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

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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 (%FEV_1) and percent predicted forced vital capacity (%FVC) more than 1.2% were independent predictors of mortality in patients with CPFE too. Prediction of prognosis of these patients by minimally invasive methods may be quite useful.

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

Abstract

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

Design: Single centre retrospective cohort study.

Setting: Teaching hospital in Japan.

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

Interventions: There were no interventions.

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

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

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

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

There is no additional data available

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

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

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

Methods

Study Population and HRCT Assessment

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

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

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

Statistical Methods

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

Results

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

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

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

Among the 93 patients, twenty-two (24%) developed AE, which met the ATS/ERS criteria (15). We performed univariate analysis to determine

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

HRCT Imaging and Predictors of Mortality

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

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

Discussion

Previous studies have reported a high prevalence of PAH and lung cancer in CPFE patients (1,10). These comorbidities were associated with poor

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

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

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

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

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

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

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

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

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

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Figure Legends:

Figure 1; Flow diagram in CPFE patients

Figure 2; Survival curve in CPFE patients

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

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

TABLE 1. Patient clinical characteristics in CPFE

	Survivors (n= 26)	Non-survivors (n= 67)	p-value
Age, year (mean)	73.19 ± 1.18 (57-84)	73.83 ± 7.07 (56-91)	0.5815
Male sex, %	85	81	0.6570
Pack-year	60 ± 22.0(5-110)	64 ± 31.4 (0-180)	0.5754
mMRC scale	2.6 ± 0.88 (1-4)	2.5 ± 0.93 (1-4)	0.5091
Dyspnea duration months	11.04 ± 5.73 (0-18)	13.07 ± 14.20 (0-96)	0.4821
Clubbing, %	12	55	< 0.0001
KL-6, IU/L	852 ± 278 (505-1200)	1174 ± 725 (201-4250)	0.0413
Systolic PAP, mmHg	45	75	< 0.0001
Baseline FEV_1,%	71.14 ± 8.72 (59.6-103.9)	70.88 ± 9.25 (31.4-106.3)	0.9128

Baseline FVC,%	68.52 ± 9.09 (57-99.7)	61.89 ± 9.48 (24.9-82.3)	0.0058
HOT , %	12	43	0.0035
Paraseptal emphysema, %	19	69	< 0.0001
Acute exacerbation, n(%)	0 (0)	22 (32)	0.0007
%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; FEV_1= forced expired volume in one second; FVC = forced vital capacity; HOT = Home Oxygen Therapy

Table 2. Predictor of acute exacerbation in CPFE patients

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

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

Table 3. HRCT Imaging in CPFE patients

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

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

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

	Hazards ratio	95% CI	P-value
Finger clubbing	2.2620	1.1746-4.3560	0.015
$\%FEV_1/\%FVC$ (> 1.2)	1.9259	1.0057-3.6883	0.048

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