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Comparison of clinical characteristics and outcomes between combined pulmonary fibrosis and emphysema associated with usual interstitial pneumonia pattern and non-usual interstitial pneumonia

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Abstract. *Background:* Recently, combined pulmonary fibrosis and emphysema (CPFE) has been recognized worldwide. However, actually CPFE had a variety of extent of emphysema or pulmonary fibrosis. *Objectives:* The objectives of this study were to compare the clinical characteristics and outcomes between CPFE associated with usual interstitial pneumonia pattern (UIP) and CPFE with non-UIP divided based on chest high resolution computed tomography (HRCT) images, as well as to elucidate prognostic factors. *Methods:* A cohort of 57 CPFE and 64 IPF patients at a single institution was analyzed retrospectively. The HRCT imaging patterns of definite UIP pattern and possible UIP pattern were defined as UIP, and inconsistent with UIP pattern as non-UIP. Clinical characteristics and outcomes were compared in 3 subgroups with CPFE/UIP, CPFE/non-UIP, and IPF alone, respectively. The prognostic factors were performed using Cox proportional hazards. *Results:* The incidences of primary lung cancer and acute exacerbation (AE) were 10.4%/10.9% in CPFE/UIP, 0%/27.3% in CPFE/non-UIP, and 6.3%/35.9% in IPF, respectively. The survival in CPFE/UIP had significantly worse than that in other 2 subgroups (CPFE/non-UIP, IPF) (P = 0.011, P = 0.043). The multivariate Cox regression model showed that the prognostic factors of CPFE were UIP pattern and high-composite physiologic index (CPI). CPI thresholds of 45 provided the greatest prognostic separation in patients with CPFE. CPFE/UIP with high-CPI (CPI ≥ 45) had a worst prognosis compared with the other groups. *Conclusions:* This study demonstrated that the presence of UIP pattern and high-CPI in CPFE patients were associated with poorer mortality. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 129-137)*

Key words: idiopathic pulmonary fibrosis; combined pulmonary fibrosis and emphysema; usual interstitial pneumonia; non-usual interstitial pneumonia; acute exacerbation; composite physiologic index

Abbreviations List:

AE: acute exacerbation
AUC: area under curve
CI: confidence interval
CPFE: combined pulmonary fibrosis and emphysema
CPI: composite physiologic index
DIP: desquamative interstitial pneumonia
DLco: diffusing capacity for carbon monoxide
esPAP: estimated systolic pulmonary arterial pressure
FEV_1: forced expiratory volume in 1 s
FVC: forced vital capacity
HR: hazard ratio
HRCT: high resolution computed tomography

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IPF: idiopathic pulmonary fibrosis
mMRC: modified Medical Research Council
NSIP: nonspecific interstitial pneumonia
PFT: pulmonary function test
RB-ILD: respiratory bronchiolitis with interstitial lung disease
ROC: receiver operating characteristic
SD: standard deviation
UIP: usual interstitial pneumonia

Introduction

A consensus definition of combined pulmonary fibrosis and emphysema (CPFE) is not obtainable at present. Although this term proposed by Cottin et al. (1) was defined emphysema in the upper lobes and fibrosis in the lower lobes on chest high-resolution computed tomography (HRCT), actually patients with CPFE had a variety of extent of emphysema or pulmonary fibrosis. Consequently, previous studies have led to a different outcome for survival of CPFE compared to IPF (2-6). Moreover, some studies may include the possibility of chronic fibrosing interstitial pneumonia such as fibrotic non-specific interstitial pneumonia (f-NSIP) other than idiopathic pulmonary fibrosis (IPF). In fact, we have experienced an autopsied case of f-NSIP associated with emphysema and severe pulmonary hypertension (7). In addition, there may be also influence of emphysema subtypes (8). On the other hand, it is difficult for CPFE patients to ascertain histological diagnosis of pulmonary fibrosis by performing surgical lung biopsy, because most of these patients have severe cardiopulmonary damages. Recently, we reported that patients with CPFE associated with usual interstitial pneumonia (UIP) pattern had a worse prognosis than those with IPF alone, especially CPFE patients with paraseptal emphysema associated with high estimated pulmonary artery pressure (esPAP) had an extremely poor prognosis (9). However, to our knowledge, little has been reported on comparison of clinical characteristics and outcomes for CPFE patients definitely identified as UIP and non-UIP pattern.

Herein, we compared the clinical features and outcomes among CPFE associated with UIP, CPFE with non-UIP, and IPF alone divided based on chest HRCT patterns, as well as to elucidate prognostic factors.

Methods

Study population

The study cohort included patients enrolled at Toho University Omori Medical Center in Japan between April 2003 and March 2012. During the study period, 57 patients with CPFE and 64 patients with IPF alone were analyzed retrospectively. The HRCT imaging patterns of definite UIP pattern and possible UIP pattern were defined as UIP pattern, and inconsistent with UIP pattern as non-UIP pattern in accordance with the 2011 guidelines (10). CPFE patients were divided into CPFE/UIP (n = 46) and CPFE/non-UIP (n = 11) groups. Patients with primary lung cancer and acute exacerbation (AE) at the initial visit were excluded. In addition, Patients with following diagnoses were not included in this study: (i) connective tissue disease; (ii) drug-induced lung disease; (iii) pneumoconiosis; (iv) hypersensitivity pneumonitis; (v) sarcoidosis.

The diagnosis of IPF was made by a multidisciplinary clinic-radiological-pathological review of the patient data. The diagnosis of emphysema was based on upper lobe predominant and scattered distribution of low attenuation areas on chest HRCT, either no wall or with wall of less than 1 mm in thickness. Based on these findings, CPFE was defined as ≥ 10% emphysema and pulmonary fibrosis on chest HRCT by modified criteria proposed by Ryerson, et al. (6).

AE of IPF was diagnosed by criteria proposed by Collard et al. (11) and all of the following 4 conditions must be satisfied: i) unexplained worsening or development of dyspnea within 30 days; ii) chest HRCT scan with new bilateral ground-glass opacities and/or consolidation superimposed on a background reticular or honeycombing pattern; iii) no evidence of pulmonary infection by bronchoalveolar lavage or endotracheal aspiration or sputum culture, in combination with negative blood tests for other potentially infectious pathogens (e.g. Pneumocystis jiroveci, Cytomegalovirus) exclusion of left heart failure, pulmonary embolism and alternative causes for acute lung injury.

The Ethics Committee of the Toho University Omori Medical Center approved this study (approval number 19-54).

Measurement of the levels of the serum markers

The serum level of Krebs vonden Lungen-6 (KL-6) (normal < 500 U/ml) was measured by an enzyme-linked immunosorbent assay (ELISA) using the ELTEST KL-6 kit (Eisai, Tokyo, Japan), and that of SP-D (normal < 110 ng/ml) was measured by a commercial ELISA kit (Yamasa, Tokyo, Japan).

Chest CT scan

Chest CT scans were performed by a helical CT scanner (Aquilion 16, Toshiba, Tokyo, Japan). Routine scanning of the entire lung was performed with slice thicknesses of 5-10 mm, followed by HRCT images at full inspiration with 1-2 mm section thicknesses (120 kVp, 300 mA, pitch 1.0). HRCT images were photographed with a window setting appropriate for the lungs (window level from -600 Hounsfield Units [HU]; width from 1600 HU) for all patients.

Upper, middle, and lower lung fields were defined as the area of the lung above the level of the tracheal carina, below the level of the inferior pulmonary vein, and between the upper and lower fields, respectively. The extent of lung fibrosis was calculated as reticular abnormalities in each of the 6 fields and then summed (12). The presence of emphysema was assessed in each patient according to the methods by Ryerson et al. (6). A consensus reading of the CT images was analyzed independently by 2 pulmonologists (K.S., S.H.) and 1 radiologist (A.K.).

Pulmonary function test

Spirometry and the measurement of diffusing capacity for carbon monoxide (DLco) were performed using a pulmonary function test (PFT) system (Chestac-33, CHEST Co. Ltd., Tokyo, Japan). The diffusion capacity was measured by the single breath technique. The composite physiologic index (CPI) was calculated by the following formula: {91 – (0.65 x percent predicted DLco) – (0.53 x percent predicted forced vital capacity (FVC)) + (0.34 x percent predicted forced expiratory volume in 1 s (FEV_1))} (13).

Doppler echocardiography

The estimated systolic pulmonary arterial pressure (esPAP) was calculated from measurements using transthoracic Doppler echocardiography with room air by specific technicians. The transtricuspid pressure gradient was calculated using the modified Bernoulli equation and was considered to be equal to the equal to the esPAP in the absence of right ventricular outflow obstruction: esPAP = transtricuspid pressure gradient + right atrial pressure.

Statistical analysis

Data were expressed as mean ± standard deviation. Statistical analysis for continuous data between 2 groups was performed using the Wilcoxon rank sum test or the Student *t* test, as appropriate. When categorical variables were compared, the chi-square test and Fisher's exact test were used, as appropriate. The optimal cut-off value of CPI threshold for the analysis of prognostic factors in CPFE patients, which can discriminate survivors from non-survivors, was derived from the receiver operating characteristic (ROC) curve. Cox proportional hazard models were used to identify significant variables predicting survival. Variables selected by univariate analysis ($p < 0.05$) were evaluated in the multivariate analysis. To avoid multicollinearity, only one of the highly correlated variables (Pearson's correlation coefficient ≥ 0.8) was to be entered in the multivariate model, if present. The incidence of AE was obtained from the Kaplan-Meier survival curve by treating AE as the death variable. Survival was calculated by the Kaplan-Meier method and the log rank test. A p-value < 0.05 was regarded as statistically significant. Data analyses were performed using statistical software (JMP, version 10.0.0, SAS Institute, Cary, NC, USA).

Results

Comparison of baseline clinical characteristics, pulmonary function tests, serum markers, esPAP, and HRCT scores

Baseline characteristics of this study are presented in Table 1 and 2.

CPFE/UIP versus CPFE/non-UIP

There were no significant differences between patients with CPFE/UIP and CPFE/non-UIP in the baseline clinical characteristics, subtypes of em-

Table 1. Baseline clinical characteristics of the study population

Variable	CPFE/UIP	CPFE/non-UIP	*P* value†	IPF alone	*P* value‡	*P* value¶
Patients n	46	11		64		
Age, yrs	72.9 ± 6.7	72.0 ± 7.3	0.671	73.6 ± 6.8	0.631	0.477
Sex, male/female	41/5	10/1	0.885	48/16	0.063	0.244
Smoking history, Current/Ever/Never	14/31/1	1/10/0	0.293	8/41/15	0.002	0.160
Smoking index#	1156 ± 688	1229 ± 899	0.766	648 ± 598	< 0.0001	< 0.0001
Histological examination	UIP, 2; probable UIP, 4	NF, 2; f-NSIP, 1		UIP, 11; probable UIP, 2		
mMRC score, (0/I/II/III/IV)	1.9±1.2 (9/4/20/9/4)	1.5±1.2 (3/3/2/3/0)	0.340	1.5±0.9 (8/28/18/8/2)	0.003	0.392
Subtypes of emphysema (CL/PS/mixed)	15/18/13	7/3/1	0.144	3/9/5		
Long-term oxygen therapy (%)	8 (17.4)	3 (27.3)	0.477	5 (7.8)	0.114	0.053
Acute exacerbation (%)	5 (10.9)	3 (27.3)	0.159	23 (35.9)	0.003	0.577
Primary lung cancer (%)	5 (10.9)	0 (0)	0.252	4 (6.3)	0.383	0.394

#Smoking index; number of cigarettes consumed per day multiplied by years of smoking. †: CPFE/UIP vs. CPFE/non-UIP, ‡: CPFE/UIP vs. IPF alone, ¶: CPFE/non-UIP vs. IPF alone
Data are presented as mean ± SD. CPFE: combined pulmonary fibrosis and emphysema, UIP: usual interstitial pneumonia, NF: nonclassifiable fibrosis, f-NSIP: fibrotic-nonspecific interstitial pneumonia, IPF: idiopathic pulmonary fibrosis, mMRC: modified Medical Research Council, CL: centrilobular, PS: paraseptal

Table 2. Comparison of pulmonary function tests, serum markers, esPAP, and radiologic scores among patients with CPFE/UIP, CPFE/non-UIP, and IPF alone

Variable	CPFE/UIP (n = 46)	CPFE/non-UIP (n = 11)	*P* value†	IPF alone (n = 64)	*P* value‡	*P* value¶
FVC % predicted	88.6 ± 22.2	89.2 ± 23.9	0.945	74.0 ± 18.6	0.0004	0.019
FEV_1/FVC, %	77.3 ± 10.2	79.9 ± 9.1	0.454	88.6 ± 22.2	< 0.0001	0.018
FEV_1 % predicted	98.2 ± 21.5	103.7 ± 36.5	0.521	91.1 ± 20.9	0.087	0.107
DLco % predicted	52.6 ± 17.5	56.4 ± 16.3	0.507	52.8 ± 18.3	0.947	0.535
DLco/VA, %	54.6 ± 13.9	57.7 ± 19.9	0.558	70.3 ± 18.1	< 0.0001	0.043
CPI	44.4 ± 16.8	38.9 ± 9.8	0.318	50.2 ± 14.9	0.058	0.021
KL-6, U/ml	955 ± 646	1368 ± 636	0.061	1097 ± 613	0.243	0.182
SP-D, ng/ml	192 ± 133	260 ± 158	0.150	248 ± 155	0.051	0.816
esPAP, mmHg	32.1 ± 10.9	33.5 ± 11.6	0.711	31.1 ± 8.9	0.608	0.440
Fibrosis score	12.3 ± 4.6	8.5 ± 3.8	0.013	16.7 ± 2.8	< 0.0001	< 0.0001
Emphysema score	22.1 ± 9.8	23.2 ± 8.4	0.745	5.5 ± 1.6	< 0.0001	< 0.0001

Data are presented as mean ± SD.
†: CPFE/UIP vs. CPFE/non-UIP, ‡: CPFE/UIP vs. IPF alone, ¶: CPFE/non-UIP vs. IPF alone
CPFE: combined pulmonary fibrosis and emphysema, UIP: usual interstitial pneumonia,
IPF: idiopathic pulmonary fibrosis, FVC; forced vital capacity, FEV_1; forced expiratory volume in 1 s, DLco; diffusing capacity for carbon monoxide, DLco/VA; diffusing capacity divided by the alveolar volume, CPI: composite physiologic index, KL-6: Kreb von den Lungen-6, SP-D: surfactant protein D, esPAP: estimated systolic pulmonary arterial pressure

physema, pulmonary function tests, serum markers, esPAP value. However, the level of fibrosis score was significantly higher in patients with CPFE/UIP than in those with CPFE/non-UIP.

CPFE/UIP or CPFE/non-UIP versus IPF alone

The smoking history, smoking index values, and mMRC score values were significantly higher in patients with CPFE/UIP than in those with IPF alone. The incidence of AE at a 3-year and 5-year in patients with CPFE/UIP was significantly lower than those with IPF alone {AE/3y: 28.1% vs. 10.5%, P = 0.012, AE/5y: 43.4% vs. 17.9%, P = 0.028}. Baseline values of % FVC in CPFE/UIP and

CPFE/non-UIP patients were significantly higher than those in IPF alone, whereas % FEV_1/FVC and % DLco/VA were significantly lower for CPFE/UIP and CPFE/non-UIP patients, respectively. In addition, CPFE/UIP patients had significantly a greater decrease of CPI compared with IPF alone patients. The fibrosis score was significantly lower in patients with CPFE/UIP and CPFE/non-UIP than in those with IPF alone, respectively.

Survival and prognostic factors

Survival time was significantly shorter in patients with CPFE/UIP than in those with CPFE/non-UIP and IPF alone, respectively (CPFE/UIP vs. CPFE/non-UIP; P = 0.011, CPFE/UIP vs. IPF alone; P = 0.043) (Figure. 1). With regard to prognostic factors for CPFE patients, the univariate Cox proportional hazard regression model revealed the presence of honeycombing, UIP pattern, an increase in esPAP, fibrosis score, and CPI, a decrease in % FVC, % FEV_1, and % DLco (Table 3). In the multivariate Cox proportional hazard regression model, UIP pattern (HR 10.528, 95% CI 1.979-92.934; P = 0.004) and the CPI (HR 1.281, 95% CI 1.012-1.655; P = 0.039) were selected as most significant (Table 3). Next, to identify the optimal cut-off value of CPI for outcome in CPFE patients, multiple ROCs analysis were performed using threshold values (range, 30-70 points). As a result, CPI thresholds of 45 provided the greatest prognostic separation in patients with CPFE (AUC; 0.792, 95% CI; 0.664-0.879) (Table 4). Thus, we classified these patients into 4 groups; CPFE/UIP with high-CPI (CPI ≥ 45), CPFE/UIP with low-CPI (CPI < 45), CPFE/non-UIP with high-CPI, and CPFE/non-UIP with low-CPI. Survival in CPFE/UIP with high-CPI was significantly worse than that in the other 3 subgroups (P < 0.0001) (Figure. 2).

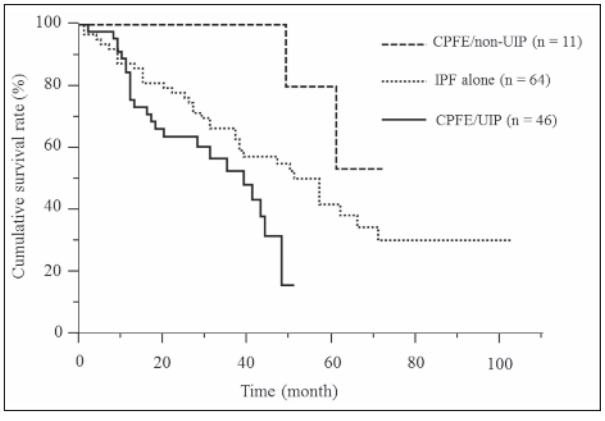

Fig. 1. The Kaplan-Meier survival curve in the patients with idiopathic pulmonary fibrosis (IPF) alone, combined pulmonary fibrosis and emphysema/usual interstitial pneumonia (CPFE/UIP), and CPFE/non-UIP.
Survival time was significantly shorter in patients with CPFE/UIP than in those with CPFE/non-UIP and IPF alone, respectively (CPFE/UIP vs. CPFE/non-UIP; P = 0.011, CPFE/UIP vs. IPF alone; P = 0.043)

Table 3. Prognostic factors for mortality of patients with CPFE using Cox proportional hazards regression models

Parameters	HR (95% CI)	P value
Univariate analysis		
Age, yrs	1.008 (0.947-1.076)	0.799
Male sex	0.692 (0.232-2.964)	0.573
mMRC	1.279 (0.916-1.819)	0.150
UIP pattern	5.929 (1.624-38.583)	0.005
esPAP, mmHg, per 10 mmHg	1.549 (1.064-2.281)	0.022
FVC % predicted, per 10%	0.662 (0.562-0.774)	< 0.0001
FEV_1 % predicted, per 10%	0.756 (0.606-0.933)	0.009
DLco % predicted, per 10%	0.620 (0.447-0.832)	0.001
Emphysema score	1.015 (0.974-1.053)	0.472
Fibrosis score	1.141 (1.990-50.611)	0.004
CPI, per 5 points	1.495 (1.273-1.783)	< 0.0001
Multivariate analysis		
UIP pattern	10.528 (1.979-92.934)	0.004
CPI, per 5 points	1.281 (1.012-1.655)	0.039

CI: confidence interval, mMRC: modified Medical Research Council, UIP; usual interstitial pneumonia, esPAP: estimated systolic pulmonary arterial pressure, FVC; forced vital capacity, FEV_1; forced expiratory volume in 1 s, DLco; diffusing capacity for carbon monoxide, CPI: composite physiologic index

Comparison of baseline patient characteristics between high-CPI versus low-CPI group

There were no significant differences in age, sex, smoking history, the presence of honeycombing, and UIP pattern between the 2 groups. However, baseline values of % FVC, % FEV_1, % DLco, and % DLco/VA in CPFE patients with CPI ≥ 45 were significantly lower than those in CPFE patients with CPI < 45, whereas % FEV_1 / FVC, KL-6, esPAP, fibrosis score, and emphysema score were significantly higher for CPFE patients with CPI ≥ 45 (Table 5).

Table 4. Sensitivity, specificity, positive predictive value, and negative predictive value for prognostic factors

Variable	AUC	95% CI	Sensitivity	Specificity	PPV	NPV	*P* value
CPI ≥ 30	0.646	0.538-0.740	91.7	37.5	51.6	86.1	0.022
CPI ≥ 35	0.729	0.602-0.828	83.3	62.5	61.8	83.7	0.001
CPI ≥ 40	0.776	0.648-0.867	83.3	71.9	68.3	85.6	0.0002
CPI ≥ 45	0.792	0.664-0.879	83.3	75.0	70.8	86.1	< 0.0001
CPI ≥ 50	0.750	0.619-0.847	62.5	87.5	78.4	76.2	0.0003
CPI ≥ 55	0.714	0.597-0.807	45.8	96.9	91.5	71.1	0.003
CPI ≥ 60	0.630	0.528-0.722	29.2	96.9	87.3	65.3	0.022
CPI ≥ 65	0.568	0.485-0.647	16.7	96.9	79.7	61.5	0.114
CPI ≥ 70	0.547	0.472-0.619	12.5	96.9	74.6	60.4	0.211

Data of sensitivity, specificity, PPV, and NPV expressed as percentages, AUC: area under curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, CPI: composite physiologic index

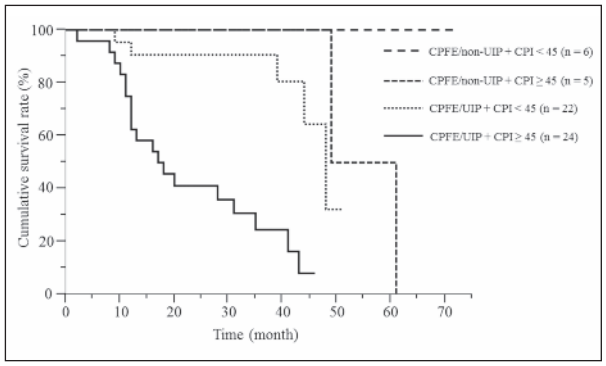

Fig. 2. The Kaplan-Meier survival curve in subgroups of combined pulmonary fibrosis and emphysema (CPFE); CPFE/usual interstitial pneumonia (UIP) with high-CPI (composite physiological index) (CPI ≥ 45), CPFE/UIP with low-CPI (CPI < 45), CPFE/non-UIP with high-CPI, and CPFE/non-UIP with low-CPI. Survival in CPFE/UIP with high-CPI was significantly worse than that in the other 3 subgroups ($P < 0.0001$)

Causes of death

The most frequent cause of death was pulmonary infection in CPFE/UIP [7 of 23 deaths (29.2%)], right heart failure in CPFE/non-UIP [2 of 2 deaths (100%)], and AE in IPF alone [15 of 35 deaths (42.9%)], respectively. In particular, the mortality due to AE in IPF alone was significantly higher than that in CPFE/UIP ($P = 0.034$) (Table 6).

Discussion

This is the first report that demonstrated differences of clinical features and outcomes in 2 subtypes of CPFE divided distinctly UIP pattern and non-UIP pattern on chest HRCT.

The reasons for the coexistence of pulmonary emphysema and pulmonary fibrosis are still unclear. Furthermore, whether CPFE represents a unique disorder entity or a coexistence of 2 pulmonary disorders related to cigarette smoking remain obscure. However, cigarette smoking or dust exposure such as asbestos has been thought as a risk factor for both IPF and pulmonary emphysema (14, 15), and that IPF is often mixed with emphysema is known. Therefore, the pathogenesis and development of CPFE may be linked with genetic susceptibility factors in addition to environmental triggers such as cigarette smoking or dust exposure (16, 17).

In 1990, Wiggins et al. (18) reported 8 patients with the combination of emphysema and pulmonary fibrosis which had emphysema in the upper lobes and fibrosis in the lower lobes on chest HRCT. It was also recognized that during its natural history IPF is sometimes associated with emphysema and bullae in the upper lobes, and such cases were classified as a subtype of IPF in Japan (19). In 2005, Cottin et al. (1) termed this condition"CPFE"and characterized for the first time. Most studies reported that CPFE was characterized as predominantly male, a history of cigarette smoking, relatively preserved spirometric values, and severe reduced DLco (2-6). While our data indicated similar clinical features between CPFE/UIP and CPFE/non-UIP, the incidence of AE at a 3-year and 5-year in patients with CPFE/UIP was significantly lower than in those with IPF alone. In addition, complication of AE was not of prognostic significant in CPFE from the statistical analysis. Most importantly, the Kaplan-Meier analysis demonstrated that CPFE/UIP had worse survival when compared to CPFE/non-UIP and IPF alone. Therefore, we suppose that

Table 5. Comparison of baseline patient characteristics between high-CPI group versus low-CPI group

	CPI ≥ 45 (n = 29)	CPI <45 (n = 28)	*P* value
Age, yrs	73.9 ± 7.2	71.6 ± 6.2	0.213
Sex, male/female	24/5	27/1	0.093
Smoking history, Current/Ever/Never	5/23/1	10/18/0	0.196
mMRC score, 0/I/II/III/IV	1/3/15/7/3	9/4/8/5/2	0.057
FVC % predicted	74.3 ± 17.7	103.7 ± 15.9	< 0.0001
FEV_1/FVC, %	82.8 ± 9.0	73.1 ± 8.4	0.0001
FEV_1 % predicted	89.9 ± 20.2	103.8 ± 20.0	0.011
DLco % predicted	43.0 ± 10.9	64.6 ± 13.8	< 0.0001
DLco/VA, %	48.0 ± 10.4	61.3 ± 16.0	0.001
KL-6, U/ml	1259 ± 679	802 ± 559	0.008
SP-D, ng/ml	238 ± 158	172 ± 111	0.072
esPAP, mmHg	36.7 ± 11.1	27.8 ± 9.0	0.002
Fibrosis score	13.2 ± 4.7	9.9 ± 4.1	0.007
Emphysema score	25.2 ± 10.6	19.3 ± 7.2	0.018
Honeycombing (%)	19 (65.5)	15 (53.6)	0.358
UIP pattern (%)	24 (82.8)	22 (78.6)	0.689

Data are presented as mean ± SD.
CPI: composite physiologic index, mMRC; modified Medical Research Council, FVC; forced vital capacity, FEV_1; forced expiratory volume in 1 s, DLco; diffusing capacity for carbon monoxide, DLco/VA; diffusing capacity divided by the alveolar volume, KL-6: Kreb von den Lungen-6, SP-D: surfactant protein D, esPAP: estimated systolic pulmonary arterial pressure, UIP: usual interstitial pneumonia

Table 6. Comparison of causes of death among patients with CPFE/UIP, CPFE/non-UIP, and IPF alone

Causes	CPFE/UIP	CPFE/non-UIP	IPF alone	*P* value[#]
Mortality, n	24	2	35	
Pulmonary infection	7 (29.2)	0 (0)	7 (20.0)	0.416
Acute exacerbation	4 (16.7)	0 (0)	15 (42.9)	0.034
Respiratory failure	3 (12.5)	0 (0)	5 (14.3)	0.844
Primary lung cancer	2 (8.3)	0 (0)	2 (6.7)	0.816
Right heart failure	2 (8.3)	2 (100)	0 (0)	0.082
Others	2 (8.3)[†]	0 (0)	4 (11.4)[‡]	0.699
Unknown	4 (17.4)	0 (0)	2 (5.7)	0.172

Data are presented as number. (%).
[#]: CPFE/UIP vs. IPF alone
[†]Acute myocardial infarction; 1, Liver failure; 1
[‡]Liver failure; 1, Pneumothorax; 1, Gastric cancer; 1, Left heart failure; 1

CPFE would be recognized as a distinct disorder entity.

On the other hand, prognosis of CPFE has been described to be better or worse than that of those with pulmonary fibrosis alone (2-6). The main reasons for these conflicting results is unclear, but may be affected by including proportion of non-IPF such as NSIP, desquamative interstitial pneumonia (DIP), or respiratory bronchiolitis with interstitial lung disease (RB-ILD), a variety of emphysema subtypes such as paraseptal, centrilobular, or mixed type, and influence of retrospective study.

Furthermore, previous studies have used different percentage of emphysema. The percentage of emphysema of CPFE in our study was equal to definition used by Mejia et al. (4) and Ryerson et al. (6) (total emphysema score at a threshold of ≥ 10%). We demonstrated that the presence of UIP pattern on chest HRCT and high-CPI (CPI ≥ 45) were the strongest predictors of survival in patients with CPFE. In addition, clinical features of CPFE patients with CPI ≥ 45 had advanced pulmonary emphysema and fibrosis associated with increased esPAP and severe decreased DLco.

As proposed by Wells et al. (13), the CPI was developed to improve on previous prognostic indicators in IPF and also predicted mortality than the individual pulmonary function tests in IPF with emphysema. Moreover, Lasti et al. (20) reported that the CPI was the strongest determinant of survival in

IPF/UIP and NSIP. However, Schmidt et al. (21) described that CPI was not an effective longitudinal measure in IPF patients with moderate to severe emphysema and change in FEV_1 appeared to be the best predicting factor for mortality. Furthermore, they speculated that FEV_1 and FVC have opposite effects on the CPI, resulting in keeping balance. Future prospective research will be needed to address whether CPI values in CPFE are associated with mortality or not.

Indeed, patients with possible UIP may often include a differential diagnosis of f-NSIP, chronic hypersensitivity pneumonitis, or smoking related lung disease (e.g. DIP, RB-ILD). In contrast, some cases can be diagnosed as having histological UIP, nevertheless chest HRCT appearances are apparently inconsistent with UIP. Expert interpretation of chest HRCT images and multidisciplinary discussion will be essentially required to make a more precise diagnosis. However, we think that it is difficult to be certain about a robust definite diagnosis in clinical practice. In spite of a few disadvantages, this study found that CPFE patients with a UIP pattern on chest HRCT had significantly worse survival compared to those with a non-UIP pattern. Therefore, we believe that this simplified classification would be very useful in clinical practice. More important approaches may be to observe carefully and determine patterns of disease behavior in each case according to ATS/ERS update of classification of the idiopathic interstitial pneumonias (22).

The limitations of this study are as follows. Firstly, there is a lack of serial changes in physiological parameters in the analysis. Recently, Schmidt et al. (21) reported that longitudinal changes in FEV_1 predict survival. However, serial changes in physiology cannot be measured at initial diagnosis. Predicting survival from parameters at diagnosis is very important. Secondly, most of CPFE patients were not able to diagnose pathologically. However, we believe that surgical lung biopsy is rarely performed because they have severe cardiopulmonary damages. Thirdly, the threshold of 45 for CPI established by our study may be different in other studies. However, this does not influence our results that patients with high-CPI were significantly poorer than those with low-CPI. Moreover, stratification of these patients is crucial for clinical practice in order to evaluate the prediction of refractory disorders. Finally, this was a retrospective study at a single center and included a relatively small number of patients. Therefore, our results may not be representative of the entire CPFE population. In the future, prospective studies of larger series are needed to confirm our results.

Our results demonstrated that patients with CPFE/UIP have a worse prognosis than those with CPFE/non-UIP. In particular, CPFE/UIP patients associated with high-CPI have an extremely poor prognosis.

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Author Contributions

KS: study design, data analysis/HRCT scoring and interpretation, manuscript drafting

SH: study design and conception, data analysis and interpretation, manuscript proofing

KS, NY, TI, TI, SS: data collection, data analysis

All authors read and approved the final manuscript.

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