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Coexistent emphysema delays the decrease of vital capacity in idiopathic pulmonary fibrosis

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Received 7 September 2008; accepted 2 February 2009

Available online 28 February 2009

KEYWORDS

Idiopathic pulmonary fibrosis;
Pulmonary emphysema;
Respiratory function;
Vital capacity;
Diffusing capacity

Summary

Although previous authors have reported single data point, yearly changes in respiratory function have not been examined in combined pulmonary fibrosis and emphysema (CPFE). To quantify the annual changes in respiratory function of patients with CPFE and to examine the difference in survival between CPFE patients and patients with idiopathic pulmonary fibrosis without emphysema (IPF alone), 26 patients with CPFE and 33 IPF alone patients, whose respiratory function had been monitored for at least a year, were selected. The baseline of vital capacity percent predicted (VC% pred) in CPFE patients was greater than that in IPF-alone patients ($86.6 \pm 24.0\%$ vs. $72.8 \pm 19.4\%$, $p = 0.018$). The annual decrease in VC% pred was significantly less in CPFE patients than in IPF-alone patients ($-1.2 \pm 4.8\%$ vs. $-8.0 \pm 7.4\%$, $p < 0.001$). Baseline ratio of forced expiratory volume in one second to forced vital capacity (FEV₁/FVC%) in CPFE patients was lower than that in IPF-alone patients ($76.6 \pm 8.5\%$ vs. $85.2 \pm 6.7\%$, $p < 0.001$). In the CPFE group, FEV₁/FVC% tended to decrease with time ($-0.5 \pm 2.2\%$ per year), but, in contrast, it increased in IPF-alone patients ($+1.1 \pm 3.4\%$ per year) ($p = 0.036$). Baseline of diffusing capacity percent predicted (DLco% pred) was significantly lower in CPFE patients than in IPF-alone patients ($45.3 \pm 15.0\%$ vs. $60.7 \pm 19.8\%$, $p = 0.003$). The annual decrease in DLco% pred was lower in CPFE patients than in IPF-alone patients ($-3.7 \pm 7.9\%$ vs. $-10.7 \pm 8.8\%$, $p = 0.042$). There was no significant difference in the survival duration between 26 CPFE and 33 IPF-alone patients according to Kaplan–Meier analysis.

Ventilatory and gas-exchange deterioration during the course of IPF became mild when emphysema was coexistent.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial pneumonia with the histology of usual interstitial pneumonia (UIP).^{1–3} Steroid treatment minimally improves pulmonary function and the prognosis is poor.^{1,3–8} Combined pulmonary fibrosis and emphysema (CPFE) has been described previously.^{9–13} Smoking is associated with the pathogenesis and development of pulmonary emphysema, especially emphysema of the upper lobes of the lungs,¹⁴ and has been identified as a risk factor for IPF.³

Although the combination of pulmonary emphysema and fibrosis may be incidental in smokers, recent studies have identified common pathways of cellular and molecular activation that result in different morphological and physiological outcomes. Smad3 is considered a key molecule linking fibrosis with emphysema.¹⁵ Smad3-null mice, deficient in TGF- β signal transmission, are resistant to bleomycin- and TGF- β -mediated fibrosis but spontaneously develop age-related air-space enlargement, which is consistent with emphysema, and lack the ability to repair tissue damage appropriately.¹⁵ TNF α ,¹⁶ IL-1 β ,¹⁷ MMP-12,¹⁸ VEGF,^{19,20} and PDGF²¹ have been reported to be responsible for the pathogenesis and development of both pulmonary fibrosis and emphysema.

In CPFE, the decrease in diffusing capacity (DLco) is substantial because of the additive effect of emphysema and fibrosis. A decrease in lung volume in IPF is associated with decreased compliance and increased flow rates. An increase in lung volume in emphysema is associated with increased compliance and decreased flow rates due to expiratory flow limitation and air trapping. When pulmonary fibrosis and emphysema are coexistent, ventilatory function appears normal because of their opposing effects²² mentioned above. Previous authors have reported single data point in CPFE, but yearly changes in respiratory function have not been examined.

We retrospectively enrolled patients with IPF and compared vital capacity (VC), the ratio of forced expiratory volume in one second to forced vital capacity (FEV₁/FVC%), total lung capacity (TLC), carbon monoxide diffusing capacity (DLco), and DLco/VA (transfer factor) between patients with CPFE and patients with IPF but no emphysema (IPF alone). Time-dependent fluctuations in ventilatory and gas-exchange functions in the two disorders are reported herein.

An additional aim of our study was to determine the prognosis for IPF patients with or without emphysema. Kaplan–Meier survival curves were compared between the two groups of patients.

Materials and methods

Patient population

We reviewed medical files of all patients admitted to the Department of Respiratory Medicine at Fukuoka University Hospital from 1988 to 2007 and identified those who were diagnosed with IPF at discharge. Of this subset of patients, 55 who met the following criteria were classified as IPF patients without emphysema (IPF-alone group): 1) presence of dyspnea of insidious onset; 2) a computed tomography

(CT) scan showing patterns compatible with IPF, including bilateral reticular opacities and/or honeycombing of a predominantly peripheral, subpleural, and basal location, as main findings, as proposed by the American Thoracic Society (ATS) and the European Respiratory Society (ERS),¹ but no evidence of well-demarcated areas of low attenuation typical of emphysema; 3) impaired ventilatory capacity as indicated by measurements of VC or TLC and/or impaired diffusing capacity (decreased DLco); and 4) absence of known causes of pulmonary fibrosis such as collagen vascular disease, hypersensitivity pneumonitis, and drug-induced lung disease.

Thirty-two patients who met the following criteria were categorized as CPFE patients: 1) as for criterion 1) for IPF-alone patients; 2) a CT scan showing well-demarcated areas of low attenuation typical of emphysema located predominantly in the upper lung zones and patterns compatible with IPF (as for IPF-alone patients); 3) as for criterion 3) for IPF-alone patients; and 4) as for criterion 4) for IPF-alone patients.

Among these patients, 33 IPF-alone and 26 CPFE patients who had undergone repeated respiratory function tests for at least a year were selected for further analysis.

The Fukuoka University Hospital review board approved the study and waived the requirement for informed consent.

Clinical data

Records of clinical data such as sex, age, and smoking in pack-years were reviewed to identify differences between the characteristics of the CPFE and IPF-alone groups. The duration of the follow-up period was estimated from the interval between the first and last visits to our clinic or between the first visit to our clinic and death. Death of the patients who had left our hospital was determined by the telephone call to their families or the next hospitals they visited. If the patients were alive, the follow-up period was from their first visit of our hospital to the time of the telephone call.

Interstitial pneumonia pattern according to chest CT

Chest CT patterns of interstitial pneumonia were divided into two patterns with the reference to the classification by Sumikawa et al.²³; one was definite UIP pattern and the other was the pattern consistent with UIP.

- 1) Definite UIP: The CT was classified as definite UIP when CT scans showed honeycombing in a predominantly peripheral and basal distribution.
- 2) Consistent with UIP: The CT was classified as consistent with UIP when it demonstrated a reticular pattern in a predominantly peripheral and basal distribution but only minimal or no honeycombing, or when the extent of honeycombing in the upper lobes was almost similar to that in the lower lobes, but honeycombing was peripherally distributed. The CT scan was also classified as consistent with UIP when honeycombing dominantly existed in the lower lobes, but it was distributed not only in the peripheral zone but also in the inner zone.

Emphysema pattern according to chest CT

Pulmonary emphysema detected by chest CT was categorized as centrilobular, panlobular, or paraseptal.²⁴

Respiratory function parameters

Forced expiratory volume in one second (FEV₁) and VC were measured using spirometry conducted with the patient in a seated position. Results are expressed as absolute values (mL) and as percentages of predicted values (% pred) calculated using Baldwin's formulae²⁵ adjusted according to sex, height, and age. TLC, functional reserve capacity (FRC), residual volume (RV), and RV/TLC were measured using the helium gas dilution method and DLco and DLco/VA (transfer factor) were measured using the single-breath-holding method.²⁶ Predicted values for each lung volume parameter were estimated using Grimby's formula²⁵ and predicted values for DLco and DLco/VA were estimated using Burrows' formula.²⁷ These data were expressed as absolute values (mL) and/or percentages of predicted values.

Baseline and follow-up respiratory function data

Respiratory function tests were repeated during the course of the study. Baseline respiratory function was estimated from the first tests conducted at our hospital. To estimate the annual change in pulmonary function, we used data from patients who had undergone pulmonary function tests at least twice during a follow-up period of one year or more. Annual changes in pulmonary function were estimated from linear regressions, assuming time-dependency and linearity.

Survival

Survival curves were determined using the Kaplan–Meier method not only for the 26 CPFE and 33 IPF-alone patients with repeated respiratory function tests but also for all patients in this study (32 CPFE and 55 IPF-alone patients).

Statistical analysis

Numerical variables are expressed as means and standard deviations. The baseline values and changes per year in VC, FEV₁/FVC%, TLC, FRC, RV, DLco, and DLco/VA of the CPFE and IPF-alone groups were compared using unpaired *t*-test. Categorical variables such as sex, smoking history, and steroid treatment were evaluated using Fisher's exact test. Survival analysis was performed using the Kaplan–Meier method and the log-rank test. Null-hypothesis probability values of <0.05 were considered significant.

Results

Patient characteristics

Patient characteristics of the 26 CPFE and 33 IPF-alone patients are summarized in Table 1. The follow-up period after the first visit did not differ significantly between the CPFE and IPF-alone patients (4.67 ± 2.15 years vs. 3.73 ± 2.42 years, respectively, *p* = 0.126).

Eight patients in the IPF-alone group and two in the CPFE group denied their smoking history. The pack-year for the CPFE group (54.9 ± 38.7) was significantly greater than that for the IPF-alone group (30.2 ± 33.1) (*p* = 0.011). When patients who had never smoked were excluded from the analysis, the pack-year for the CPFE group (59.5 ± 36.7) was not significantly greater than that for the IPF-alone group (39.9 ± 32.5) (*p* = 0.053).

The body mass index (BMI) of CPFE patients (24.0 ± 3.4) was significantly greater than that of IPF-alone patients (22.0 ± 3.4) (*p* = 0.027).

There were no significant differences between CPFE and IPF-alone patients in the number of patients who were administered steroids or who were histologically diagnosed by surgical lung biopsy and/or autopsy.

Interstitial pneumonia patterns according to chest CT

As CT films were not available in three patients with IPF alone and two with CPFE, we considered these patients as those with UIP from the comments by radiologists in the medical records, and they were not included in the IPF sub-classification. After excluding patients with IPF alone or CPFE pathologically confirmed by surgical lung biopsy and/or autopsy and patients whose CT films were not available, 16 CPFE and 18 IPF-alone patients were categorized according to the interstitial pneumonia patterns on chest CT. Of the 16 CPFE patients, 13 were categorized as definite UIP, and 3 were as consistent with UIP. Of the 18 IPF-alone patients, 11 were categorized as definite UIP, and 7 were as consistent with UIP.

Emphysema patterns according to chest CT

As the CT films of two CPFE patients were not available, CPFE diagnosis was dependent on comments made by

Table 1 Clinical features of 26 CPFE and 33 IPF-alone patients.

	CPFE (<i>n</i> = 26)	IPF alone (<i>n</i> = 33)	<i>p</i> values
Male/female	23/3	22/11	0.100 ^a
Age at first visit	65.1 ± 8.5	66.5 ± 9.2	0.531 ^b
Follow-up periods (years)	4.67 ± 2.15	3.73 ± 2.42	0.126 ^b
Patients with/without smoking history	24/2	25/8	0.183 ^a
Pack-year for all patients	54.9 ± 38.7	30.2 ± 33.1	0.011 ^b
Pack-year for patients with smoking history	59.5 ± 36.7 (<i>n</i> = 24)	39.9 ± 32.5 (<i>n</i> = 25)	0.053 ^b
Body mass index	24.0 ± 3.4	22.0 ± 3.4	0.027 ^b
Patients with/without steroid treatment	10/16	15/18	0.589 ^a
Patients with surgical lung biopsy and/or autopsy	8	12	0.751 ^a

Continuous values show means and standard deviations.

^a Fisher's exact test.

^b unpaired *t*-test.

radiologists in their medical records. These two patients were not included in the emphysema sub-classification.

Thirteen of 24 patients had paraseptal emphysema as the dominant pattern (Fig. 1) with centrilobular emphysema as a minor component. One patient had paraseptal emphysema alone without centrilobular emphysema. Ten patients had centrilobular-dominant emphysema (Fig. 2) with paraseptal emphysema as a minor component.

Respiratory function data

Baseline data

Both VC absolute volume and VC% pred were significantly greater in the CPFE group (2823 ± 844 mL and $86.6 \pm 24.0\%$) than in the IPF-alone group (2220 ± 768 mL and $72.8 \pm 19.4\%$) ($p = 0.006$ and 0.018 , respectively). FEV₁/FVC% in CPFE patients ($76.6 \pm 8.5\%$) was significantly less than in IPF-alone patients ($85.2 \pm 6.7\%$) ($p < 0.001$). TLC absolute volume was significantly greater in the CPFE group (4236 ± 1014 mL) than in the IPF-alone group (3472 ± 921 mL) ($p = 0.005$). However, TLC% pred did not differ significantly between the CPFE and IPF-alone groups ($78.2 \pm 17.4\%$ vs. $70.0 \pm 16.4\%$, respectively, $p = 0.070$). Both DLco% pred and DLco/VA% pred were significantly lower in the CPFE group ($43.5 \pm 15.0\%$ and $51.8 \pm 3.8\%$) than in the IPF-alone group ($60.7 \pm 19.8\%$ and $80.1 \pm 23.2\%$) ($p = 0.003$ and $p < 0.001$, respectively) (Table 2).

Changes per year

The duration of the follow-up periods for measurement of VC in the CPFE (3.07 ± 1.86 years) and IPF-alone groups (2.48 ± 1.14 years) was not significantly different between the groups ($p = 0.139$). During the follow-up period, VC was measured 7.6 ± 5.4 times in CPFE patients and 8.7 ± 7.7 times in IPF-alone patients; there was no significant difference between the groups. The number of measurements of lung volume parameters (TLC, FRC, and RV) during the follow-up periods for the CPFE and IPF-alone groups were 6.1 ± 3.6 and 6.2 ± 3.3 , respectively, without significant difference. The number of measurements of DLco in CPFE group (3.3 ± 2.0) was smaller than that in IPF-alone group (5.7 ± 3.6), but not to a significant extent ($p = 0.054$).

The annual decreases in both VC absolute volume and VC% pred were significantly less in the CPFE group (-37 ± 147 mL and $-1.2 \pm 4.8\%$) than in the IPF-alone group

(-244 ± 187 mL and $-8.0 \pm 7.4\%$) ($p < 0.001$, in both comparisons) (Table 3).

In the CPFE group, FEV₁/FVC% tended to decrease with time ($-0.5 \pm 2.2\%$ per year). In contrast, FEV₁/FVC% tended to increase in patients with IPF alone ($+1.1 \pm 3.4\%$ per year) ($p = 0.036$).

The annual decreases in both TLC absolute volume and TLC% pred in the CPFE group (-118 ± 256 mL and $-2.4 \pm 4.7\%$) were significantly less than those in the IPF-alone group (-296 ± 138 mL and $-6.0 \pm 3.1\%$) ($p = 0.014$ and 0.011 , respectively).

The annual decrease in DLco% pred in CPFE patients ($-3.7 \pm 7.9\%$) was significantly less than in patients with IPF alone ($-10.7 \pm 8.8\%$) ($p = 0.042$). However, the decrease in DLco/VA% pred per year in CPFE patients was not significantly different from that in IPF-alone patients (Table 3).

Survival

When survival rate was compared between all CPFE and IPF-alone patients in this study, patients with CPFE survived longer than those with IPF alone, according to the Kaplan–Meier analysis, although the statistical significance was marginal ($p = 0.050$) (Fig. 3).

Of the 26 patients with CPFE, nine died of the disease, 11 died of other causes (six died of lung cancer), four lived, and follow-up consultations for two were terminated because we lost them after they left our hospital. Of the 33 patients with IPF alone, 19 died of the disease, three died of lung cancer, seven lived, and follow-up consultations for four were terminated because we lost them after they left our hospital. When survival rate was compared between the 26 CPFE and the 33 IPF-alone patients, the difference was not statistically significant ($p = 0.212$) (Fig. 4).

Survival curves were also drawn and compared between males and females, patients with or without steroid treatment, and patients classified according to the median values for BMI (23.1) or pack-year (37.5). These factors did not affect survival rate.

Discussion

Technical advances in CT have facilitated the detection of small, round, low-attenuation areas suggestive of emphysema in the upper lung lobes. Chest radiographs do not

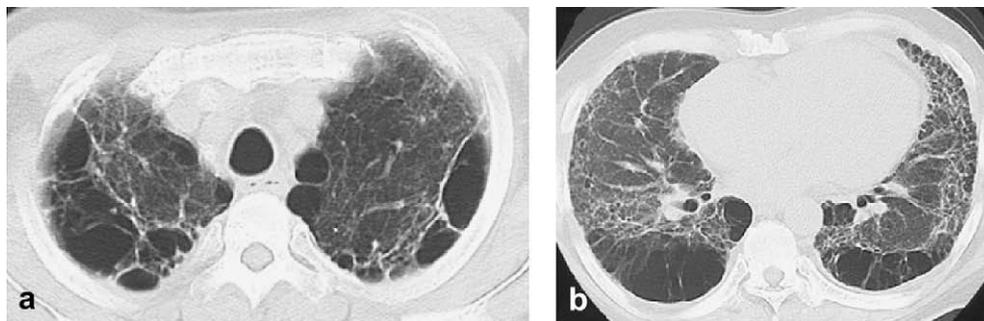


Figure 1 Chest CT of a 55-year-old man with paraseptal emphysema and definite UIP. Multiple round subpleural cystic changes suggestive of paraseptal emphysema are evident in the bilateral upper and lower lobes (panels a and b). Subpleural reticular opacity with honeycombing was noted in the bilateral lower lobes (panel b).

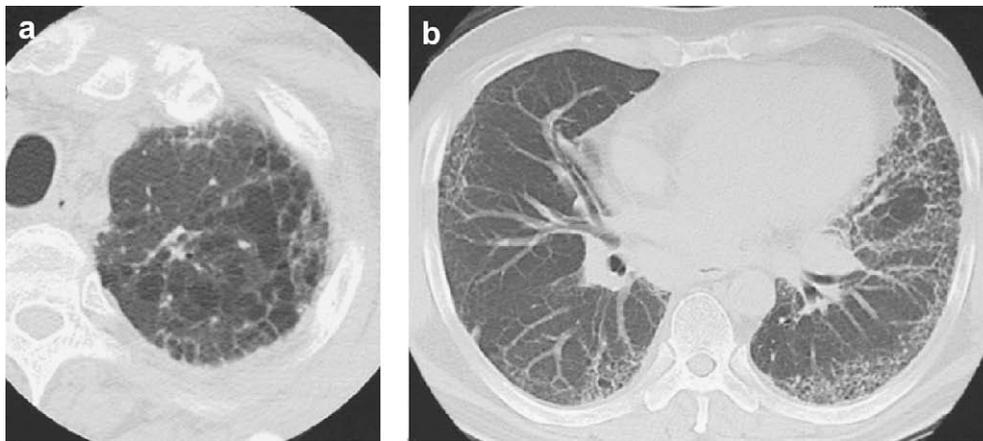


Figure 2 Chest CT of a 49-year-old man with centrilobular emphysema and pulmonary fibrosis consistent with UIP. Multiple round areas lacking recognizable walls or with thin walls are evident in the left upper lobe, which is suggestive of centrilobular emphysema (panel a). Subpleural reticular and ground-glass opacities were noted in the bilateral lower lobes, which were associated with traction bronchiectasis in the left B8 (panel b).

detect such areas. It is now known that cigarette smoking is a risk factor for idiopathic pulmonary fibrosis²⁸ as well as pulmonary emphysema.

When emphysema is combined with pulmonary fibrosis, emphysema may obscure ventilatory characteristics typical of a restrictive disease. Lung volumes of CPFE patients may be preserved whereas FEV₁ and FEV₁/FVC% may be similar to those of normal subjects because the supervening fibrosis prevents the early airway closure observed in emphysema.

The baseline ventilatory capacity characteristics of the CPFE group in our study were similar to those described by others,^{12,13,22} viz., lung volumes were relatively well preserved in CPFE patients compared with patients with IPF alone, and FEV₁/FVC% of CPFE patients appeared normal but was significantly less than that of patients with IPF alone. The baseline DLco in CPFE patients was also similar to that reported in the literature. The decrease in DLco at baseline was more advanced in CPFE patients than in patients with IPF alone, probably because of the additive effect of two disorders that both reduce diffusing capacity.

This report is the first to compare the yearly dynamics of pulmonary function parameters of CPFE patients with those

of patients with IPF alone. The most salient results were: 1) the rate of decrease of VC and TLC in CPFE patients was significantly less than that of patients with IPF alone; 2) although FEV₁/FVC% in patients with IPF alone increased gradually, it decreased in CPFE patients; and 3) the yearly rate of decrease of DLco in CPFE patients was also significantly less than that in patients with IPF alone. When fibrosis and emphysema are coexistent, ventilatory impairment is cancelled, resulting in normal-appearing lung volume. In addition, yearly decrease in lung volume is modest. Such a modest decline of ventilatory function might palliate the deterioration of ventilation-perfusion mismatch that is mainly responsible for the impaired DLco.

The prognosis of CPFE patients was better than that of IPF-alone patients when all CPFE and IPF-alone patients were included in the analysis. However, analysis of patients whose respiratory function had been monitored for at least one year showed no significant difference in the duration of survival between the two groups. This was probably a result of selection of patients who had survived long enough to undergo repeated pulmonary function tests.

Schwartz et al. showed that a high FEV₁/FVC% is associated with an adverse prognosis in patients with IPF.²⁹

Table 2 Baseline respiratory function data.

	CPFE	IPF alone	<i>p</i> values ^a
VC (absolute volume, mL)	2823 ± 844 (<i>n</i> = 26)	2220 ± 768 (<i>n</i> = 33)	0.006
VC% pred	86.6 ± 24.0 (<i>n</i> = 26)	72.8 ± 19.4 (<i>n</i> = 33)	0.018
FEV ₁ /FVC%	76.6 ± 8.5 (<i>n</i> = 26)	85.2 ± 6.7 (<i>n</i> = 33)	<0.001
TLC (absolute volume, mL)	4236 ± 1014 (<i>n</i> = 25)	3472 ± 921 (<i>n</i> = 31)	0.005
TLC% pred	78.2 ± 17.4 (<i>n</i> = 25)	70.0 ± 16.4 (<i>n</i> = 31)	0.070
FRC (absolute volume, mL)	2540 ± 751 (<i>n</i> = 25)	2224 ± 666 (<i>n</i> = 31)	0.102
FRC% pred	78.3 ± 18.9 (<i>n</i> = 25)	76.1 ± 21.8 (<i>n</i> = 31)	0.694
RV (absolute volume, mL)	1476 ± 494 (<i>n</i> = 25)	1364 ± 384 (<i>n</i> = 31)	0.340
RV% pred	74.6 ± 22.6 (<i>n</i> = 25)	76.1 ± 26.7 (<i>n</i> = 31)	0.825
DLco% pred	45.3 ± 15.0 (<i>n</i> = 23)	60.7 ± 19.8 (<i>n</i> = 30)	0.003
DLco/VA% pred	51.8 ± 3.8 (<i>n</i> = 23)	80.1 ± 23.2 (<i>n</i> = 29)	<0.001

Data show means and standard deviations.

^a unpaired *t*-test.

Table 3 Changes per year in respiratory function data.

	CPFE	IPF alone	<i>p</i> values ^a
VC (absolute volume, mL)	-37 ± 147 (n = 26)	-244 ± 187 (n = 33)	<0.001
VC% pred	-1.2 ± 4.8 (n = 26)	-8.0 ± 7.4 (n = 33)	<0.001
FEV ₁ /FVC%	-0.5 ± 2.2 (n = 26)	+1.1 ± 3.4 (n = 33)	0.036
TLC (absolute volume, mL)	-118 ± 256 (n = 16)	-296 ± 138 (n = 19)	0.014
TLC% pred	-2.4 ± 4.7 (n = 16)	-6.0 ± 3.1 (n = 19)	0.011
FRC (absolute volume, mL)	-123 ± 205 (n = 16)	-183 ± 144 (n = 19)	0.315
FRC% pred	-5.6 ± 8.2 (n = 16)	-7.2 ± 6.4 (n = 19)	0.538
RV (absolute volume, mL)	-77 ± 148 (n = 16)	-113 ± 152 (n = 19)	0.488
RV% pred	-5.4 ± 9.0 (n = 16)	-7.9 ± 10.6 (n = 19)	0.457
DLco% pred	-3.7 ± 7.9 (n = 12)	-10.7 ± 8.8 (n = 15)	0.042
DLco/VA% pred	-4.1 ± 9.4 (n = 12)	-7.3 ± 11.7 (n = 15)	0.457

Data show means and standard deviations.

^a unpaired *t*-test.

However, the temporal relationship between FEV₁/FVC% and the survival of both groups in our study (data not shown) appears inconsistent with their findings. As stated, it is difficult to predict the prognosis of IPF simply from changes in ventilatory impairment. Detection of coexistent emphysema using CT is important to avoid making an incorrect prognosis.

Paraseptal emphysema was frequently observed in CPFE patients. Cottin et al.¹² reported results similar to ours. It is well known that centrilobular emphysema is smoking related.³⁰ Paraseptal emphysema appears to be peculiar to smoking-induced CPFE. Further studies are warranted to elucidate the etiology of paraseptal emphysema in CPFE.

Our study had several limitations. First, it was a retrospective study with a small sample size; additional prospective studies with large sample sizes are warranted to confirm our results. Second, diagnosis of CPFE and IPF alone was mainly dependent on CT findings and less than half of the diagnoses were validated by the results of a surgical lung biopsy or an autopsy. Some patients with chronic interstitial pneumonia other than UIP such as fibrotic nonspecific interstitial pneumonia and respiratory bronchiolitis-interstitial lung disease could be included in

our patient groups, especially in the "consistent with UIP" patient group. In addition, we did not analyze the relationship between the extent of emphysema or fibrosis and functional impairment or survival. Third, the number of measurements per patient used to estimate the linear decrease per year in DLco and DLco/VA was less than that used to estimate the linear decrease per year in VC and TLC. DLco may be a better prognostic indicator of CPFE than VC or TLC; the effects of two concurrent disorders on gas-exchange capacity are additive whereas the effects of two concurrent disorders on VC and TLC may cancel each other out. The equation describing the temporal decrease in DLco and DLco/VA would have been more accurate if measurements had been obtained more frequently. More frequent measurement of DLco and DLco/VA may reveal a more significant difference in the temporal decrease between groups.

Although we did not demonstrate the yearly change of respiratory function parameters is related to the prognosis of CPFE and IPF alone, separating CPFE from IPF patients may be necessary to make the role of respiratory functions clear in the prognosis of IPF.

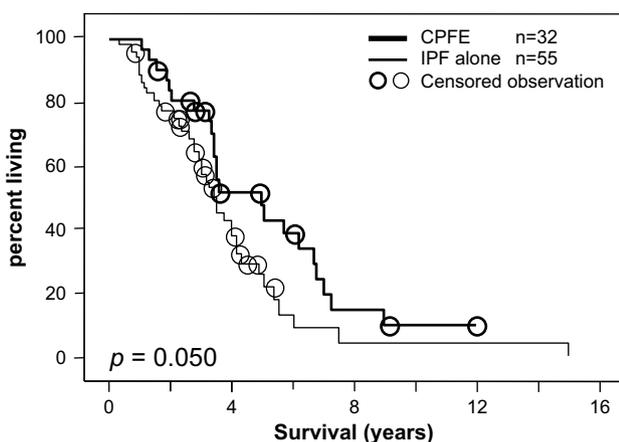


Figure 3 Kaplan–Meier survival curves for all patients enrolled in this study. CPFE patients (thick line) survived longer than patients with IPF alone (thin line), but the statistical significance of the difference was marginal ($p = 0.050$).

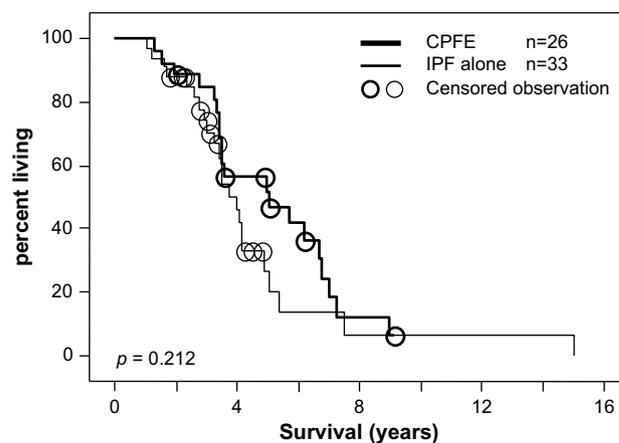


Figure 4 Kaplan–Meier survival curves were drawn for CPFE and IPF-alone patients whose respiratory functions had been monitored at least twice with at least a one-year interval. There was no significant difference in the duration of survival between patients with CPFE ($n = 26$, thick line) and IPF alone ($n = 33$, thin line) ($p = 0.212$).

In conclusion, we are the first to show that the yearly decrease in VC and TLC of patients with CPFE is less than that of patients with IPF alone. In CPFE patients, initial DLco was significantly less than in patients with IPF alone, but the decrease in DLco per year thereafter was modest compared with that of patients with IPF alone. Determining whether emphysema is coexistent in "IPF" is important for correct interpretation of the results of respiratory function tests and for accurate prediction of prognosis. Further studies to elucidate the roles of gas-exchange and ventilatory impairments as prognostic factors are warranted.

Conflict of interest

The authors have no potential conflict of interest.

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