** mortality; acute exacerbation; finger clubbing;
30 KL-6 ; %FEV₁/%FVC
31

32 **There is no additional data available**

33
34 **Key words:** mortality; acute exacerbation; finger clubbing;
35 KL-6 ; %FEV₁/%FVC
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39 **Total Abstract Count: 247**
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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.

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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)(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

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5 the American Thoracic Society/ European Respiratory Society (ATS/ERS)
6 statement (15). Among all ILD patients, we identified 93 CPFE patients
7 through multidisciplinary discussion including our pulmonologists and
8 radiologists. We excluded patients if; 1) they were without HRCT imaging,
9 2) had connective tissue disease (CTD), 3) had drug-associated ILD, and 4)
10 had occupationally related ILD, such as asbestosis and silicosis.

11
12 Demographic and clinical data were obtained, including age, gender,
13 smoking history, dyspnea duration, comorbidity, crackles, clubbing, Krebs
14 von den Lungen-6 (KL-6) levels and Ultrasound
15 Cardiography(UCG) findings. In terms of pulmonary arterial hypertension
16 (PAH), we estimated with UCG .We also checked physiological data
17 including forced expiratory volume in 1 second (FEV₁), %FEV₁, forced vital
18 capacity (FVC), and %FVC. We only included pulmonary function data
19 determined within six months of the date of HRCT.
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29 The HRCT scan imaging patterns were evaluated according to the
30 ATS/ERS criteria (15). We diagnosed IPF patients using the new ATS/ERS
31 and Japanese Respiratory Society /Latin America Thoracic Association
32 criteria (16). Patients who met the following criteria, as described by Cottin
33 et al. (1), were diagnosed as having CPFE: (1) the presence of emphysema
34 on CT, defined as well-demarcated areas of decreased attenuation
35 compared with contiguous normal lung, margined by a very thin (<1 mm)
36 wall or no wall, and/or multiple bullae (>1 cm) with upper-zone
37 predominance, and (2) the presence of significant pulmonary fibrosis on
38 CT, defined as reticular opacities with peripheral and basal predominance,
39 with or without traction bronchiectasis that occurs with or without
40 honeycombing. Regarding acute exacerbation, we defined by the following
41 criteria (18):(1) sudden deterioration of dyspnea within 30 days (2) new
42 bilateral infiltration on chest radiograph (3)pulmonary infection or other
43 known causes were excluded by bronchoalveolar lavage(BAL). Survival
44 time was defined from the date of HRCT to death or last observation date.
45 The Ethics Committee of Okinawa Chubu Hospital approved this study
46 protocol.
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Statistical Methods

Clinical data are presented as means \pm 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 forty-two (45 %) had finger clubbing. The baseline percent predicted forced expiratory volume in 1 second (FEV₁) (FEV₁/average %FEV₁ 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.

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The mean partial pressures of oxygen (PaO₂) and carbon dioxide (PaCO₂) 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 %FEV₁ to %FVC showed poor survival in CPFE patients (Figure 2) (Figure 3). Regarding ratio of %FEV₁ 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, PaO₂, and %FEV₁ / % FVC >

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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 %FEV₁ 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 FEV₁ 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

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6 less emphysema area compared with the previously reported cases.
7 Another possibility is that the patients might have been in a different
8 phase of CPFE. Recently, Rogliani, et al. reported the pathology of IPF and
9 emphysema (24). They evaluated 17 biopsy-proven usual interstitial
10 pneumonia (UIP) patients and found fibroblasts in areas of parenchymal
11 destruction from emphysema/UIP-expressed matrix metalloproteinase
12 (MMP)-2, MMP-9, MMP-7 and membrane type 1 (MT1)-MMP at
13 significantly higher levels when compared with emphysema subjects. On
14 the basis of this result, similar to the findings of the study by Rogliani et al.
15 cited above, interstitial fibroblast activation could be stimulated to a
16 greater degree in the areas of lung destruction in CPFE compared with
17 emphysema alone, as in exaggerated tissue remodeling. Therefore, some
18 of the CPFE patients may have had more intense fibrosis, which
19 contributed to reduced FVC.
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29 In the analysis of the HRCT images, the patients were divided into two
30 groups by UIP (usual interstitial pneumonia) pattern and NSIP pattern
31 according to the ATS/ERS criteria (15,16). All of the UIP-pattern patients
32 had honeycombing, and the NSIP-pattern patients more often had
33 consolidation (60% vs. 29%) and ground-glass opacity (100% vs. 34%).
34 These findings were very similar to those from a recent report on HRCT for
35 NSIP (25). In addition, Sumikawa et al. reported that traction
36 bronchiectasis and fibrosis scores were associated with poor prognosis in
37 pathological UIP patients (26). In the present study, HRCT pattern was not
38 an independent prognostic predictor. CPFE patients usually have more
39 severe PAH, low cardiac index (6) and are disabled (27), which we
40 observed in our cohort. Thus, most CPFE patients cannot tolerate invasive
41 procedures such as VATS. Therefore, we cannot compare biopsy-proven
42 UIP with CPFE equally.
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53 Acute exacerbation (AE) is a relentlessly progressive status and is
54 associated with poor outcome (28). Thus, we evaluated AE of CPFE.
55 During the observation period (mean: 30.7 months), twenty-two patients
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5 (24 %) developed AE. The annual incidence of AE is 9.4%. This finding is
6 similar to that reported in IPF recently (29). Kondoh, et al. reported that
7 high modified MRC score, high body mass index (BMI), and decline in FVC
8 at six months were significant independent risk factors for AE-IPF (30).
9 KL-6 levels in ILD patients reflect the overall extent of interstitial lesions.
10 Among the many clinical parameters, baseline serum KL-6 was the most
11 powerful predictor of AE in our CPFE patients. ROC analysis showed that
12 the useful threshold was 1050 (ROC = 0.7720).
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19 Finally, we investigated the prognostic predictors of CPFE in our cohort.
20 FVC has been reported robust powerful predictor of mortality in IPF
21 patients (31). DLco often show variable value, so reproducibility is rather
22 poor. In addition when FVC is reduced, DLco cannot be obtained with
23 single breath method. Therefore, we chose %FEV₁ ,% FVC and ratio of
24 these value as important indices out of pulmonary function parameters.
25 Univariate analysis revealed that KL-6, finger clubbing, PaO₂, and ratio
26 of %FEV₁ to % FVC were independent predictors. Regression analysis
27 using a Cox proportional hazards model showed that finger clubbing and
28 ratio of %FEV₁ to % FVC more than 1.2 were the strongest independent
29 predictors of mortality in CPFE at our hospital. In CPFE patients,lung
30 volume is usually preserved. Therefore, absolute value of FVC or %FVC
31 itself has been reported to be not robust predictor of critical event.
32 However, ratio of %FEV₁ to % FVC may be useful parameter in subgroup of
33 CPFE patients. In terms of different cut-off value of this ratio, CPFE
34 patients tend to have more mild restrictive impairment compared with that
35 of IPF patients. Another interesting finding was that finger clubbing which
36 is associated with poor survival in CPFE patients. Finger clubbing usually
37 shows chronicity in ILD patients. However, it predicted clinical course in
38 CPFE patients at our cohort. So, we insisist on the importance of initial
39 careful evaluation of physical findings in CPFE.
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54 Regarding prognosis, CPFE patients showed poor survival similar to that
55 of IPF patients in our cohort. Therefore, even if lung volume is seemingly
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5 preserved, we should follow-up these patients carefully with
6 multi-dimensions.
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10 This time, we did not evaluate the treatment in CPFE patients. Currently,
11 there is no consensus on treatment of CPFE with PAH (32,33). This is a
12 vital topic for future study.
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15 There were several limitations in our study. First, this was a single center,
16 uncontrolled design, retrospective study, which means that it is possible
17 that important data was not collected. In addition, the results cannot be
18 generalized to all CPFE patients. Second, we did not measure the exact
19 areas of emphysema and fibrosis. Therefore, our cohort may have been at
20 a different stage compared with previous CPFE patients. Third, most of our
21 patients could not undergo surgical biopsy because of disability and
22 reduced lung function. Thus, we could not evaluate the detailed pathology
23 of our CPFE patients. Fourth, we did not evaluate serial pulmonary
24 function. Recently, Du Bois et al. reported that percent predicted FVC and
25 the 24 week change in FVC were useful predictors of mortality in IPF (34).
26 Therefore, it might be helpful to measure serial FVC as a prognostic
27 predictor in CPFE. Lastly, in keeping with previous reports, our study
28 patients were all heavy smokers. Therefore, we could not distinguish CPFE
29 from smoking-related NSIP (35). However, even considering these
30 limitations, prediction of prognosis using minimally invasive methods in
31 these patients may be quite useful.
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44 In conclusion, our CPFE patients showed poor survival compared to that
45 of IPF patients. CPFE patients often develop AE, for which baseline serum
46 KL-6 was a useful predictor. Finger clubbing and %FEV1 / % FVC more
47 than 1.2 were independent prognostic predictors of mortality in patients
48 with CPFE. A multicenter study of this new entity is warranted for further
49 research.
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54 55 **ACKNOWLEDGEMENTS** 56 57 58 59 60

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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	Non-survivors	
	(n= 26)	(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 FEV₁,%	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
%FEV₁ / %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; FEV₁= 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

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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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6 **319 interstitial lung disease(ILD) patients were identified**
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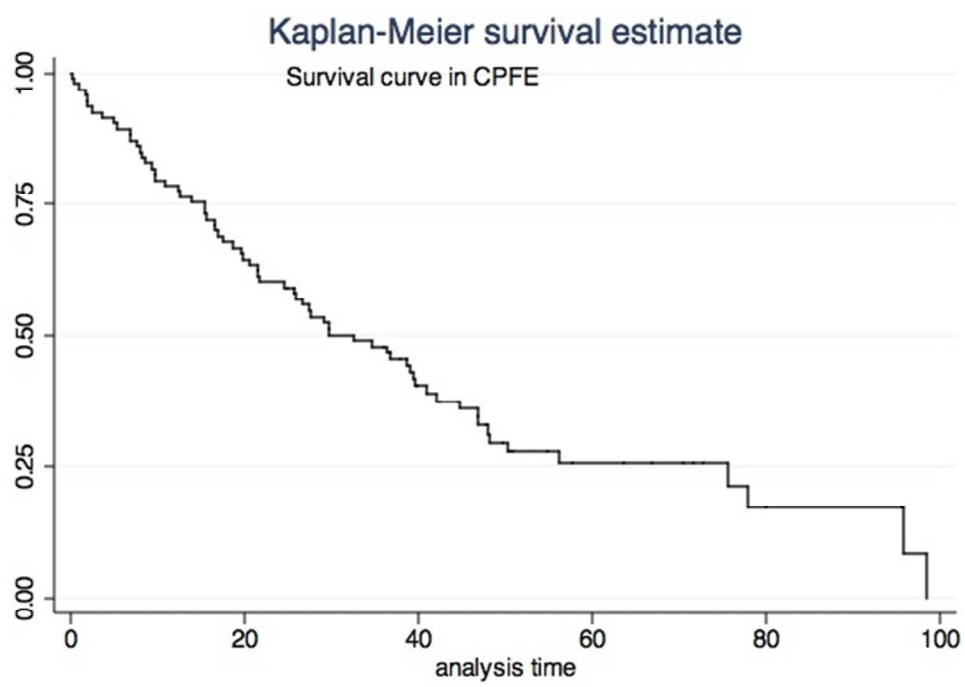


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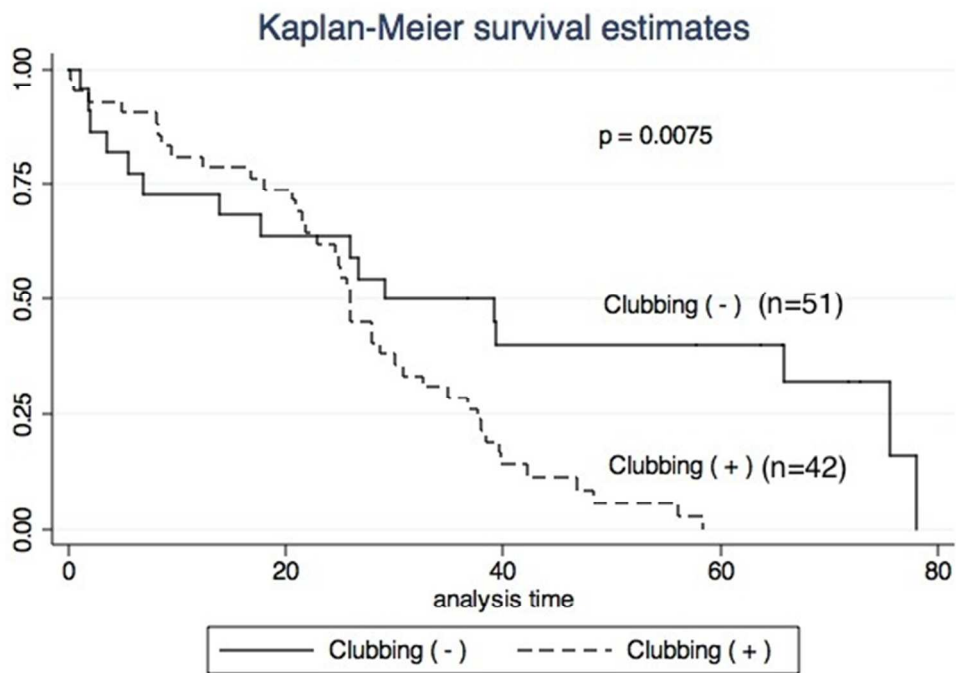
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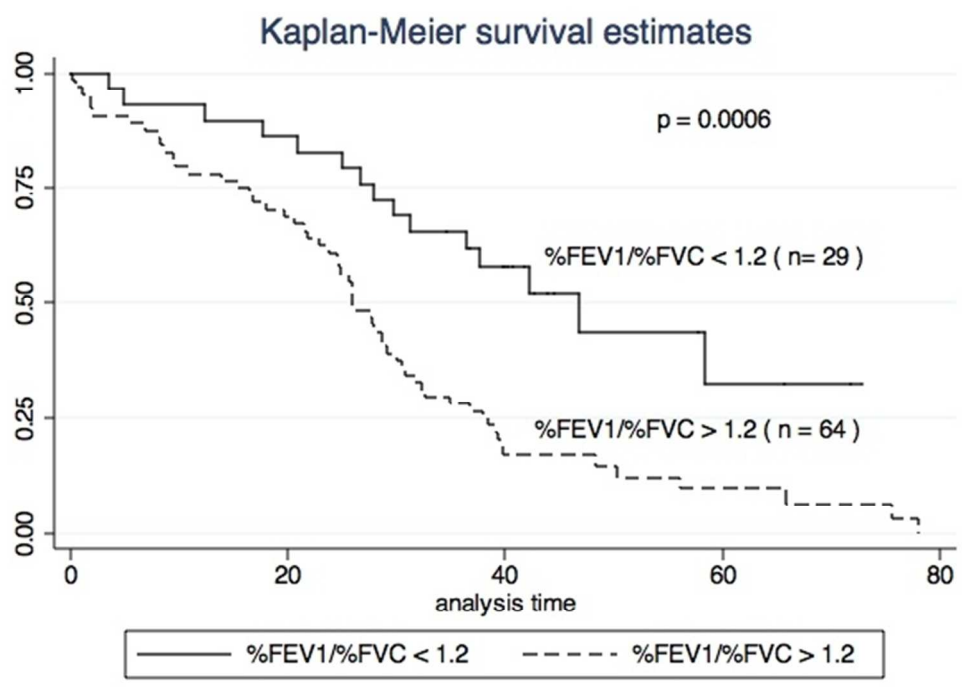
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A Cohort Study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema

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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

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5 interpretation of data, and drafting and finalization of the manuscript.

6
7 Y Shimaoka, H Fukuyama, K Yoshida, M Tanaka, S Yamashiro: Study design,
8 and acquisition and interpretation of data.

9
10 **Subject Heading: Mortality predictors in CPFE**

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

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

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

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

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

26
27 **Key Messages:** From a clinical point of view, finger clubbing is useful
28 predictor of mortality in CPFE. In addition, ratio of percent predicted forced
29 expiratory volume in 1 second (%FEV₁) and percent predicted forced vital
30 capacity (%FVC) more than 1.2% were independent predictors of mortality in
31 patients with CPFE too. Prediction of prognosis of these patients by minimally
32 invasive methods may be quite useful.

33
34 **Strengths and Limitations:** This study's strength was the definition of
35 noninvasive, easily obtainable clinical and physiological measures of
36 prognosis in CPFE. The major limitation of the study is the single-center
37 retrospective design.

38 39 **Abstract**

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

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44 **Design:** Single centre retrospective cohort study.

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46 **Setting:** Teaching hospital in Japan.

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

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6 **Interventions:** There were no interventions.

7 **Methods:** Medical records and HRCT scans from January 2002 through
8
9 December 2007 were reviewed retrospectively at our hospital. Ninety-three
10 patients had CPFE.

11 **Results:** The mean age of CPFE patients was 74 years. IPF and nonspecific
12 interstitial pneumonia (NSIP) were observed as distinct HRCT patterns.

13
14 Forty two patients showed finger clubbing. Mean serum Krebs von den
15 Lungen-6 (KL-6) and percent predicted forced vital capacity (%FVC) were
16 1089 IU/L, 63.86% respectively. Twenty-two patients developed acute
17 exacerbation during observation period. Baseline KL-6 was a strong
18 predictor of acute exacerbation. (Odds Ratio = 1.0016, P = 0.009). Finger
19 clubbing (Hazards Ratio = 2.2620, P = 0.015) and percent predicted forced
20 expiratory volume in 1 second (%FEV₁) / % FVC more than 1.2 (Hazards
21 Ratio = 1.9259, P = 0.048) were independent predictors of mortality in CPFE.

22
23 **Conclusions:** Baseline serum KL-6 was a useful predictor of acute
24 exacerbation (cutoff = 1050, ROC: 0.7720), which occurred in 24% (22/93) of
25 the CPFE patients. Finger clubbing and %FEV₁ / %FVC more than 1.2 were
26 independent predictors of mortality.
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28 **Key words:** mortality; acute exacerbation; finger clubbing;

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30 KL-6 ; %FEV₁/%FVC

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32 There is no additional data available

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34 **Key words:** mortality; acute exacerbation; finger clubbing;

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36 KL-6 ; %FEV₁/%FVC
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43 **Total Abstract Count:** 243

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

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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)

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5 had occupationally related ILD, such as asbestosis and silicosis.
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7 Demographic and clinical data were obtained, including age, gender,
8 smoking history, dyspnea duration, comorbidity, crackles, clubbing, Krebs
9 von den Lungen-6 (KL-6) levels and Ultrasound
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11 Cardiography(UCG)findings. In terms of pulmonary arterial hypertension
12 (PAH), we estimated with UCG .We also checked physiological data
13 including forced expiratory volume in 1 second (FEV₁), %FEV₁, forced vital
14 capacity (FVC), and %FVC. We only included pulmonary function data
15 determined within six months of the date of HRCT.
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21 The HRCT scan imaging patterns were evaluated according to the
22 ATS/ERS criteria (15). We diagnosed IPF patients using the new ATS/ERS
23 and Japanese Respiratory Society /Latin America Thoracic Association
24 criteria (16). Patients who met the following criteria, as described by Cottin
25 et al. (1), were diagnosed as having CPFE: (1) the presence of emphysema
26 on CT, defined as well-demarcated areas of decreased attenuation
27 compared with contiguous normal lung, margined by a very thin (<1 mm)
28 wall or no wall, and/or multiple bullae (>1 cm) with upper-zone
29 predominance, and (2) the presence of significant pulmonary fibrosis on
30 CT, defined as reticular opacities with peripheral and basal predominance,
31 with or without traction bronchiectasis that occurs with or without
32 honeycombing. Regarding acute exacerbation, we defined by the following
33 criteria (18):(1) sudden deterioration of dyspnea within 30 days (2) new
34 bilateral infiltration on chest radiograph (3)pulmonary infection or other
35 known causes were excluded by bronchoalveolar lavage(BAL). Survival
36 time was defined from the date of HRCT to death or last observation date.
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38 The Ethics Committee of Okinawa Chubu Hospital approved this study
39 protocol.
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50 51 Statistical Methods

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

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

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20 The flow diagram in Figure 1 shows how the patients were identified.
21 Ninety-three CPFE patients (76 men , 17 women) were identified between
22 2002 and 2007. The mean age was 73 years, and 82 % of the patients were
23 males. The mean time from symptoms to diagnosis was 12.68 months (0–
24 96 months). The mean follow-up period was 30.7 months (0–74.6 months).
25 All patients had histories of smoking (mean: 62 pack-years). The mean
26 modified Medical Research Council (mMRC) breathlessness score was 2.5.
27 Bibasilar fine crackles were auscultated in all patients and forty-two
28 (45 %) had finger clubbing. The baseline percent predicted forced
29 expiratory volume in 1 second (FEV₁) (FEV₁/average %FEV₁ for similar
30 age, sex and body composition) was 70.95%, and the baseline percent
31 predicted forced vital capacity (FVC) was 63.86%. During observation
32 period, sixty-seven patients (72 %) died. The clinical characteristics of
33 both survivors and non-survivors are summarized in Table 1.
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46 The mean partial pressures of oxygen (PaO₂) and carbon dioxide (PaCO₂)
47 were 63 mmHg and 43 mmHg, respectively. Thirty-two patients (34%)
48 received home oxygen therapy and 36 (39%) had pulmonary arterial
49 hypertension. The mean systolic pulmonary arterial pressure was 62
50 mmHg. CPFE patients frequently have been reported to have lung cancer,
51 especially squamous cell carcinoma (10,17). However, in our cohort, only
52 twelve (13 %) patients developed lung cancer.
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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 %FEV₁ to %FVC showed poor survival in CPFE patients (Figure 2) (Figure 3). Regarding ratio of %FEV₁ 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, PaO₂, and %FEV₁ / % 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 %FEV₁ 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

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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 FEV₁ 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

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6 the basis of this result, similar to the findings of the study by Rogliani et al.
7 cited above, interstitial fibroblast activation could be stimulated to a
8 greater degree in the areas of lung destruction in CPFE compared with
9 emphysema alone, as in exaggerated tissue remodeling. Therefore, some
10 of the CPFE patients may have had more intense fibrosis, which
11 contributed to reduced FVC.
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16 In the analysis of the HRCT images, the patients were divided into two
17 groups by UIP (usual interstitial pneumonia) pattern and NSIP pattern
18 according to the ATS/ERS criteria (15,16). All of the UIP-pattern patients
19 had honeycombing, and the NSIP-pattern patients more often had
20 consolidation (60% vs. 29%) and ground-glass opacity (100% vs. 34%).
21 These findings were very similar to those from a recent report on HRCT for
22 NSIP (25). In addition, Sumikawa et al. reported that traction
23 bronchiectasis and fibrosis scores were associated with poor prognosis in
24 pathological UIP patients (26). In the present study, HRCT pattern was not
25 an independent prognostic predictor. CPFE patients usually have more
26 severe PAH, low cardiac index (6) and are disabled (27), which we
27 observed in our cohort. Thus, most CPFE patients cannot tolerate invasive
28 procedures such as VATS. Therefore, we cannot compare biopsy-proven
29 UIP with CPFE equally.
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40 Acute exacerbation (AE) is a relentlessly progressive status and is
41 associated with poor outcome (28). Thus, we evaluated AE of CPFE.
42 During the observation period (mean: 30.7 months), twenty-two patients
43 (24 %) developed AE. The annual incidence of AE is 9.4%. This finding is
44 similar to that reported in IPF recently (29). Kondoh, et al. reported that
45 high modified MRC score, high body mass index (BMI), and decline in FVC
46 at six months were significant independent risk factors for AE-IPF (30).
47 KL-6 levels in ILD patients reflect the overall extent of interstitial lesions.
48 Among the many clinical parameters, baseline serum KL-6 was the most
49 powerful predictor of AE in our CPFE patients. ROC analysis showed that
50 the useful threshold was 1050 (ROC = 0.7720).
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6 Finally, we investigated the prognostic predictors of CPFE in our cohort.
7 FVC has been reported robust powerful predictor of mortality in IPF
8 patients (31). DLco often show variable value, so reproducibility is rather
9 poor. In addition when FVC is reduced, DLco cannot be obtained with
10 single breath method. Therefore, we chose %FEV₁, % FVC and ratio of
11 these value as important indices out of pulmonary function parameters.
12 Univariate analysis revealed that KL-6, finger clubbing, PaO₂, and ratio
13 of %FEV₁ to % FVC were independent predictors. Regression analysis
14 using a Cox proportional hazards model showed that finger clubbing and
15 ratio of %FEV₁ to % FVC more than 1.2 were the strongest independent
16 predictors of mortality in CPFE at our hospital. In CPFE patients, lung
17 volume is usually preserved. Therefore, absolute value of FVC or %FVC
18 itself has been reported to be not robust predictor of critical event.
19 However, ratio of %FEV₁ to % FVC may be useful parameter in subgroup of
20 CPFE patients. In terms of different cut-off value of this ratio, CPFE
21 patients tend to have more mild restrictive impairment compared with that
22 of IPF patients. Another interesting finding was that finger clubbing which
23 is associated with poor survival in CPFE patients. Finger clubbing usually
24 shows chronicity in ILD patients. However, it predicted clinical course in
25 CPFE patients at our cohort. So, we insist on the importance of initial
26 careful evaluation of physical findings in CPFE.
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40 This time, we did not evaluate the treatment in CPFE patients. Currently,
41 there is no consensus on treatment of CPFE with PAH (32,33). This is a
42 vital topic for future study.
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46 There were several limitations in our study. First, this was a single center,
47 uncontrolled design, retrospective study, which means that it is possible
48 that important data was not collected. Second, we did not measure the
49 exact areas of emphysema and fibrosis. Therefore, our cohort may have
50 been at a different stage compared with previous CPFE patients. Third,
51 most of our patients could not undergo surgical biopsy because of
52 disability and reduced lung function. Thus, we could not evaluate the
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6 detailed pathology of our CPFE patients. Fourth, we did not evaluate serial
7 pulmonary function. Recently, Du Bois et al. reported that percent
8 predicted FVC and the 24 week change in FVC were useful predictors of
9 mortality in IPF (34). Therefore, it might be helpful to measure serial FVC
10 as a prognostic predictor in CPFE. Lastly, in keeping with previous reports,
11 our study patients were all heavy smokers. Therefore, we could not
12 distinguish CPFE from smoking-related NSIP (35). However, even
13 considering these limitations, prediction of prognosis using minimally
14 invasive methods in these patients may be quite useful.
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21 In conclusion, CPFE patients showed poor survival in our cohort. CPFE
22 patients often develop AE, for which baseline serum KL-6 was a useful
23 predictor. Finger clubbing and %FEV1 / % FVC more than 1.2 were
24 independent prognostic predictors of mortality in patients with CPFE. A
25 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 FEV₁,%	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
%FEV₁ / %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; FEV₁= 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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For peer review only

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

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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

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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 (%FEV₁) 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

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6 interstitial pneumonia (NSIP) were observed as distinct HRCT patterns.
7 **Forty two** patients showed finger clubbing. Mean serum Krebs von den
8 Lungen-6 (KL-6) and percent predicted forced vital capacity (%FVC) were
9 1089 IU/L, 63.86% respectively. Twenty-two patients developed acute
10 exacerbation during observation period. Baseline KL-6 was a strong
11 predictor of acute exacerbation. (Odds Ratio = 1.0016, P = 0.009). Finger
12 clubbing (Hazards Ratio = 2.2620, P = 0.015) and percent predicted forced
13 expiratory volume in 1 second (%FEV₁) / % FVC more than 1.2 (Hazards
14 Ratio = 1.9259, P = 0.048) were independent predictors of mortality in CPFE.
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Key words: mortality; acute exacerbation; finger clubbing;

KL-6 ; %FEV₁/%FVC

There is no additional data available

Key words: mortality; acute exacerbation; finger clubbing;

KL-6 ; %FEV₁/%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

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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

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6 (PAH), we estimated with UCG .We also checked physiological data
7 including forced expiratory volume in 1 second (FEV₁), %FEV₁, forced vital
8 capacity (FVC), and %FVC. We only included pulmonary function data
9 determined within six months of the date of HRCT.
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13 The HRCT scan imaging patterns were evaluated according to the
14 ATS/ERS criteria (15). We diagnosed IPF patients using the new ATS/ERS
15 and Japanese Respiratory Society /Latin America Thoracic Association
16 criteria (16). Patients who met the following criteria, as described by Cottin
17 et al. (1), were diagnosed as having CPFE: (1) the presence of emphysema
18 on CT, defined as well-demarcated areas of decreased attenuation
19 compared with contiguous normal lung, margined by a very thin (<1 mm)
20 wall or no wall, and/or multiple bullae (>1 cm) with upper-zone
21 predominance, and (2) the presence of significant pulmonary fibrosis on
22 CT, defined as reticular opacities with peripheral and basal predominance,
23 with or without traction bronchiectasis that occurs with or without
24 honeycombing. Regarding acute exacerbation, we defined by the following
25 criteria (18):(1) sudden deterioration of dyspnea within 30 days (2) new
26 bilateral infiltration on chest radiograph (3)pulmonary infection or other
27 known causes were excluded by bronchoalveolar lavage(BAL). Survival
28 time was defined from the date of HRCT to death or last observation date.
29 The Ethics Committee of Okinawa Chubu Hospital approved this study
30 protocol.
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43 Statistical Methods

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

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

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12 The flow diagram in Figure 1 shows how the patients were identified.

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14 **Ninety-three CPFE patients (76 men , 17 women) were identified between**
15 **2002 and 2007.** The mean age was 73 years, and 82 % of the patients were
16 males. The mean time from symptoms to diagnosis was 12.68 months (0–
17 96 months). The mean follow-up period was 30.7 months (0–74.6 months).
18 All patients had histories of smoking (mean: 62 pack-years). The mean
19 modified Medical Research Council (mMRC) breathlessness score was 2.5.
20 Bibasilar fine crackles were auscultated in all patients and forty-two
21 (45 %) had finger clubbing. The baseline percent predicted forced
22 expiratory volume in 1 second (FEV₁) (FEV₁/average %FEV₁ for similar
23 age, sex and body composition) was 70.95%, and the baseline percent
24 predicted forced vital capacity (FVC) was 63.86%. During observation
25 period, sixty-seven patients (72 %) died. The clinical characteristics of
26 both survivors and non-survivors are summarized in Table 1.
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38 The mean partial pressures of oxygen (PaO₂) and carbon dioxide (PaCO₂)
39 were 63 mmHg and 43 mmHg, respectively. Thirty-two patients (34%)
40 received home oxygen therapy and 36 (39%) had pulmonary arterial
41 hypertension. The mean systolic pulmonary arterial pressure was 62
42 mmHg. CPFE patients frequently have been reported to have lung cancer,
43 especially squamous cell carcinoma (10,17). However, in our cohort, only
44 twelve (13 %) patients developed lung cancer.
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51 Among the 93 patients, twenty-two (24%) developed AE, which met the
52 ATS/ERS criteria (15). We performed univariate analysis to determine
53 predictors of AE. Age, mMRC score, ctpattern, and baseline serum KL-6
54 were identified as possible predictors of AE. Logistic regression analysis
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5 was performed for these four factors, baseline serum KL-6 was found to be
6 the strongest predictor of AE in the CPFE patients [Odds Ratio = 1.0016, P
7 = 0.009] . (Table 2) Using receiver operator characteristic curve (ROC)
8 analysis, the useful KL-6 threshold was determined to be 1050 (ROC:
9 0.7720).

14 HRCT Imaging and Predictors of Mortality

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

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25 The mean survival of CPFE patients was 30.7 months(0.10–75.63 months).
26 (Figure 1). Patients with finger clubbing or increased ratio of %FEV₁
27 to %FVC showed poor survival in CPFE patients (Figure 2) (Figure 3).
28 Regarding ratio of %FEV₁ to %FVC, we chose 1.2 which was most useful
29 threshold for predictor of mortality with using ROC analysis(ROC: 0.7671).
30 Initially, we performed univariate analysis with a cutoff value of 0.1, which
31 showed that baseline KL-6, finger clubbing, PaO₂, and %FEV₁ / % FVC >
32 1.2 were independent predictors of mortality. Cox proportional hazards
33 regression analysis showed that finger clubbing (HR = 2.2620, P = 0.015)
34 and ratio of %FEV₁ to % FVC more than 1.2 (HR = 1.9259, P = 0.048) were
35 the strongest independent predictors of mortality in CPFE patients at our
36 hospital (Table 4).

47 Discussion

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50 Previous studies have reported a high prevalence of PAH and lung cancer
51 in CPFE patients (1,10). These comorbidities were associated with poor
52 prognosis; the 1-year survival rate for CPFE patients with PAH was only
53 60% (6,11). Among these patients, high mean pulmonary arterial pressure,
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6 high pulmonary vascular resistance, high heart rate, and low diffusing
7 capacity for carbon monoxide (DLco) were significantly associated with
8 poor outcome. In one study, CPFE patients had a five fold higher mortality
9 risk (adjusted HR: 5.10, 95%CI:1.75–14.9) in non-malignant situations (19).
10 In the present study, only twelve of 93 patients had lung cancer in contrast
11 to the number reported in a previous study (10). Our institution is a
12 teaching and community hospital, and the patient population may be
13 different from that of a university hospital.
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20 The pulmonary function indices of the CPFE patients included in the
21 present study were rather different from those in previous reports (1, 20).
22 The CPFE patients in those studies had greater preserved lung volume
23 despite reduced DLco, reduced transfer coefficient for carbon monoxide
24 (Kco), and hypoxemia. Jankowich, et al. reported that CPFE altered
25 physiology but had a mortality rate similar to that of IPF (21). In addition,
26 Peng M, et al. reported similar physiology results for CPFE (22). In our
27 study, the mean percent predicted FVC was 63.86% and that of FEV₁ was
28 70.95%, which showed more restrictive impairment compared with
29 previous cases. This finding can be explained by the greater volume loss
30 of the lower lung field due to severe fibrosis rather than by the offset effect
31 of emphysema (23). This finding might also be because our cohort had
32 less emphysema area compared with the previously reported cases.
33 Another possibility is that the patients might have been in a different
34 phase of CPFE. Recently, Rogliani, et al. reported the pathology of IPF and
35 emphysema (24). They evaluated 17 biopsy-proven usual interstitial
36 pneumonia (UIP) patients and found fibroblasts in areas of parenchymal
37 destruction from emphysema/UIP-expressed matrix metalloproteinase
38 (MMP)–2, MMP–9, MMP–7 and membrane type 1 (MT1)–MMP at
39 significantly higher levels when compared with emphysema subjects. On
40 the basis of this result, similar to the findings of the study by Rogliani et al.
41 cited above, interstitial fibroblast activation could be stimulated to a
42 greater degree in the areas of lung destruction in CPFE compared with
43 emphysema alone, as in exaggerated tissue remodeling. Therefore, some
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5 of the CPFE patients may have had more intense fibrosis, which
6 contributed to reduced FVC.
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10 In the analysis of the HRCT images, the patients were divided into two
11 groups by UIP (usual interstitial pneumonia) pattern and NSIP pattern
12 according to the ATS/ERS criteria (15,16). All of the UIP-pattern patients
13 had honeycombing, and the NSIP-pattern patients more often had
14 consolidation (60% vs. 29%) and ground-glass opacity (100% vs. 34%).
15 These findings were very similar to those from a recent report on HRCT for
16 NSIP (25). In addition, Sumikawa et al. reported that traction
17 bronchiectasis and fibrosis scores were associated with poor prognosis in
18 pathological UIP patients (26). In the present study, HRCT pattern was not
19 an independent prognostic predictor. CPFE patients usually have more
20 severe PAH, low cardiac index (6) and are disabled (27), which we
21 observed in our cohort. Thus, most CPFE patients cannot tolerate invasive
22 procedures such as VATS. Therefore, we cannot compare biopsy-proven
23 UIP with CPFE equally.
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27 Acute exacerbation (AE) is a relentlessly progressive status and is
28 associated with poor outcome (28). Thus, we evaluated AE of CPFE.
29 During the observation period (mean: 30.7 months), twenty-two patients
30 (24 %) developed AE. The annual incidence of AE is 9.4%. This finding is
31 similar to that reported in IPF recently (29). Kondoh, et al. reported that
32 high modified MRC score, high body mass index (BMI), and decline in FVC
33 at six months were significant independent risk factors for AE-IPF (30).
34 KL-6 levels in ILD patients reflect the overall extent of interstitial lesions.
35 Among the many clinical parameters, baseline serum KL-6 was the most
36 powerful predictor of AE in our CPFE patients. ROC analysis showed that
37 the useful threshold was 1050 (ROC = 0.7720).
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41 Finally, we investigated the prognostic predictors of CPFE in our cohort.
42 FVC has been reported robust powerful predictor of mortality in IPF
43 patients (31). DLco often show variable value, so reproducibility is rather
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6 poor. In addition when FVC is reduced, DLco cannot be obtained with
7 single breath method. Therefore, we chose %FEV₁, % FVC and ratio of
8 these value as important indices out of pulmonary function parameters.
9 Univariate analysis revealed that KL-6, finger clubbing, PaO₂, and ratio
10 of %FEV₁ to % FVC were independent predictors. Regression analysis
11 using a Cox proportional hazards model showed that finger clubbing and
12 ratio of %FEV₁ to % FVC more than 1.2 were the strongest independent
13 predictors of mortality in CPFE at our hospital. In CPFE patients, lung
14 volume is usually preserved. Therefore, absolute value of FVC or %FVC
15 itself has been reported to be not robust predictor of critical event.
16 However, ratio of %FEV₁ to % FVC may be useful parameter in subgroup of
17 CPFE patients. In terms of different cut-off value of this ratio, CPFE
18 patients tend to have more mild restrictive impairment compared with that
19 of IPF patients. Another interesting finding was that finger clubbing which
20 is associated with poor survival in CPFE patients. Finger clubbing usually
21 shows chronicity in ILD patients. However, it predicted clinical course in
22 CPFE patients at our cohort. So, we insist on the importance of initial
23 careful evaluation of physical findings in CPFE.
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35 This time, we did not evaluate the treatment in CPFE patients. Currently,
36 there is no consensus on treatment of CPFE with PAH (32,33). This is a
37 vital topic for future study.
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41 There were several limitations in our study. First, this was a single center,
42 uncontrolled design, retrospective study, which means that it is possible
43 that important data was not collected. Second, we did not measure the
44 exact areas of emphysema and fibrosis. Therefore, our cohort may have
45 been at a different stage compared with previous CPFE patients. Third,
46 most of our patients could not undergo surgical biopsy because of
47 disability and reduced lung function. Thus, we could not evaluate the
48 detailed pathology of our CPFE patients. Fourth, we did not evaluate serial
49 pulmonary function. Recently, Du Bois et al. reported that percent
50 predicted FVC and the 24 week change in FVC were useful predictors of
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5 mortality in IPF (34). Therefore, it might be helpful to measure serial FVC
6 as a prognostic predictor in CPFE. Lastly, in keeping with previous reports,
7 our study patients were all heavy smokers. Therefore, we could not
8 distinguish CPFE from smoking-related NSIP (35). However, even
9 considering these limitations, prediction of prognosis using minimally
10 invasive methods in these patients may be quite useful.
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16 In conclusion, CPFE patients showed poor survival in our cohort. CPFE
17 patients often develop AE, for which baseline serum KL-6 was a useful
18 predictor. Finger clubbing and %FEV1 / % FVC more than 1.2 were
19 independent prognostic predictors of mortality in patients with CPFE. A
20 multicenter study of this new entity is warranted for further research.
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29 collection of medical records at Okinawa Chubu Hospital. In addition, we
30 thank Dr. Yasutani for interpretation for radiological findings.
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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; FEV₁= 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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**319 interstitial lung disease(ILD) patients were identified
from 2002 to 2007**

226 patients were excluded

→ due to ineligibility



93 patients followed up



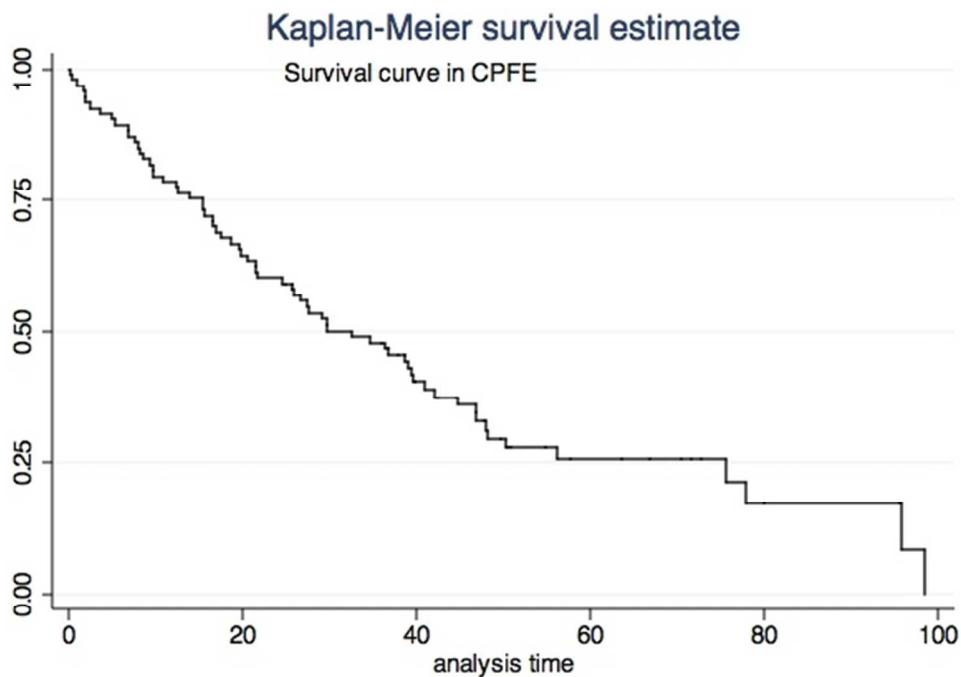
**UIP/CPFE
(n = 68)**



**NSIP/CPFE
(n = 25)**

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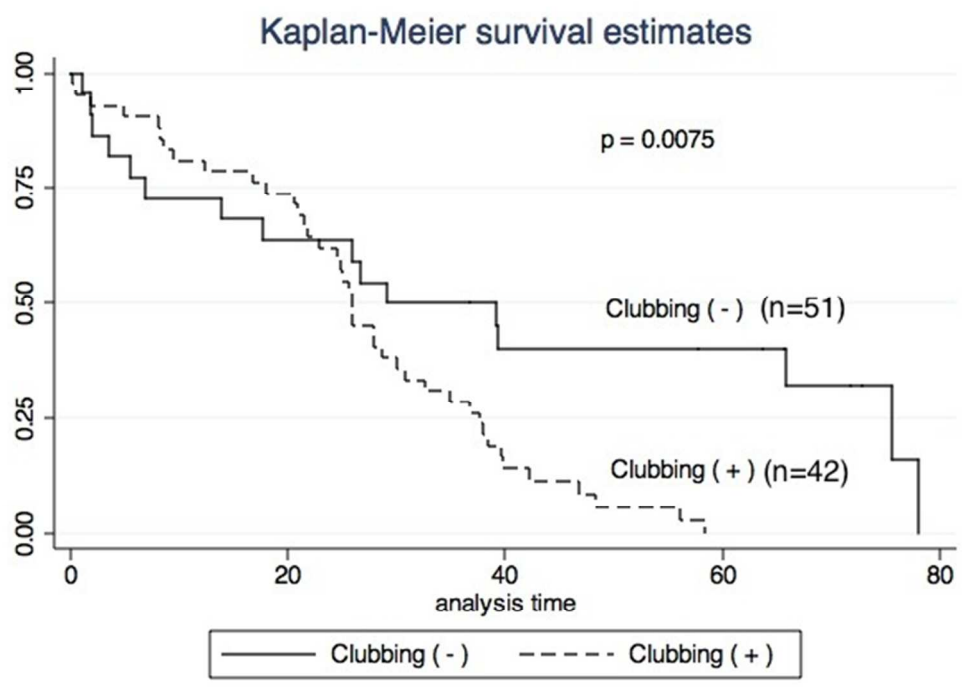
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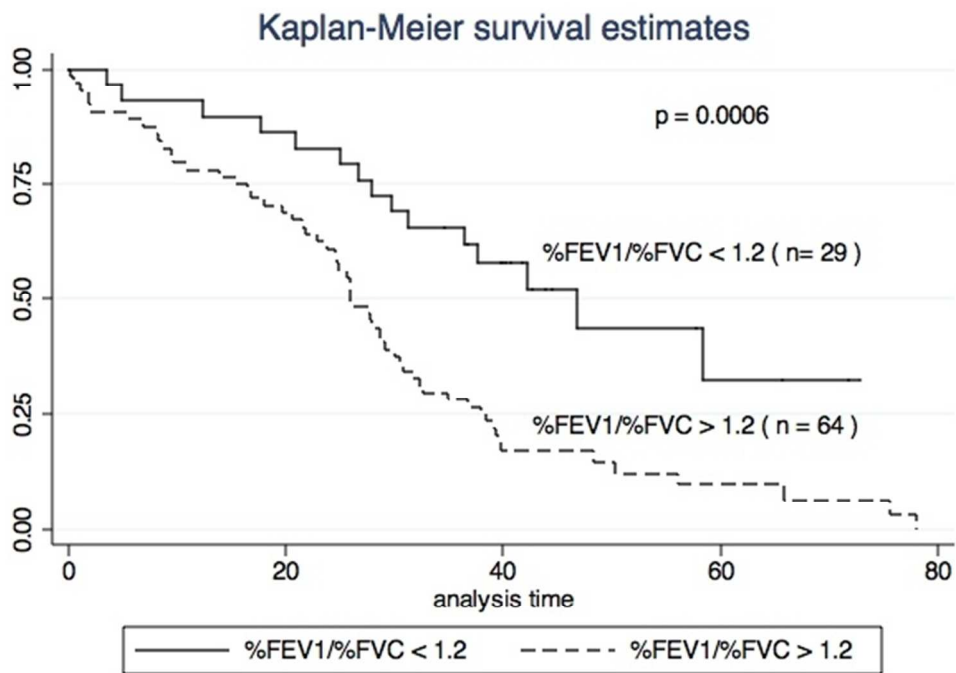
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