The Preoperative Composite Physiologic Index May Predict Mortality in Lung Cancer Patients with Combined Pulmonary Fibrosis and Emphysema

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Keywords

Combined pulmonary fibrosis and emphysema · Lung cancer · Composite physiologic index · Mortality

Abstract

Background: It remains unclear whether the preoperative pulmonary function parameters and prognostic indices that are indicative of nutritional and immunological status are associated with prognosis in lung cancer patients with combined pulmonary fibrosis and emphysema (CPFE) who have undergone surgery. **Objective:** The aim of this study is to identify prognostic determinants in these patients. **Methods:** The medical records of all patients with lung cancer associated with CPFE who had undergone surgery at Shinshu University Hospital were retrospectively reviewed to obtain clinical data, including the results of preoperative pulmonary function tests and laboratory examinations, chest high-resolution computed tomography (HRCT), and survival. **Results:** Univariate Cox proportional hazards regression analysis showed that a high pathological stage of the lung cancer, a higher preoperative serum carcinoembryonic antigen level, and a higher preoperative composite physiologic index (CPI) were associated with a high risk of death. Multivariate

analysis showed that a high pathological stage of the lung cancer (HR: 1.579; $p = 0.0305$) and a higher preoperative CPI (HR: 1.034; $p = 0.0174$) were independently associated with a high risk of death. In contrast, the severity of fibrosis or emphysema on chest HRCT, the individual pulmonary function parameters, the prognostic nutritional index, the neutrophil-to-lymphocyte ratio, and the platelet-to-lymphocyte ratio were not associated with prognosis. In the Kaplan-Meier analysis, the log-rank test showed significant differences in survival between the high-CPI and the low-CPI group ($p = 0.0234$). **Conclusion:** The preoperative CPI may predict mortality and provide more powerful prognostic information than individual pulmonary function parameters in lung cancer patients with CPFE who have undergone surgery.

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Introduction

Combined pulmonary fibrosis and emphysema (CPFE) is a unique disorder defined by radiological findings on chest high-resolution computed tomography (HRCT) [1–5] and clinically characterized by subnormal spirometry (mild airflow limitation and mild lung vol-

ume restriction), severe impairment of gas exchange, and desaturation during exercise [1]. A higher prevalence of lung cancer has been reported in patients with CPFE in comparison to patients with emphysema/COPD alone [3, 6] or idiopathic pulmonary fibrosis (IPF) alone [7]. The prevalence of CPFE in the lung cancer population has been found to be higher than that of isolated pulmonary fibrosis [8]. CPFE was found to be independently associated with shorter disease-free and overall survival in patients with resected non-small cell lung cancer (NSCLC) [9].

Previous studies have suggested various clinical prognostic determinants as predictors of the prognosis of CPFE. Male sex, advanced age, a low body mass index, body weight loss, and an advanced clinical stage of the lung cancer predict a poor prognosis in lung cancer patients with CPFE who have undergone surgery [10, 11]. An elevated serum Krebs von den Lungen-6 (KL-6) level and an upper lobe mass are associated with a poor prognosis, and the serum KL-6 level at the time of the diagnosis is an independent prognostic determinant in lung cancer patients with CPFE [12]. Moreover, previous studies have also suggested that pulmonary function parameters predict the prognosis of CPFE. Longitudinal changes in the composite physiologic index (CPI), which was developed to improve the previous prognostic measures in IPF by adjusting for emphysema on chest HRCT and pulmonary function tests [13], predicts mortality in patients with CPFE [14, 15]. The CPI, which is correlated with the extent of pulmonary fibrosis on chest HRCT, more accurately predicts mortality than the individual pulmonary function tests alone in patients with IPF [13]. A lower vital capacity (VC) preoperatively is associated with a poor prognosis in lung cancer patients with CPFE who have undergone surgery [10].

Recently, prognostic indices that are indicative of the nutritional and immunological status have been found to be associated with recurrence and prognosis in lung cancer patients. The preoperative prognostic nutritional index (PNI), which is calculated based on serum albumin levels and the total lymphocyte count in peripheral blood, is a predictor of recurrence [16] or of a poor prognosis [17, 18] in NSCLC patients who have undergone surgery. An elevated neutrophil-to-lymphocyte ratio (NLR) [19] and an elevated platelet-to-lymphocyte ratio (PLR) [20] are associated with a poor prognosis in lung cancer patients.

However, there continues to be a lack of information on the prognostic determinants in lung cancer patients with CPFE who have undergone surgery. In particular, it

remains unclear whether the preoperative pulmonary function parameters, the CPI (which represents a combination of pulmonary ventilation and diffusing capacity), and the prognostic indices that are indicative of the nutritional and immunological status (such as the PNI, NLR, and PLR) are prognostic determinants in these patients. We sought to retrospectively assess the association of these parameters and indices with prognosis in a single academic institution.

Methods

Study Design

The medical records of all patients with lung cancer associated with CPFE who had undergone surgery at Shinshu University Hospital between August 2001 and October 2015 were retrospectively reviewed to obtain clinical data, including the results of preoperative pulmonary function tests and laboratory examinations, chest HRCT, the pathological stage of the lung cancer, and survival. The diagnosis of CPFE was made based on imaging criteria as described below. The PNI, NLR, and PLR, which had previously been reported to be prognostic determinants of lung cancer [16–20], were calculated based on the laboratory data. The CPI, which represents a combination of pulmonary ventilation and diffusing capacity, was calculated based on the pulmonary function data. The formula for calculating the CPI was as follows: $CPI = 91.0 - (0.65 \times \text{percent predicted diffusion capacity for carbon monoxide [DLCO]}) - (0.53 \times \text{percent predicted forced vital capacity [FVC]}) + (0.34 \times \text{percent predicted forced expiratory volume in 1 s [FEV}_1\text{]})$. We retrospectively assessed the association of these parameters and indices with prognosis. Our institutional review board approved this retrospective study, and provided all of the necessary ethical permissions (permission No. 3445).

Imaging Criteria

Emphysema and pulmonary fibrosis were evaluated using chest HRCT as previously described [3, 21, 22]. Briefly, emphysema was scored visually in the bilateral upper, middle, and lower lung fields according to the methods of Goddard et al. [23]. The score for each of the 6 dimensions was calculated according to the percentage of low attenuation area (%LAA) in each lung field as follows: score 0, %LAA <5%; score 1, $5\% \leq \%LAA < 25\%$; score 2, $25\% \leq \%LAA < 50\%$; score 3, $50\% \leq \%LAA < 75\%$; and score 4, $75\% \leq \%LAA$. The severity of emphysema was graded in accordance with the sum of the scores of the 6 dimensions, as follows: grade 0, total score = 0; grade 1, total score = 1–6; grade 2, total score = 7–12; grade 3, total score = 13–18; and grade 4, total score = 19–24 [24, 25]. The detection of significant pulmonary fibrosis on HRCT, defined as the presence of honeycombing, reticular opacity, ground-glass opacity, consolidation, traction bronchiectasis, peribronchovascular interstitial thickening, and architectural distortion, was performed visually as previously described [1, 3, 21, 22]. The extent of pulmonary fibrosis was scored visually to grade the severity as previously described [26]. Patients with CPFE were characterized by the coexistence of significant emphysema (grade ≥ 2) and significant pulmonary fibrosis. The diagnosis of CPFE required a consensus among the reviewers. The

Table 1. Clinical characteristics of the patients with lung cancer associated with combined pulmonary fibrosis and emphysema ($n = 59$)

Age, years	71.6±0.9	Pulmonary function tests	
Gender (female/male)	2/57	VC, L	3.37±0.09
Body mass index	22.88±0.46	%VC, %	100.56±2.07
Brinkman index, pack-years	63.3±3.9	FVC, L	3.33±0.10
Histologic diagnoses of lung cancer, n (%)		%FVC, %	101.14±2.33
Small-cell carcinoma	1 (1.7)	FEV ₁ , L	2.33±0.08
Squamous cell carcinoma	34 (57.6)	%FEV ₁ , %	89.92±2.51
Adenocarcinoma	22 (37.3)	FEV ₁ /FVC, %	69.98±1.21
Large-cell carcinoma	0 (0.0)	%TLC, %	107.18±2.71
Other non-small-cell carcinoma	2 (3.9)	%DLCO, %	53.60±2.25
Pathological stage of lung cancer, n (%)		%DLCO/VA, %	71.08±3.15
Stage IA, B	35 (59.3)	Composite physiologic index	33.13±1.83
Stage IIA, B	12 (20.3)	Operative procedure, n	
Stage IIIA, B	9 (15.3)	VATS/thoracotomy	35/24
Stage IV	3 (5.1)	Lobectomy/partial resection	43/16
Advanced stage (IIIB, IV)	5 (8.5)	ND ≥2a or 2a-1/ND ≤1 or 1b	33/26
Primary site of lung cancer, n (%)		Respiratory complications following operation, n (%)	
Right upper lobe	16 (27.1)	Acute exacerbation of pulmonary fibrosis	7 (11.7)
Right middle lobe	1 (1.7)	Bacterial pneumonia	2 (3.4)
Right lower lobe	22 (37.3)	Pyothorax	5 (8.5)
Left upper lobe	17 (28.8)	Hypoxemia	12 (20.3)
Left lower lobe	3 (5.1)	Prolonged air leak	6 (10.2)
Chest HRCT findings		Paroxysmal atrial fibrillation	4 (6.8)
LAA score	11.31±0.67	Others	4 (6.8)
Severity of pulmonary fibrosis		Postoperative recurrence of lung cancer (+/-), n	26/33
(minimum/moderate/severe), n	36/19/4		
Honeycombing (+/-), n	33/26		
Tumor size (max. diameter), mm	29.69±2.00		
Laboratory data			
Serum LDH, IU/L	205.31±5.44		
Serum KL-6, U/mL	651.05±58.13		
Serum CEA, ng/mL	8.04±1.34		
Prognostic nutritional index	50.21±0.68		
Neutrophil-to-lymphocyte ratio	2.11±0.11		
Platelet-to-lymphocyte ratio	106.48±4.64		

Values are presented as means ± SE unless indicated otherwise. HRCT, high-resolution computed tomography; LAA, low attenuation areas; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; CEA, carcinoembryonic antigen; VC, vital capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; TLC, total lung capacity; DLCO, diffusing capacity for carbon monoxide; DLCO/VA, diffusing capacity for carbon monoxide corrected for alveolar volume; VATS, video-assisted thoracic surgery; ND, node dissection.

CT images were reviewed independently by 2 pulmonologists (F.U. and Y.K.) with no knowledge of the patients' clinical data. The intraobserver reproducibility of visual scoring was tested by 1 observer (Y.K.), and the interobserver reproducibility of visual scoring was determined by 2 observers (F.U. and Y.K.), in the same manner as described in our previous report [25]. The rates of concordance in both intraobserver and interobserver reproducibility were >90%.

Pulmonary Function Tests

Spirometry and measurement of DLCO were performed using a pulmonary function testing system (Chestac-8900; Chest Co. Ltd, Tokyo, Japan). Functional residual capacity was measured using a body plethysmograph (Body Box; MGC Diagnostics, Ann Arbor, MI, USA), after which the subjects immediately inspired to total lung capacity and expired maximally to residual volume. The local Japanese reference data [27], developed by the Japanese Respiratory Society, were used to determine the predicted values for FEV₁ and VC, while the predicted values for DLCO, DLCO/alveolar volume, and lung volumes (residual volume and total lung capacity)

measured using body plethysmograph were determined using the formulas described by Nishida et al. [28] and Boren et al. [29], respectively. The pulmonary function tests were performed by 2 special technicians according to the American Thoracic Society criteria. Two or 3 tests were made to guarantee repeatability.

Analysis

The data are presented as the mean ± standard error or ratios with percentages, as appropriate. Univariate Cox proportional hazards regression analysis followed by multivariate analysis was used to identify determinants of a high risk of death. Logistic regression analysis was used to identify determinants of a high risk of recurrence. Variables with a p value <0.05 in the univariate analyses were considered for inclusion in the multivariate model. Survival in each group was estimated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. All the statistical analyses were performed using a Windows-compatible software program (StatFlex version 6; Artech Co. Ltd, Osaka, Japan). p values <0.05 were considered to indicate statistical significance in all the statistical analyses.

Fig. 1. Kaplan-Meier curve of the overall survival of the 59 lung cancer patients with combined pulmonary fibrosis who had undergone surgery. MST, median survival time.

Results

A total of 1,345 patients had undergone surgery for primary lung cancer at our institution during the study period. Seventy-three of these patients also had both emphysema and pulmonary fibrosis on chest HRCT based on our imaging criteria. Fourteen of the 73 patients were excluded from the study because of insufficient pulmonary function data. The data on the remaining 59 patients were reviewed in this study. Table 1 shows the clinical characteristics of the 59 lung cancer patients with CPFE who had undergone surgery. Figure 1 shows the Kaplan-Meier curve for the overall survival of these patients. The median survival time was 2.934 years. There were no patients with pulmonary hypertension – which is well known to deteriorate the prognosis of CPFE [1], because patients with pulmonary hypertension are excluded for resection for lung cancer at our institution.

The univariate Cox proportional hazards regression analysis showed that a high pathological stage of the lung cancer (HR: 1.618; 95% CI: 1.117–2.343; $p = 0.0109$), a higher preoperative serum carcinoembryonic antigen (CEA) level (HR: 1.036; 95% CI: 1.008–1.065; $p = 0.0116$),

and a higher preoperative CPI (HR: 1.027; 95% CI: 1.003–1.052; $p = 0.0280$) were associated with a high risk of death (Table 2). The multivariate analysis showed that a high pathological stage of the lung cancer (HR: 1.579; 95% CI: 1.044–2.389; $p = 0.0305$) and a higher preoperative CPI (HR: 1.034; 95% CI: 1.006–1.062; $p = 0.0174$) were independently associated with a high risk of death (Table 3). The univariate logistic regression analysis showed that only a high pathological stage of the lung cancer (HR: 2.747; 95% CI: 1.371–5.501; $p = 0.0044$) was associated with a high risk of recurrence (Table 4). In contrast, the preoperative BMI, the severity of the fibrosis or emphysema on chest HRCT, the individual preoperative pulmonary function parameters, and prognostic indices that are indicative of systemic inflammation, such as the PNI, NLR, and PLR, were not associated with a high risk of death or recurrence.

In addition, these patients were categorized into 2 groups: a high-CPI group (CPI >41; $n = 18$) and a low-CPI group (CPI ≤41; $n = 41$). This cutoff value for the CPI was based on a previous study which described predictive factors for 3-year survival in patients with IPF [30]. In the Kaplan-Meier analysis, the log-rank test showed significant differences in survival between the high-CPI and the low-CPI group ($p = 0.0234$) (Fig. 2). There was no significant difference in the proportion of patients with recurrence between the high-CPI and the low-CPI group (50.0 vs. 41.5%; $p = 0.5431$). Some patients had undergone adjuvant chemotherapy following surgery for lung cancer and/or chemotherapy following recurrence. However, there was no significant difference in the proportion of these patients between the high-CPI and the low-CPI group.

Discussion

This is the first report to focus on the association of preoperative pulmonary function parameters and prognostic indices that are indicative of the nutritional and immunological status, such as the PNI, NLR, and PLR, with prognosis in lung cancer patients with CPFE who have undergone surgery. We found that the preoperative CPI, which represents a combination of pulmonary ventilation and diffusing capacity, was an independent prognostic determinant in these patients; however, the individual preoperative pulmonary function parameters PNI, NLR, and PLR were not associated with prognosis. A high pathological stage of lung cancer was the only determinant that was associated with recurrence.

Table 2. Univariate Cox proportional hazards regression analysis of the risk of death ($n = 59$)

Variable	HR	95% CI	<i>p</i> value
Age (years)	1.01013	0.96766–1.05448	0.6455
Body mass index	1.02211	0.93076–1.12243	0.6471
Brinkman index (pack-years)	1.00649	0.99552–1.01758	0.2471
Chest HRCT findings			
Severity of emphysema (LAA score)	0.99905	0.93636–1.06594	0.9771
Severity of pulmonary fibrosis	1.32542	0.83386–2.10676	0.2334
Tumor size (max. diameter; mm)	1.00003	0.97810–1.02244	0.9981
Primary site of lung cancer: upper lobe	1.19302	0.61715–2.30621	0.5997
Pathological stage of lung cancer	1.61756	1.11690–2.34266	0.0109
Laboratory data			
Serum LDH (IU/L)	0.99832	0.98987–1.0684	0.6982
Serum KL-6 (U/mL)	1.00031	0.99943–1.00119	0.4870
Serum CEA (ng/mL)	1.03623	1.00799–1.06525	0.0116
Prognostic nutritional index	0.99535	0.92690–1.06886	0.8980
Neutrophil-to-lymphocyte ratio	1.16709	0.74108–1.83799	0.5049
Platelet-to-lymphocyte ratio	1.00052	0.99051–1.01063	0.9194
Pulmonary function tests			
VC (L)	0.65033	0.38998–1.08449	0.0991
%VC (%)	0.99027	0.96913–1.01186	0.3743
FVC (L)	0.70993	0.46536–1.08303	0.1119
%FVC (%)	0.99251	0.97575–1.00955	0.3868
FEV ₁ (L)	0.77590	0.47573–1.26547	0.3093
%FEV ₁ (%)	1.00531	0.98769–1.02325	0.5572
FEV ₁ /FVC (%)	1.02027	0.98509–1.05670	0.2624
%TLC (%)	0.99773	0.97942–1.01637	0.8097
%DLCO (%)	0.98241	0.96325–1.00195	0.0774
%DLCO/VA (%)	0.99019	0.97412–1.00652	0.2376
Composite physiologic index	1.02696	1.00287–1.05163	0.0280
Operative procedure			
VATS	0.86888	0.43678–1.72845	0.6888
Partial resection	1.04578	0.47463–2.30425	0.9116
ND $\geq$ 2a or 2a-1	0.92301	0.47416–1.79675	0.8136

HRCT, high-resolution computed tomography; LAA, low attenuation areas; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; CEA, carcinoembryonic antigen; VC, vital capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; TLC, total lung capacity; DLCO, diffusing capacity for carbon monoxide; DLCO/VA, diffusing capacity for carbon monoxide corrected for alveolar volume; VATS, video-assisted thoracic surgery; ND, node dissection.

Table 3. Multivariate Cox proportional hazards regression analysis of the risk of death ($n = 59$)

Variable	HR	95% CI	<i>p</i> value
Composite physiologic index	1.03363	1.00582–1.06221	0.0174
Serum CEA, ng/mL	1.01956	0.98797–1.05216	0.2277
Pathological stage of lung cancer	1.57926	1.04385–2.38931	0.0305
CEA, carcinoembryonic antigen.			

Table 4. Univariate logistic regression analysis of the risk of recurrence ($n = 59$)

Variable	HR	95% CI	<i>p</i> value
Age (years)	0.98175	0.91173–1.05714	0.6256
Body mass index	0.96078	0.82693–1.11630	0.6012
Brinkman index (pack-years)	1.00142	0.98414–1.01901	0.8729
Chest HRCT findings			
Severity of emphysema (LAA score)	0.97042	0.87688–1.07394	0.5615
Severity of pulmonary fibrosis	1.75158	0.74944–4.09374	0.1956
Tumor size(max. diameter; mm)	0.99310	0.95970–1.02766	0.6915
Primary site of lung cancer: upper lobe	0.73684	0.26221–2.07062	0.5624
Pathological stage of lung cancer	2.74680	1.37146–5.50137	0.0044
Laboratory data			
Serum LDH (IU/L)	0.99875	0.98638–1.01129	0.8448
Serum KL-6 (U/mL)	1.00063	0.99920–1.00205	0.3877
Serum CEA (ng/mL)	1.08635	0.98762–1.19494	0.0884
Prognostic nutritional index	1.09884	0.98651–1.22396	0.0867
Neutrophil-to-lymphocyte ratio	0.92496	0.51027–1.67668	0.7972
Platelet-to-lymphocyte ratio	0.99918	0.98474–1.01385	0.9126
Pulmonary function tests			
VC (L)	1.04905	0.50654–2.17257	0.8974
%VC (%)	1.02083	0.98677–1.05606	0.2337
FVC (L)	1.18297	0.60020–2.33157	0.6274
%FVC (%)	1.02443	0.99353–1.05628	0.1225
FEV ₁ (L)	1.33091	0.58631–3.02112	0.4943
%FEV ₁ (%)	1.02243	0.99382–1.05185	0.1255
FEV ₁ /FVC (%)	1.02277	0.96664–1.08216	0.4343
%TLC (%)	0.98853	0.96220–1.01558	0.4023
%DLCO (%)	0.99302	0.96337–1.02358	0.6505
%DLCO/VA (%)	0.99936	0.97819–1.02100	0.9536
Composite physiologic index	1.00056	0.96442–1.03805	0.9762
Operative procedure			
VATS	0.37267	0.12778–1.08687	0.0707
Partial resection	0.98246	0.30902–3.12350	0.9761
ND $\geq$ 2a or 2a-1	1.50588	0.53004–4.27828	0.4422

HRCT, high-resolution computed tomography; LAA, low attenuation areas; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; CEA, carcinoembryonic antigen; VC, vital capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; TLC, total lung capacity; DLCO, diffusing capacity for carbon monoxide; DLCO/VA, diffusing capacity for carbon monoxide corrected for alveolar volume; VATS, video-assisted thoracic surgery; ND, node dissection.

A previous study reported that a lower VC predicted a poor prognosis in lung cancer patients with CPFE who had undergone surgery [10]. However, a lower VC was not significantly associated with risk of death in this study. The difference between these results may be due to the difference in imaging criteria for emphysema. In this study, emphysema was defined as the presence of significant emphysema of grade ≥ 2 , as previously described [3, 9, 10], and patients with low-grade emphysema (grade 1) were not considered to have CPFE. In contrast, the extent of emphysema was not measured in the previous study

[10]. Thus, the proportion of patients with severe emphysema was likely higher in this study than in the previous study, which may have affected VC. A specific clinical diagnosis as well as criteria for classifying CPFE must be established.

We found that the cross-sectional preoperative CPI was an independent prognostic determinant in lung cancer patients who had undergone surgery. In contrast, previous studies reported that a ≥ 5 -point increase in CPI per year was a predictor of mortality in patients with CPFE [14, 15], including patients with and patients without

Fig. 2. Kaplan-Meier curves of the analyses between the high-CPI group (CPI >41; $n = 18$) and the low-CPI group (CPI ≤ 41 ; $n = 41$). Differences in survival were assessed using the log-rank test ($p = 0.0234$). CPI, composite physiologic index; MST, median survival time.

lung cancer. We assume that resection for primary lung cancer causes the decreases in DLCO, FVC, and FEV₁, which are included in the formula of the CPI. Thus, the longitudinal changes in CPI in patients who undergo surgery differ from those in patients who do not. The longitudinal changes in CPI may also differ based on differences in operational procedure; thus, it is assumed to be an inappropriate prognostic determinant in cases of lung cancer patients who have undergone surgery.

Previous studies have reported that the preoperative PNI, NLR, and PLR are predictors of a poor prognosis in NSCLC patients who have undergone resection for primary lung cancer [16–18]. In contrast, this study revealed that these indices were not predictors of a poor prognosis in lung cancer patients with CPFE who had undergone surgery, suggesting that CPFE itself has a significant impact on these indices. However, further studies are needed to elucidate the precise reason for the difference. One possible reason is a difference in statistical methods. These previous studies converted continuous data into 2 groups. A great deal of information may be lost in this

dichotomization; thus, the statistical power to detect a relationship between the variable and the patient outcome may be reduced [31]. Dichotomization may also increase the risk of a positive result being a false positive [31]. Thus, we used continuous data without dichotomization when a Cox proportional hazards regression analysis or logistic regression analysis was used to identify the determinants of a high risk of death or recurrence.

Based on the results of the univariate Cox proportional hazards regression analysis, we found that serum CEA level may be associated with prognosis in lung cancer patients with CPFE who have undergone surgery. CEA is the most widely used tumor marker in patients with NSCLC [32]. Several studies have suggested that the pre-operative serum CEA level is an independent prognostic determinant of NSCLC [33–35]. On the other hand, Fahim et al. [36] reported that the serum CEA level is elevated in approximately half of patients with IPF, and that serum CEA level is correlated with disease severity and significantly negatively correlated with lung function ($p = 0.005$, $R^2 = 0.20$ for FVC; $p = 0.006$, $R^2 = 0.20$ for DLCO). These previous studies revealed that the serum CEA level may reflect not only the prognosis of NSCLC following resection for lung cancer but also pulmonary function parameters in IPF, including FVC and DLCO – which may be consistent with our results, because FVC and DLCO are included in the formula for calculating the CPI.

We assumed that the heterogeneity of CPFE, in which emphysema in the upper lobe coexists with pulmonary fibrosis in the lower lobe, results in different clinical courses and outcomes between patients with CPFE with an upper lobe mass and those with a lower lobe mass. Indeed, the previous study revealed that an upper lobe mass was associated with a poor prognosis in lung cancer patients with CPFE [12]. In contrast, the present study and previous studies [9, 10] revealed that an upper lobe mass was not associated with a poor prognosis in lung cancer patients with CPFE who have undergone surgery. Consequently, in cases of patients who have undergone resection for primary lung cancer, the location of resection may not have any significant impact on the prognosis.

KL-6 is a high-molecular-weight glycoprotein that is classified as “Cluster9 (MUC1)” for lung tumors and differentiation antigens according to the findings of immunohistochemical and flow cytometry [37, 38]. KL-6 has been reported to serve as a sensitive serum marker for interstitial pneumonia [39, 40] and is clinically used to detect the presence of interstitial pneumonia in Japan. Kishaba et al. [41] reported that the baseline serum KL-6 level is useful for predicting acute exacerbations, which occurs in

24% of patients with CPFE. In the present study, 7 of the 59 patients had an acute exacerbation following surgery. Four of these 7 patients showed a high preoperative serum KL-6 level, and the remaining 3 patients showed a normal serum KL-6 level. Consequently, the preoperative serum KL-6 level is not a predictor of an acute exacerbation in lung cancer patients with CPFE who have undergone surgery. We assume that one reason for the difference between these results may be the presence or absence of triggers of an acute exacerbation following lung surgery regardless of the serum KL-6 level. One of the triggers of acute exacerbation following lung surgery is considered to be prolonged ventilation at a large tidal volume with oxygen supplementation at a high concentration [42].

There are several limitations to this study. First, this was a retrospective single-center study. Additional prospective studies with large sample sizes should be performed to confirm our results. Second, assessment of emphysema was performed using a visual scoring method, rather than a software-based method. However, the reproducibility of the visual scoring system had been demonstrated in our previous report [25]. Third, we did not measure the exact areas of fibrosis. Instead, the extent of fibrosis on chest HRCT was assessed semiquantitatively, as previously described [26], because it was difficult to

determine the extent of fibrosis in the upper regions of the lungs when mixed emphysema and fibrosis was present. Fourth, as described in the Methods, 14 of the 73 lung cancer patients with CPFE who had undergone surgery were excluded from the study because no measurement of DLCO had been performed. There is the possibility that fewer patients with normal spirometry underwent measurement of DLCO, in comparison to patients with abnormal spirometry, who were suspected of having obstructive or restrictive lung diseases. Thus, the proportion of patients with abnormal spirometry might possibly have been higher in the present study, which might have resulted in a selection bias.

In conclusion, the cross-sectional preoperative CPI may predict mortality and provide more powerful prognostic information than the individual function parameters in lung cancer patients with CPFE who have undergone surgery. In contrast, the severity of emphysema or pulmonary fibrosis on chest HRCT, the individual preoperative pulmonary function parameters, and the prognostic indices that are indicative of the nutritional and immunological status, such as the PNI, NLR, and PLR, are not associated with prognosis. A high pathological stage of lung cancer may be the only determinant that is associated with recurrence.

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