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Original Article

Serum biomarker changes in pulmonary fibrosis with lung cancer and their correlation with patient survival prognosis

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Abstract: This study aimed to characterize serum tumor markers - cytokeratin 19 fragment (Cyfra21-1), carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and squamous cell carcinoma antigen (SCC) - together with arterial blood gas and pulmonary function parameters (partial pressure of oxygen [PO_2], forced vital capacity [FVC], diffusing capacity of the lung for carbon monoxide [DLCO], DLCO adjusted for alveolar volume [DLCO/VA], and lung reserve rate) in patients with pulmonary fibrosis (PF), lung cancer (LC), and PF combined with lung cancer (PF+LC), and to evaluate their prognostic value for 2-year overall survival (OS) and lung cancer-specific mortality. A retrospective analysis was conducted on 485 PF patients, 135 LC patients, 187 PF+LC patients, and 100 healthy controls enrolled between February 2010 and April 2023. Baseline demographics, tumor markers, and pulmonary function data were compared across groups. Serum markers followed the trend: PF+LC ≈ LC > PF > controls, while pulmonary function was markedly impaired in PF+LC patients compared with PF patients. In PF patients, Cyfra21-1, FVC, DLCO, and age ≥65 years were independent predictors of 2-year OS. For PF+LC patients, Cyfra21-1, FVC, DLCO, age ≥65 years, and fibrosis type were significant prognostic factors, while TNM staging did not correlate with OS. Competing risk analysis identified Cyfra21-1, FVC, fibrosis type, and pirfenidone therapy as independent predictors of lung cancer-specific mortality. These findings demonstrate that serum tumor markers and pulmonary function parameters reflect disease heterogeneity between PF and PF+LC, with Cyfra21-1, FVC, DLCO, age, and fibrosis type serving as important survival determinants. Additionally, pirfenidone therapy may reduce lung cancer-related mortality, underscoring its potential therapeutic benefit in managing PF+LC.

Keywords: Pulmonary fibrosis, lung cancer, serum tumor markers, pulmonary function, diagnostic performance, prognosis, competing risk model

Introduction

Pulmonary fibrosis (PF) encompasses a range of interstitial lung diseases characterized by alveolar wall structural damage, chronic inflammation, and progressive pulmonary fibrosis, with clinical manifestations including dyspnea, dry cough, and declining pulmonary function [1]. Common types include idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated PF, occupational PF, and drug-related PF [2]. As the population ages and environmental exposures increase, the incidence of PF is rising annually, becoming a major chronic lung disease that seriously affects patients' quality of life and survival [3]. Lee et al. [4] reported that 18.8% of patients with connective tissue disease-associated interstitial lung disease (ILD) develop progressive pulmonary fibrosis (PPF), with a significantly increased mortality risk (HR: 3.856), indicating the importance of assessing progressive fibrosis for prognostication.

Recent studies indicate that PF patients, particularly those with progressive fibrosis like IPF,

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are at a significantly higher risk of developing lung cancer (LC) compared to the general population [5]. PF combined with lung cancer (PF+LC) presents complex clinical challenges, including difficult diagnosis, limited treatment options, and poor prognosis. Literature indicates [6] that treating IPF patients with small cell lung cancer is extremely challenging, requiring careful balance between chemotherapy effectiveness and pulmonary function preservation, with a worse prognosis than those with isolated lung cancer. Their pulmonary imaging manifestations are often masked by underlying fibrotic lesions, obscuring early tumor signs, and histopathological examination poses risks, potentially worsening respiratory function or causing pneumothorax [7]. Additionally, PF+LC patients have poor tolerance to traditional anti-tumor treatments such as surgery, radiochemotherapy, and targeted therapy. Matsubara et al. [8] showed that the Controlling Nutritional Status (CONUT) score is an independent risk factor for prognosis and acute exacerbation in PF patients undergoing surgery for non-small cell lung cancer (NSCLC), complicating management. Therefore, identifying sensitive, non-invasive, highly specific biomarkers and pulmonary function assessment tools for risk stratification and early lung cancer detection in PF patients is crucial for improving clinical outcomes.

Current research on the PF+LC populations remains limited. Previous studies have mostly focused on either lung cancer or the independent progression of PF, with less attention given to the diagnostic characteristics and prognostic indicators in comorbid conditions [9, 10]. Tumor markers are widely used in lung cancer screening and treatment monitoring, but their expression changes in PF patients and their potential role in diagnosing combined lung cancer have not been systematically evaluated [11]. Literature shows [12] that the Advanced Lung Cancer Inflammation Index (ALI) is significantly associated with disease severity and mortality in IPF patients, underscoring the importance of comprehensive multi-indicator assessment. Furthermore, pulmonary function indicators, which reflect respiratory reserve and disease severity, warrant further exploration to evaluate their ability to identify PF combined with lung cancer and their prognostic value.

This study systematically compared baseline demographic characteristics, pulmonary function parameters, and serum tumor marker levels among healthy controls, PF patients, and PF+LC patients. The goal is to identify characteristic differences in pulmonary function and biomarker expression across these groups. Furthermore, Cox regression and competing risk models were employed to explore the impact of these indicators on 2-year overall survival (OS) and lung cancer-specific mortality, aiming to identify potential independent prognostic factors.

The innovation of this study lies in its integrated approach, combining serological and functional perspectives to analyze the multi-dimensional clinical value of tumor markers and pulmonary function parameters in PF patients. On the one hand, the study reveals an elevation trend of certain tumor markers in PF+LC patients, suggesting their potential contribution to risk stratification; on the other hand, a significant decline in pulmonary function parameters indicates disease progression and can serve as a prognostic tool. By quantifying the prognostic value of these indicators, this study aims to develop more clinically practical risk assessment tools to assist physicians in early identification and management of high-risk PF patients.

Materials and methods

Sample size calculation

This study referenced the ROC analysis of IL-17, IL-22, and IL-23 in lung cancer patients with IPF, as reported by Zhang et al. [13]. A sample size calculation method based on ROC curve analysis was used, with a significance level of $\alpha=0.05$, a test power of $1-\beta=0.80$, and the null hypothesis assuming an AUC of 0.5 (no diagnostic value). The alternative hypothesis targeted AUC values between 0.7001 and 0.8229. Using the sample size calculation formula based on normal approximation proposed by Hanley & McNeil [14] and considering the AUC value confidence interval width, the recommended sample sizes for validating single biomarkers with good diagnostic value, such as IL-17 (AUC=0.8229) and IL-22 (AUC=0.8081), are 35-38 cases per group, with a total sample size approximately 70-76 cases. For IL-23 (AUC=0.7001), approximately 55 cases per group are needed, totaling 110 cases. To com-

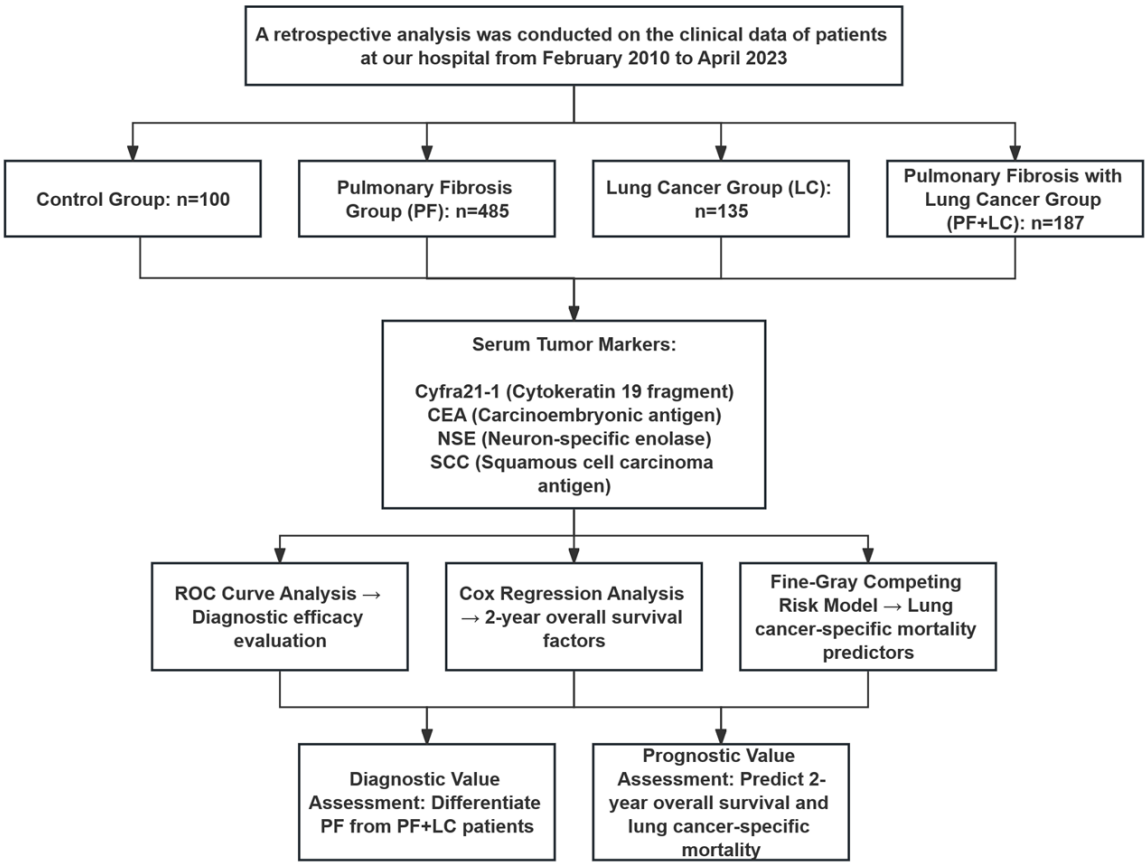


Figure 1. Sample screening flow chart.

pare the AUC differences between IL-17 and IL-22 (ΔAUC=0.0148), approximately 90 cases per group are needed, totaling 180 cases. Considering the study design, which evaluates the diagnostic efficacy of multiple biomarkers and anticipates a 10%-15% dropout rate, the minimum sample size required for this study was determined to be 65 cases per group, with a total sample size of 130 cases, which is sufficient for ROC curve diagnostic validation and multivariate analysis. The actual sample size were determined based on clinical circumstances to ensure the adequate statistical power and clinical representativeness.

General information

A retrospective analysis was conducted on the clinical data of patients at The First Affiliated Hospital of Shanxi Medical University from February 2010 to April 2023, including 485 patients with PF, 135 patients with LC, 187 patients with PF+LC, and 100 healthy individuals who underwent physical examinations. This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Shanxi Medical University (**Figure 1**).

Inclusion and exclusion criteria

Inclusion criteria: Adults aged ≥18 years; clinically diagnosed with interstitial pulmonary fibrosis (PF), meeting guideline standards (such as ATS/ERS/JRS diagnostic criteria) [15]; PF patients with confirmed lung cancer based on imaging, pathology, or tumor markers [16]; complete pulmonary function test data (e.g., partial pressure of oxygen [PO_2], forced vital capacity [FVC], diffusing capacity of the lung for carbon monoxide [DLCO]) and serum tumor marker data (e.g., cytokeratin 19 fragment [Cyfra21-1], carcinoembryonic antigen [CEA], neuron-specific enolase [NSE], and squamous cell carcinoma antigen [SCC]).

Exclusion criteria: Patients with other severe pulmonary diseases such as active pulmonary tuberculosis, lung abscess; severe heart, liver,

kidney dysfunction that could interfere with pulmonary function assessment or survival analysis; patients with other malignant tumors or a history of malignant tumor treatment that could confound the results; inability to cooperate with pulmonary function testing or blood examination; poor compliance or mental/cognitive disorders affecting data accuracy.

Clinical data collection

Clinical data were sourced from hospital's inpatient electronic medical record systems and follow-up records, covering the complete disease progression from patients' first admission to follow-up periods. Data collected included:

(1) Demographic characteristics: age (divided into ≥65 years and <65 years), gender, body mass index (BMI ≥25 kg/m^2 and <25 kg/m^2), smoking history, alcohol consumption history, diabetes history, and hypertension history.

(2) Clinical diagnosis and pathological characteristics: PF patients: fibrosis type (idiopathic pulmonary fibrosis vs. other types); PF+LC patients: lung cancer histological type (adenocarcinoma, and squamous carcinoma), tumor TNM staging (T stage, N stage, M stage), clinical staging (stage II, III, IV), and pirfenidone treatment (Yes and No).

(3) Pulmonary function testing indicators: arterial blood gas analysis (PO_2), forced vital capacity expressed as predicted percentage (FVC%Pred), carbon monoxide diffusion capacity (DLCO%Pred), diffusion capacity corrected for alveolar volume (DLCO/VA%Pred), and lung reserve rate, with all pulmonary function parameters completed by professional technicians using standardized equipment, data from pulmonary function examination report systems.

(4) Serum tumor markers: Cyfra21-1, CEA, NSE, and SCC. Blood samples were collected during patient admission and tested in the laboratory department, with results exported from the laboratory information system.

(5) Prognosis and follow-up information: 2-year overall survival (OS), tumor-related death, and non-tumor-related death. Data were confirmed via outpatient follow-up and telephone follow-up, used for subsequent survival analysis and competing risk model construction.

Laboratory indicator testing

Serum tumor markers (Cyfra21-1, CEA, NSE, and SCC) were collected from fasting venous blood at patients' first admission and centrally tested in the hospital laboratory department. All serum samples were analyzed within specified time after centrifugal separation, using electrochemiluminescence immunoassay (ECLIA) on the Roche Cobas e601 automatic immunoanalyzer. Reagents and calibrators were from original factory-matched supplies, and testing was completed by professional laboratory technicians following standard operating procedures (SOP) and quality control protocols. Test results were automatically entered and exported from the laboratory information system.

Arterial blood gas analysis (PO_2) was performed on samples obtained by radial artery puncture after at least 20 minutes of rest. All samples were immediately placed in ice slurry and analyzed within 15 minutes using the Radiometer ABL 800 blood gas analyzer (Radiometer, Denmark). Daily two-level internal quality controls and external proficiency testing ensured the accuracy and precision of measurements.

Pulmonary function testing included FVC%Pred, DLCO%Pred, DLCO/VA%Pred, and lung reserve rate. All tests were performed by trained technicians using Jaeger MasterScreen PFT instruments (German). Lung reserve rate was calculated as: $100 \times (1\text{-}VE_{peak}/MVV)$, where VE_{peak} represents peak minute ventilation during exercise cardiopulmonary testing, and MVV was obtained either directly (12-15 seconds maximal voluntary ventilation, extrapolated to 1 minute) or estimated as FEV1 × 40. The same method was applied consistently across all patients.

Definition of lung cancer death and non-lung cancer death

Lung cancer death: Death directly caused by lung cancer, including death due to tumor progression, distant metastasis (e.g., brain, liver, or bone), tumor-related complications (e.g., malignant pleural effusion, cancer pain, or severe respiratory failure), or other pathological processes clearly attributable to lung cancer.

Non-lung cancer death: Death primarily caused by PF, including PF-related respiratory failure, acute exacerbation (e.g., acute respiratory dis-

tress syndrome), PF-related pulmonary hypertension, or right heart failure.

The cause of death was determined based on hospital electronic medical records, inpatient death certificates, or follow-up documentation. Only cases with complete and verifiable death information were included in the analysis, while patients unreliable records were excluded.

Outcome measurements

Primary outcomes: Diagnostic efficacy of serum tumor markers (Cyfra21-1, CEA, NSE, SCC), arterial blood gas indicator (PO_2), and pulmonary function parameters (FVC%Pred, DLCO%Pred, DLCO/VA%Pred, lung reserve rate) in distinguishing PF patients from PF+LC patients, and their predictive value for 2-year OS in patients; Competing risk analysis for lung cancer-related deaths to evaluate the impact of various indicators on patient outcomes.

Secondary outcomes: Comparison of baseline demographic and clinical characteristics among the three patient groups; analysis of serum marker and pulmonary function differences across groups; examination of the distribution trends and changes in various indicators for diagnosis and prognosis evaluation.

Statistical analysis

All statistical analyses were completed using R 4.3.3 software. Quantitative data were fist analyzed for distribution normality. Normally distributed data were expressed as mean ± standard deviation, and inter-group comparisons was conducted using t-test or one-way analysis of variance (ANOVA); while non-normally distributed data were expressed as median [interquartile range], and compared using Mann-Whitney U test or Kruskal-Wallis H test. Categorical data were expressed as frequencies and percentages, with inter-group differences analyzed using chi-square test. For three-group comparisons (control, PF, and PF+LC), appropriate methods were selected based on the variable types, with post-hoc pairwise comparisons and multiple testing corrections applied as necessary.

For diagnostic efficacy evaluation, receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of various serum tumor markers and pulmonary function indicators, reporting the area under the curve (AUC), sensitivity, specificity, optimal cutoff values, and Youden index. AUC differences were compared using DeLong test. For prognostic analysis, Kaplan-Meier survival curves was drawn for visualization of 2-year OS rates, applying Cox proportional hazards regression models to screen independent risk factors affecting prognosis. In PF+LC patients, Fine-Gray competing risk models were further employed to analyze factors influencing lung cancer-related death versus non-lung cancer death, with subdistribution hazard ratios (sHR) calculated. All tests were two-sided, with P values <0.05 considered statistically significant.

Results

Comparisons of baseline demographics among groups

There were no significant differences among the four groups in terms of age (P=0.475) and gender (P=0.298) distributions, BMI classification (P=0.301), diabetes history (P=0.613), hypertension history (P=0.544), smoking history (P=0.469), or alcohol consumption history (P=0.441) (all P>0.05) (**Table 1**).

Comparisons of clinical characteristics among groups

Significant differences existed between PF and PF+LC groups in fibrosis type (P=0.044), with the PF+LC group showing a lower proportion of IPF (37.97%) compared to the PF group (46.60%). No significant difference was observed in pirfenidone treatment utilization between the PF and PF+LC groups (P=0.101). The LC and PF+LC groups demonstrated good comparability in tumor-related characteristics, including tumor staging (P=0.915), tumor type (P=0.630), T stage (P=0.939), N stage (P= 0.966), and M stage (P=0.926), indicating similar tumor burden and pathological characteristics between the two groups (**Table 2**).

Comparisons of pulmonary function indicators among groups

Significant differences were observed among the PF, LC, and PF+LC groups in all pulmonary function indicators, including PO_2, FVC%Pred, DLCO%Pred, DLCO/VA%Pred, and lung reserve

Table 1. Comparison of baseline demographics among groups

Variables	Control Group (n=100)	PF (n=485)	LC (n=135)	PF+LC (n=187)	Statistics	*P* Values
Age					2.499	0.475
≥65 years	51 (51.0%)	281 (57.94%)	74 (54.81%)	99 (52.94%)		
<65 years	49 (49.0%)	204 (42.06%)	61 (45.19%)	88 (47.06%)		
Gender					3.680	0.298
Male	65 (65.0%)	330 (68.04%)	81 (60.0%)	118 (63.1%)		
Female	35 (35.0%)	155 (31.96%)	54 (40.0%)	69 (36.9%)		
BMI					3.655	0.301
≥25 kg/m^2	25 (25.0%)	92 (18.97%)	34 (25.19%)	41 (21.93%)		
<25 kg/m^2	75 (75.0%)	393 (81.03%)	101 (74.81%)	146 (78.07%)		
Diabetes History					1.810	0.613
Yes	15 (15.0%)	82 (16.91%)	20 (14.81%)	24 (12.83%)		
No	85 (85.0%)	403 (83.09%)	115 (85.19%)	163 (87.17%)		
Hypertension History					2.139	0.544
Yes	25 (25.0%)	150 (30.93%)	36 (26.67%)	52 (27.81%)		
No	75 (75.0%)	335 (69.07%)	99 (73.33%)	135 (72.19%)		
Smoking History					2.537	0.469
Yes	66 (66.0%)	296 (61.03%)	76 (56.3%)	110 (58.82%)		
No	34 (34.0%)	189 (38.97%)	59 (43.7%)	77 (41.18%)		
Alcohol Consumption History					2.693	0.441
Yes	15 (15.0%)	92 (18.97%)	30 (22.22%)	41 (21.93%)		
No	85 (85.0%)	393 (81.03%)	105 (77.78%)	146 (78.07%)		

Note: PF: Pulmonary Fibrosis, LC: Lung Cancer, BMI: Body Mass Index.

rate (all P<0.001). The overall trend showed that the PF group had the highest pulmonary function, followed by the LC group and the PF+LC group, with both the PF+LC and LC groups exhibiting markedly impaired pulmonary function compared to the PF group. This suggests that, regardless of the presence of concurrent pulmonary fibrosis, lung cancer patients demonstrate significantly impaired pulmonary function reserve, with PF+LC patients showing similar impairment to those with lung cancer alone (**Table 3**).

Comparison of serum tumor markers among groups

Significant differences were found in the levels of Cyfra21-1, CEA, NSE, and SCC levels among the control, PF, LC, and PF+LC groups (all P<0.001). Among these markers, Cyfra21-1, CEA, and NSE followed normal distribution and were analyzed using analysis of variance, while SCC were analyzed using Kruskal-Wallis non-parametric testing due to non-normal distribution.

Cyfra21-1 and CEA levels followed the trend: PF+LC group ≈ LC group > PF group > control group, with statistically significant pairwise comparisons among all four groups (all P<0.001). NSE levels were highest in the LC group, followed by the PF+LC group, both of which were significantly higher than PF and control groups (P<0.001), while no significant difference existed between PF and control groups (P=0.860). SCC levels were highest in the PF group, followed by PF+LC and LC groups, with the control group showing the lowest levels. Significant pairwise comparisons were observed among all four groups (all P<0.001).

These findings suggest that PF+LC and LC patients exhibit markedly elevated serum tumor marker levels compared to PF patients and controls, indicating that tumor burden represents the primary driving factor for marker elevation, while PF patients also show moderate elevation in certain markers (such as Cyfra21-1, CEA, SCC) compared to controls (**Table 4**).

Table 2. Comparison of clinical characteristics among groups

Variables	PF (n=485)	LC (n=135)	PF+LC (n=187)	Statistics	*P* Values
Fibrosis Type				4.076	0.044
Idiopathic fibrosis	226 (46.60%)		71 (37.97%)		
Other	259 (53.40%)		116 (62.03%)		
Pirfenidone treatment				2.696	0.101
Yes	226 (46.60%)		74 (39.57%)		
No	259 (53.40%)		113 (60.43%)		
Tumor Stage				0.179	0.915
II		26 (19.26%)	33 (17.65%)		
III		73 (54.07%)	105 (56.15%)		
IV		36 (26.67%)	49 (26.20)		
Tumor Type				0.232	0.630
Adenocarcinoma		57 (42.22%)	84 (44.92%)		
Squamous carcinoma		78 (57.78%)	103 (55.08%)		
T Stage				0.404	0.939
T1		30 (22.22%)	40 (21.39%)		
T2		37 (27.41%)	52 (27.81%)		
T3		44 (32.59%)	57 (30.48%)		
T4		24 (17.78%)	38 (20.32%)		
N Stage				0.267	0.966
N0		34 (25.19%)	44 (23.53%)		
N1		29 (21.48%)	39 (20.86%)		
N2		22 (16.30%)	34 (18.18%)		
N3		50 (37.04%)	70 (37.43%)		
M Stage				0.009	0.926
M0		99 (73.33%)	138 (73.80%)		
M1		36 (26.67%)	49 (26.20%)		

Note: PF: Pulmonary Fibrosis, LC: Lung Cancer, TNM: Tumor Node Metastasis.

Diagnostic value of serum tumor markers in distinguishing control from PF groups

ROC curve analysis demonstrated that Cyfra21-1, CEA, and SCC exhibited good diagnostic performance, with AUCs of 0.847 (95% confidence interval [CI]: 0.816-0.878), 0.853 (95% CI: 0.822-0.883), and 0.823 (95% CI: 0.783-0.864), respectively. These markers demonstrated high sensitivity and specificity, effectively distinguishing PF patients from controls.

Among these, CEA had the highest sensitivity (99.00%), making it a suitable auxiliary indicator for PF screening; Cyfra21-1 and SCC also demonstrated good sensitivity (95.00% and 85.00%) and specificity (70.10% and 65.98%), providing strong diagnostic value. In contrast, NSE showed poor diagnostic performance, with an AUC of only 0.529 (95% CI: 0.467-0.590) and both sensitivity and specificity approaching random levels. Optimal cutoff values for each indicator were Cyfra21-1: 2.865, CEA: 3.105, NSE: 13.135, and SCC: 0.175, with Youden indices showing CEA (60.86%) and Cyfra21-1 (65.10%) slightly superior in overall diagnostic efficacy (**Table 5**; **Figure 2**).

Diagnostic value of serum tumor markers in distinguishing PF from PF+LC groups

ROC curve analysis was performed to evaluate the diagnostic performance of Cyfra21-1, CEA, NSE, and SCC in distinguishing PF from PF+LC groups. CEA demonstrated the best diagnostic performance, with an AUC of 0.849 (95% CI: 0.804-0.894), high specificity (97.73%) and sensitivity (74.33%), and a Youden index of 72.06%. NSE also showed good diagnostic value, with an AUC of 0.768 (95% CI: 0.718-0.817), specificity of 89.48%, and sensitivity of 63.10%. Cyfra21-1 and SCC showed relatively lower diagnostic value, with AUCs of 0.734 and 0.612, respectively, where Cyfra21-1 demon-

Table 3. Comparison of pulmonary function indicators among groups

Variable	PF (n=485)	LC (n=135)	PF+LC (n=187)	Statistics	*P* Values
PO_2 (mmHg)	74.13±13.50	61.40±19.85	59.19±19.46	72.909	<0.001
FVC%Pred	74.50 [61.30, 87.30]	67.25 [58.73, 77.28]	66.00 [55.85, 77.50]	34.784	<0.001
DLCO%Pred	57.30 [42.40, 72.20]	52.29 [41.28, 63.80]	50.70 [37.25, 63.60]	15.689	<0.001
DLCO/VA%Pred	63.30 [53.00, 76.20]	56.06 [44.95, 68.56]	52.30 [41.45, 67.60]	51.508	<0.001
Lung Reserve Rate%	75.30 [67.70, 84.60]	64.10 [55.83, 73.17]	62.90 [53.55, 73.35]	134.381	<0.001

Note: PO_2: Partial Pressure of Oxygen, FVC%Pred: Forced Vital Capacity percentage of predicted, DLCO%Pred: Diffusing Capacity for Carbon Monoxide percentage of predicted, DLCO/VA%Pred: DLCO adjusted for alveolar volume percentage of predicted.

Table 4. Comparison of serum tumor marker levels among groups

Variable	Control Group (n=100)	PF (n=485)	LC (n=135)	PF+LC (n=187)	Statistics	*P* Values
Cyfra21-1	2.19±0.48	3.47±1.12	5.14±2.41	5.22±2.35	112.911	<0.001
CEA	2.01±0.60	3.41±1.19	7.71±3.89	8.09±4.03	254.995	<0.001
NSE	13.01±3.07	13.29±3.13	20.94±8.29	19.99±8.31	116.025	<0.001
SCC	0.14 [0.11, 0.16]	0.20 [0.16, 0.24]	0.17 [0.13, 0.22]	0.18 [0.13, 0.22]	112.225	<0.001

Note: Cyfra21-1: Cytokeratin 19 fragment, CEA: Carcinoembryonic Antigen, NSE: Neuron-Specific Enolase, SCC: Squamous Cell Carcinoma antigen.

Table 5. Diagnostic performance of serum tumor markers in distinguishing control from PF groups

Markers	AUC	95% CI	Specificity	Sensitivity	Youden Index	Cut-off
Cyfra21-1	0.847	0.816-0.878	70.10%	95.00%	65.10%	2.865
CEA	0.853	0.822-0.883	61.86%	99.00%	60.86%	3.105
NSE	0.529	0.467-0.590	50.31%	58.00%	8.31%	13.135
SCC	0.823	0.783-0.864	65.98%	85.00%	50.98%	0.175

Note: AUC: Area Under the Curve, CI: Confidence Interval, Cyfra21-1: Cytokeratin 19 fragment, CEA: Carcinoembryonic Antigen, NSE: Neuron-Specific Enolase, SCC: Squamous Cell Carcinoma antigen.

strated high specificity (97.32%) but low sensitivity (46.52%), and SCC showed poor sensitivity (26.74%). Optimal cutoff values for each indicator were Cyfra21-1: 5.455, CEA: 5.63, NSE: 17.345, and SCC: 0.135. Overall, CEA and NSE demonstrated superior diagnostic value for distinguishing PF from PF+LC patients (**Table 6**; **Figure 3**).

Diagnostic value of pulmonary function indicators in distinguishing PF from PF+LC groups

ROC curve analysis was also applied to evaluate the diagnostic performance of five pulmonary function indicators (PO_2, FVC, DLCO, DLCO/VA, and lung reserve rate) in distinguishing PF from PF+LC groups.

Results showed that lung reserve rate demonstrated the best diagnostic performance, with an AUC of 0.746 (95% CI: 0.704-0.787), specificity of 83.51%, sensitivity of 55.08%, and a Youden index of 38.59%. PO_2 showed secondary diagnostic capability, with an AUC of 0.734 (95% CI: 0.688-0.780), sensitivity and specificity of 60.43% and 76.91%, respectively. FVC and DLCO/VA demonstrated moderate diagnostic ability, with AUCs of 0.630 and 0.662, respectively. DLCO exhibited weaker diagnostic effectiveness with an AUC of 0.591. Optimal cutoff values for each indicator were PO_2: 64.5, FVC: 79.25, DLCO: 70.45, DLCO/VA: 54.5, and lung reserve rate: 63.95. Overall, lung reserve rate and PO_2 provided strong clinical reference value in distinguishing PF from PF+LC patients (**Table 7**; **Figure 4**).

Efficacy comparison of serum tumor markers and pulmonary function indicators in diagnosing PF and PF+LC patients

DeLong test was used to compare the diagnostic efficacy of serum tumor markers (Cyfra21-1, CEA, NSE, SCC) and pulmonary function indicators (PO_2, FVC, DLCO, DLCO/VA,

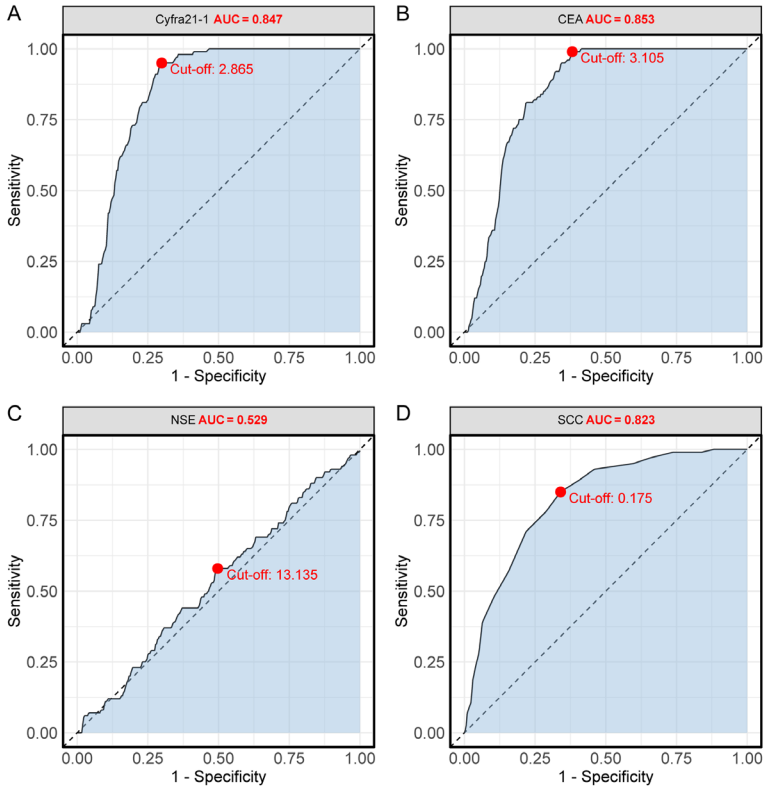


Figure 2. ROC curve analyses of serum tumor markers in distinguishing control from PF groups. A. Cyfra21-1, AUC=0.847, optimal cutoff value 2.865; B. CEA, AUC=0.853, optimal cutoff value 3.105; C. NSE, AUC=0.529, optimal cutoff value 13.135; D. SCC, AUC=0.823, optimal cutoff value 0.175. Note: Cyfra21-1: Cytokeratin 19 fragment, CEA: Carcinoembryonic Antigen, NSE: Neuron-Specific Enolase, SCC: Squamous Cell Carcinoma antigen, AUC: Area Under the Curve.

lung reserve rate) in diagnosing PF and PF+LC patients.

CEA showed significantly superior diagnostic efficacy compared to Cyfra21-1 (AUC difference 0.116, P<0.001), NSE (AUC difference 0.082, P=0.017), SCC (AUC difference 0.237, P<0.001), and all pulmonary function indicators (all P<0.05). Cyfra21-1 outperformed SCC (AUC difference 0.122, P<0.001), FVC (AUC difference 0.104, P<0.001), DLCO (AUC difference 0.142, P<0.001), and DLCO/VA (AUC difference 0.072, P=0.038). NSE significantly surpassed SCC (AUC difference 0.156, P<0.001), FVC (AUC difference 0.138, P<0.001), and DLCO (AUC difference 0.176, P<0.001). Additionally, significant differences existed between PO_2 and FVC, DLCO (all P<0.001). Lung reserve rate showed slightly inferior diagnostic efficacy compared to other pulmonary function indicators and demonstrated lower performance than Cyfra21-1, CEA, and PO_2 in multiple comparisons (all P<0.05). Overall, CEA exhibited the optimal diagnostic value, with tumor markers generally outperforming most pulmonary function indicators, suggesting high clinical application potential of serum tumor markers in differentiating PF from PF+LC patients (Table S1).

Cox regression analysis of factors affecting 2-year OS in PF patients

Univariate and multivariate Cox regression analyses were performed to evaluate the impact of serum tumor markers, pulmonary function indicators, and clinical characteristics on 2-year OS rate in PF patients.

Results demonstrated that Cyfra21-1, FVC, DLCO, age, and PF type were all independent risk factors affecting patient prognosis. Specifically, Cyfra21-1 (hazard ratio [HR] =2.031, 95% CI: 1.66-2.485, P<0.001) was identified as a significant prognostic factor in multivariate analysis, suggesting that elevated Cyfra21-1 levels correlate with decreased survival rates. Pulmonary function indicators FVC (HR=0.956, 95% CI: 0.944-0.968, P<0.001) and DLCO (HR=0.962, 95% CI: 0.951-0.973, P<0.001) were also associated with poor prognosis. Patients aged ≥65 years demonstrated increased survival risk (HR=1.6, 95% CI: 1.092-2.345, P=0.016). IPF type represented a significantly worse prognostic (HR=5.325, 95% CI: 3.562-7.961, P<0.001). Other tumor markers and clinical variables showed no significant correlations with 2-year OS (**Table 8**; **Figure 5**).

Cox regression analysis of factors affecting 2-year OS in PF+LC patients

Univariate and multivariate Cox regression analyses were again performed to evaluate the impact of serum tumor markers, pulmonary

Table 6. Diagnostic performance of serum tumor markers in distinguishing PF from PF+LC groups

Markers	AUC	95% CI	Specificity	Sensitivity	Youden Index	Cut-off
Cyfra21-1	0.734	0.683-0.784	97.32%	46.52%	43.84%	5.455
CEA	0.849	0.804-0.894	97.73%	74.33%	72.06%	5.630
NSE	0.768	0.718-0.817	89.48%	63.10%	52.59%	17.345
SCC	0.612	0.564-0.660	89.48%	26.74%	16.22%	0.135

Note: Cyfra21-1: Cytokeratin 19 fragment, CEA: Carcinoembryonic Antigen, NSE: Neuron-Specific Enolase, SCC: Squamous Cell Carcinoma antigen, AUC: Area Under the Curve, CI: Confidence Interval.

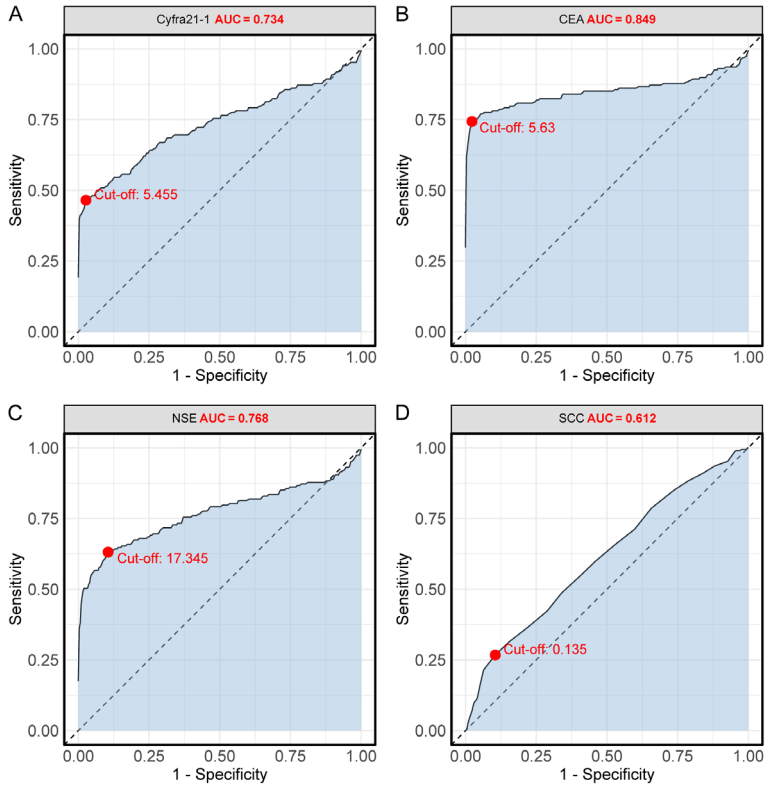


Figure 3. ROC curve analyses of serum tumor markers in distinguishing PF from PF+LC groups. A. Cyfra21-1, AUC=0.734, optimal cutoff value 5.455; B. CEA, AUC=0.849, optimal cutoff value 5.63; C. NSE, AUC=0.768, optimal cutoff value 17.345; D. SCC, AUC=0.612, optimal cutoff value 0.135. Note: Cyfra21-1: Cytokeratin 19 fragment, CEA: Carcinoembryonic Antigen, NSE: Neuron-Specific Enolase, SCC: Squamous Cell Carcinoma antigen, AUC: Area Under the Curve.

function indicators, and clinicopathological characteristics on 2-year OS in PF+LC patients.

Multivariate analysis results revealed that Cyfra21-1 (HR=1.382, 95% CI: 1.260-1.515, P<0.001), FVC (HR=0.966, 95% CI: 0.953-0.979, P<0.001), DLCO (HR=0.987, 95% CI: 0.976-0.997, P=0.013), and age ≥65 years (HR=2.132, 95% CI: 1.444-3.148, P<0.001) were independent prognostic factors affecting patient survival. Fibrosis type also showed a significant effect (HR=1.866, 95% CI: 1.298-2.684, P<0.001 in univariate; but borderline in multivariate, P=0.100). N stage did not reach statistical significance in multivariate analysis (HR=1.380, P=0.100). M stage and pirfenidone treatment were not independent prognostic factors. Other tumor markers and clinical variables showed no significant correlations (**Table 9**; **Figure 6**).

Competing risk model analysis and cumulative incidence curves for PF+LC patients

Multivariate competing risk model analysis demonstrated that Cyfra21-1 (subdistribution hazard ratio [sHR]=1.301, 95% CI: 1.164-1.454, P<0.001), IPF type (vs others: sHR=2.939, 95% CI: 1.717-5.030, P<0.001), and M1 stage (sHR=1.902, 95% CI: 1.168-3.096, P=0.010) were significantly associated with increased lung cancer death risk; FVC served as a protective factor (sHR=0.971, 95% CI: 0.958-0.985, P<0.001). Furthermore, pirfenidone treatment was associated with a reduced risk of lung cancer-specific mortality (sHR=0.350, 95% CI: 0.192-0.635, P<0.001). DLCO was significant in univariate analysis (sHR=0.976, 95% CI: 0.961-0.991, P=0.002) but did not reach statistical significance in multivariate analysis (P=0.076). N stage was not independently associated with lung cancer death risk in multivariate analysis (P=0.150). Other clinical variables (CEA, NSE, SCC, PO_2, DLCO/VA, lung reserve rate, age, gender, BMI, diabetes history, hypertension history, smoking

Table 7. Diagnostic performance of pulmonary function in distinguishing PF from PF+LC groups

Markers	AUC	95% CI	Specificity	Sensitivity	Youden Index	Cut-off
PO_2	0.734	0.688-0.780	76.91%	60.43%	37.34%	64.500
FVC	0.630	0.584-0.675	42.06%	80.21%	22.28%	79.250
DLCO	0.591	0.545-0.638	27.84%	86.63%	14.47%	70.450
DLCO/VA	0.662	0.615-0.709	72.58%	55.08%	27.66%	54.500
Lung Reserve Rate	0.746	0.704-0.787	83.51%	55.08%	38.59%	63.950

Note: PO_2: Partial Pressure of Oxygen, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity for Carbon Monoxide, DLCO/VA: DLCO adjusted for alveolar volume, AUC: Area Under the Curve, CI: Confidence Interval.

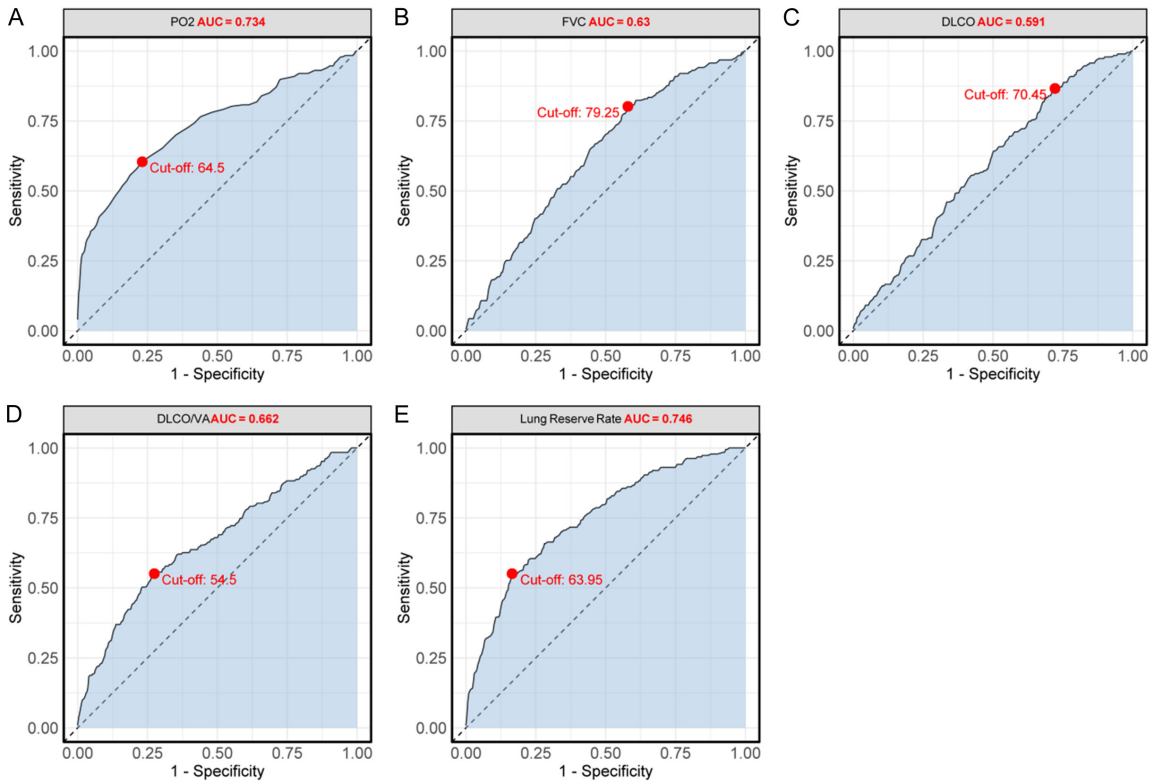


Figure 4. ROC curve analyses of pulmonary function indicators in distinguishing PF from PF+LC groups. A. PO_2, AUC=0.734, optimal cutoff value 64.5; B. FVC, AUC=0.630, optimal cutoff value 79.25; C. DLCO, AUC=0.591, optimal cutoff value 70.45; D. DLCO/VA, AUC=0.662, optimal cutoff value 54.5; E. Lung reserve rate, AUC=0.746, optimal cutoff value 63.95. Note: PO_2: Partial Pressure of Oxygen, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity for Carbon Monoxide, DLCO/VA: DLCO adjusted for alveolar volume, AUC: Area Under the Curve, CI: Confidence Interval.

history, alcohol consumption history, tumor type, and T stage) showed no statistical significance (P>0.05). Cumulative incidence curves further illustrate the impact of these variables on lung cancer and non-lung cancer deaths (**Table 10**; **Figure 7**).

Discussion

CEA demonstrated excellent performance in distinguishing PF from PF+LC, with high specificity and moderate sensitivity, positioning it as a potential non-invasive screening tool. Dai et al. [17] reported significantly elevated serum levels of CEA and CA125 in ILD patients, which were closely associated with an increased risk of lung cancer. This elevation in CEA may reflect abnormal proliferation of tumor cells in the fibrotic lung environment, suggesting its close relationship with the pathological progression of PF+LC. Fainberg et al. [11] conducted large multicenter cohort studies and identified three

Table 8. Cox regression analysis of factors affecting 2-year overall survival in PF patients

Variables	Univariate Analysis			Multivariate Analysis		
	β	*P* Value	HR (CI)	β	*P* Value	HR (CI)
Cyfra21-1	0.787	<0.001	2.197 (1.823-2.648)	0.709	<0.001	2.031 (1.66-2.485)
CEA	0.075	0.321	1.078 (0.930-1.249)			
NSE	0.044	0.123	1.045 (0.988-1.104)			
SCC	-1.439	0.378	0.237 (0.010-5.833)			
PO_2	-0.036	<0.001	0.965 (0.952-0.978)	-0.013	0.074	0.987 (0.973-1.001)
FVC	-0.061	<0.001	0.941 (0.930-0.952)	-0.045	<0.001	0.956 (0.944-0.968)
DLCO	-0.053	<0.001	0.949 (0.938-0.960)	-0.039	<0.001	0.962 (0.951-0.973)
DLCO/VA	-0.005	0.389	0.995 (0.985-1.006)			
Lung Reserve Rate	0.005	0.531	1.005 (0.990-1.020)			
Age						
<65 years	Reference			Reference		
≥65 years	0.455	0.016	1.576 (1.087-2.284)	0.470	0.016	1.600 (1.092-2.345)
Gender						
Female	Reference					
Male	-0.288	0.119	0.75 (0.522-1.077)			
BMI						
<25 kg/m^2	Reference					
≥25 kg/m^2	-0.471	0.071	0.624 (0.374-1.041)			
Diabetes History						
No	Reference					
Yes	0.146	0.526	1.157 (0.736-1.820)			
Hypertension History						
No	Reference					
Yes	-0.201	0.317	0.818 (0.552-1.213)			
Smoking History						
No	Reference					
Yes	0.000	1.000	1.000 (0.698-1.432)			
Alcohol History						
No	Reference					
Yes	0.025	0.913	1.025 (0.657-1.600)			
Fibrosis Type						
Other	Reference			Reference		
Idiopathic fibrosis	1.178	<0.001	3.247 (2.210-4.769)	1.672	<0.001	5.325 (3.562-7.961)
Pirfenidone treatment						
No						
Yes	-0.035	0.844	0.965 (0.679-1.372)			

Note: HR: Hazard Ratio, CI: Confidence Interval, Cyfra21-1: Cytokeratin 19 fragment, CEA: Carcinoembryonic Antigen, NSE: Neuron-Specific Enolase, SCC: Squamous Cell Carcinoma antigen, PO_2: Partial Pressure of Oxygen, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity for Carbon Monoxide, DLCO/VA: DLCO adjusted for alveolar volume, BMI: Body Mass Index.

distinct endotypes of pulmonary fibrosis based on blood biomarkers, with the epithelial injury cluster showing significantly elevated CYFRA21-1, CA19-9, and CA125, associated with higher mortality risk and faster FVC decline. This provides a biological explanation for the elevation of these markers in fibrosis.

Study indicates that IPF and NSCLC share common molecular and pathological mechanisms, including abnormal extracellular matrix expression, which supports the relevance of CEA and other markers in both diseases [18]. The combined application of CEA and NSE may further improve diagnostic accuracy. Kwon et al. [19]

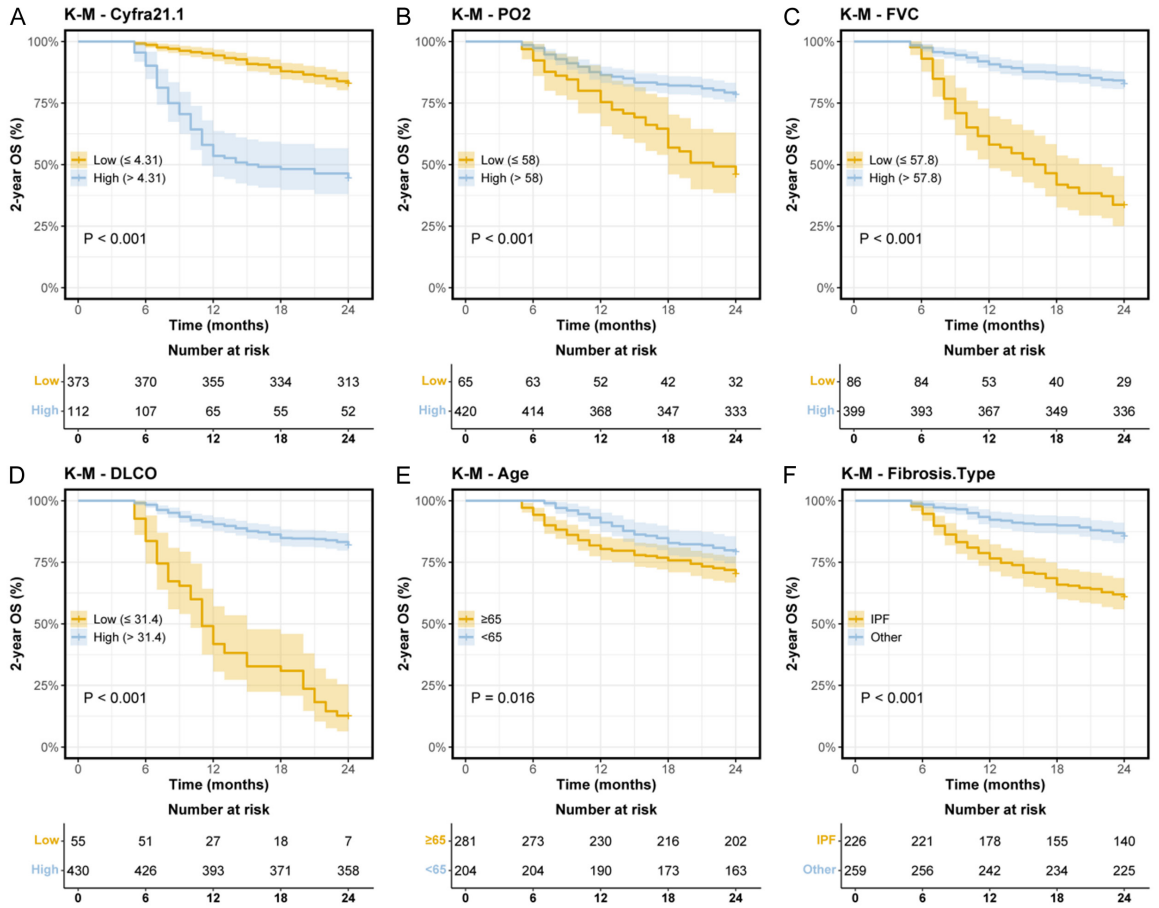


Figure 5. Kaplan-Meier curve analyses of 2-year overall survival rates in PF patients stratified using different variables. A. Survival curve comparison between patients with high and low Cyfra21-1 levels; B. Survival curve comparison between patients with high and low PO_2 levels; C. Survival curve comparison between patients with high and low FVC levels; D. Survival curve comparison between patients with high and low DLCO levels; E. Survival curve comparison between patients in different age groups; F. Survival curve comparison between patients with different fibrosis types. Note: Cyfra21-1: Cytokeratin 19 fragment, PO_2: Partial Pressure of Oxygen, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity for Carbon Monoxide, PF: Pulmonary Fibrosis.

showed that the proportion of abnormal tumor marker values in ILD patients was significantly higher than healthy controls. Yoo et al. [20] found, in a large cohort study of IPF patients, that the cumulative lung cancer incidence increased progressively over time, with male gender, smoking history, and rapid FVC decline identified as important risk factors for lung cancer development. Similar strategies, such as combining multiple markers, have also shown promise in enhancing the precision of lung cancer screening. Multi-marker prediction models based on hematological indicators have demonstrated good diagnostic efficacy in early screening of lung adenocarcinoma in patients with pulmonary fibrosis [21].

Lung reserve rate and PO_2 performed well in distinguishing PF from PF+LC, reflecting the dual damage to pulmonary function caused by both tumor and fibrosis. The lung reserve rate, as an overall pulmonary function indicator, may be related to lung tissue destruction caused by tumor invasion, while a decline in PO_2 suggests a deterioration in gas exchange capacity [22]. The diagnostic performance of FVC and DLCO was relatively weak, possibly because these parameters are often already abnormal in PF patients, making it difficult to further distinguish patients with combined lung cancer. Fisher et al. [23] emphasized that diagnosing and staging lung cancer in ILD background requires careful interpretation of CT and PET-CT

Table 9. Cox regression analysis of factors affecting 2-year overall survival in PF+LC patients

Variable	Univariate Analysis			Multivariate Analysis		
	β	*P* Value	HR (CI)	β	*P* Value	HR (CI)
Cyfra21-1	0.299	<0.001	1.349 (1.25-1.455)	0.323	<0.001	1.382 (1.260-1.515)
CEA						
NSE	-0.002	0.924	0.998 (0.958-1.040)			
SCC						
PO_2	-0.005	0.649	0.995 (0.974-1.017)			
FVC						
DLCO	1.036	0.524	2.819 (0.116-68.472)			
DLCO/VA						
Lung Reserve Rate	-0.004	0.400	0.996 (0.987-1.005)			
Age						
<65 years	-0.047	<0.001	0.954 (0.942-0.965)	-0.035	<0.001	0.966 (0.953-0.979)
≥65 years						
Gender	-0.027	<0.001	0.974 (0.963-0.984)	-0.014	0.013	0.987 (0.976-0.997)
Female						
Male	-0.001	0.906	0.999 (0.990-1.009)			
BMI						
<25 kg/m^2	0.004	0.587	1.004 (0.991-1.016)			
≥25 kg/m^2						
Diabetes History						
No	0.622	<0.001	1.862 (1.290-2.688)	0.757	<0.001	2.132 (1.444-3.148)
Yes						
Hypertension History						
No	-0.131	0.486	0.878 (0.608-1.267)			
Yes						
Smoking History						
No	-0.090	0.690	0.914 (0.589-1.420)			
Yes						
Alcohol History						
No	0.281	0.272	1.325 (0.802-2.187)			
Yes						
Fibrosis Type						
Other	0.001	0.997	1.001 (0.673-1.488)			
Idiopathic fibrosis						
Tumor Type						
Squamous carcinoma	0.169	0.364	1.184 (0.822-1.707)			
Adenocarcinoma						
T Stage						
T3+T4	0.217	0.314	1.242 (0.814-1.896)			
T1+T2						
N Stage						
N0	0.624	<0.001	1.866 (1.298-2.684)	0.322	0.100	1.380 (0.940-2.026)
N1-3						
M Stage						
M0	-0.141	0.441	0.868 (0.606-1.243)			
M1						
Pirfenidone treatment						
No	0.063	0.728	1.065 (0.746-1.522)			
Yes						

Note: HR: Hazard Ratio, CI: Confidence Interval, Cyfra21-1: Cytokeratin 19 fragment, CEA: Carcinoembryonic Antigen, NSE: Neuron-Specific Enolase, SCC: Squamous Cell Carcinoma antigen, PO_2: Partial Pressure of Oxygen, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity for Carbon Monoxide, DLCO/VA: DLCO adjusted for alveolar volume, BMI: Body Mass Index.

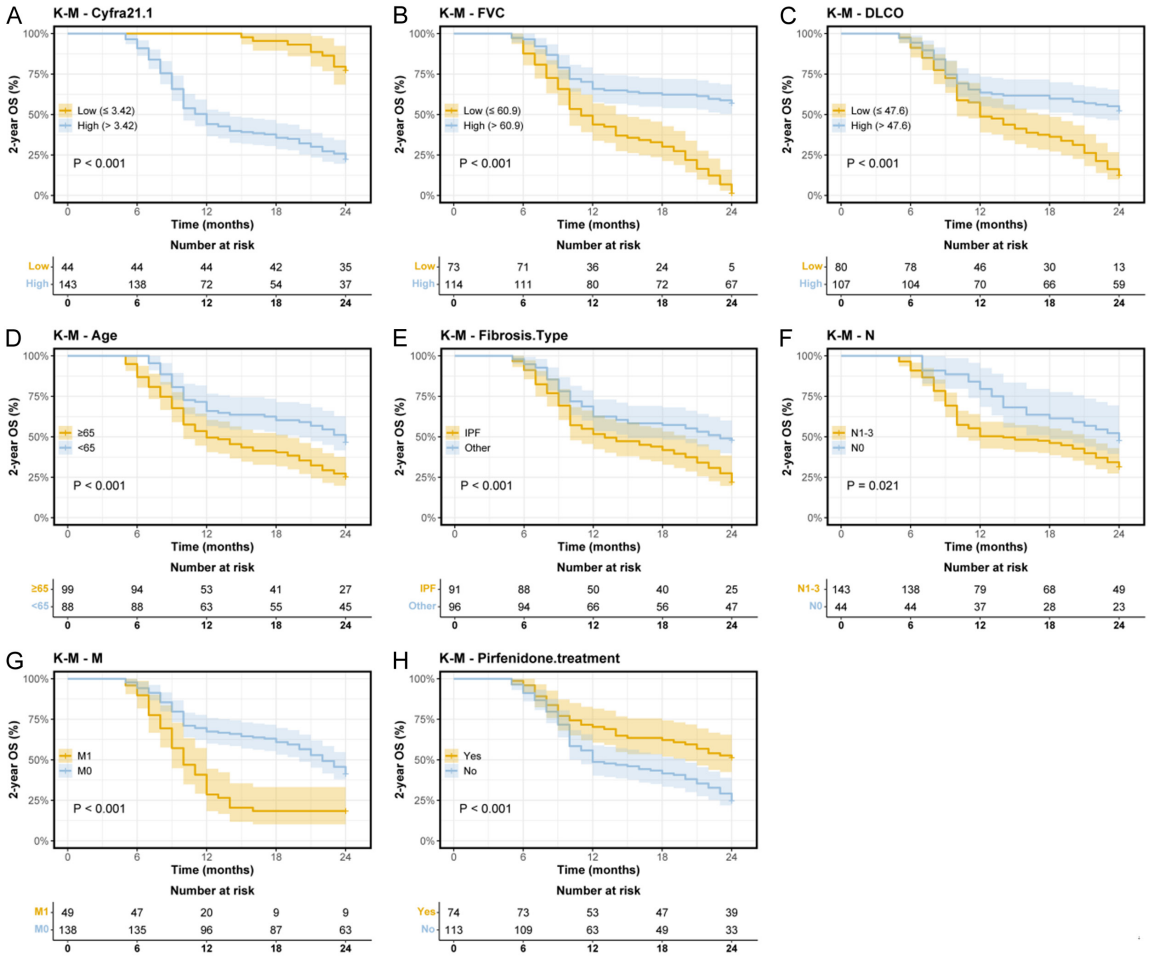


Figure 6. Kaplan-Meier curve analyses of 2-year overall survival rates in PF+LC patients stratified using different variables. A. Survival curve comparison between patients with high and low Cyfra21-1 levels; B. Survival curve comparison between patients with high and low FVC levels; C. Survival curve comparison between patients with high and low DLCO levels; D. Survival curve comparison between patients in different age groups; E. Survival curve comparison between patients with different fibrosis types; F. Survival curve comparison between patients with different N stages; G. Survival curve comparison between patients with different M stages. H. Survival curve comparison between patients with and without Pirfenidone treatment. Note: Cyfra21-1: Cytokeratin 19 fragment, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity for Carbon Monoxide, PF: Pulmonary Fibrosis, LC: Lung Cancer.

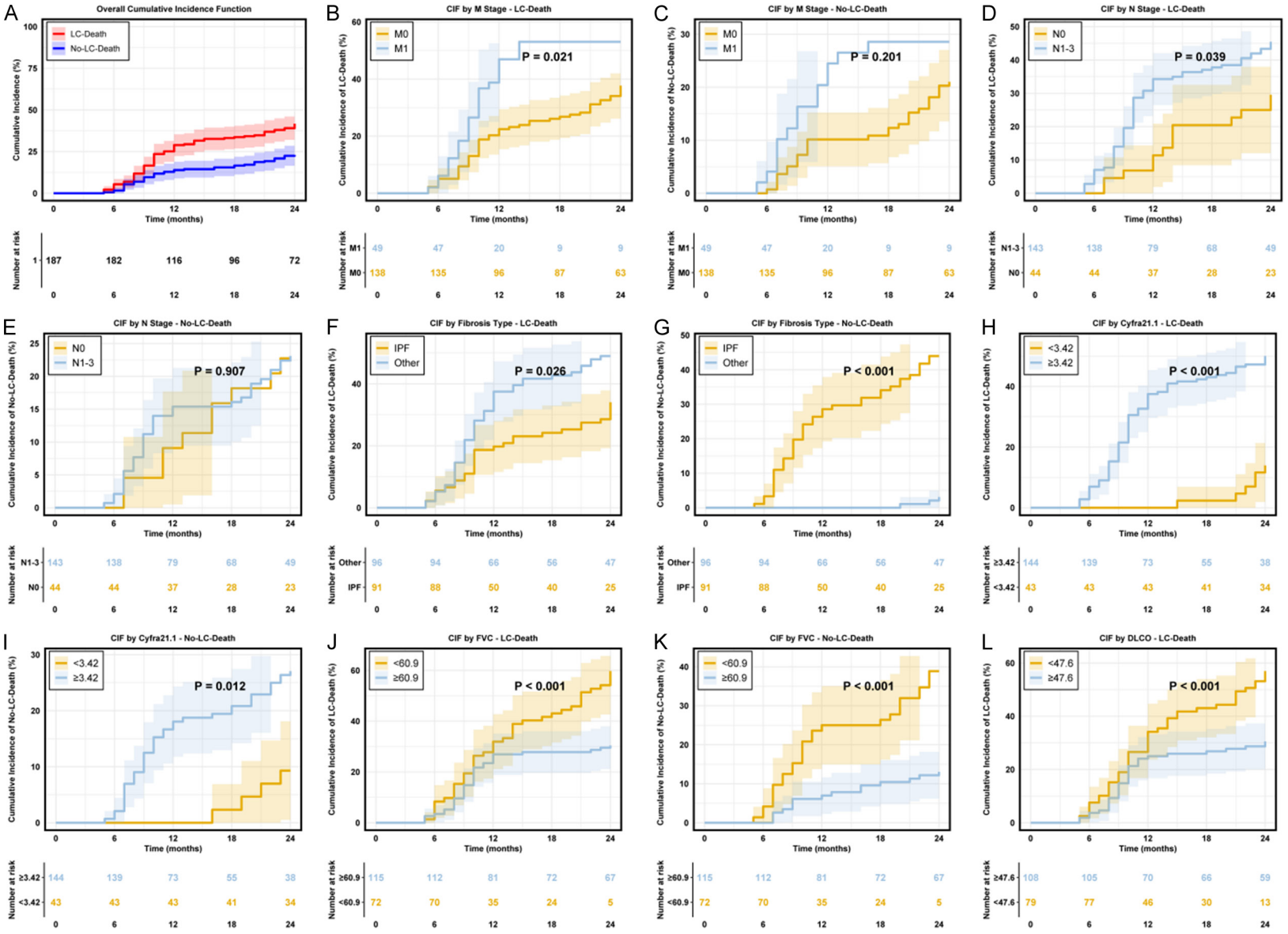
imaging to distinguish nodules from fibrotic areas. Additionally, literature suggests that, in fibrotic ILD patients, exercise- or resting-induced hypoxemia in fibrotic ILD patients is independently associated with shorter transplant-free survival [24]. The advantage of pulmonary function parameters lies in their direct reflection of the physiological impact of the disease on the respiratory system, providing a more comprehensive assessment when combined with serum markers. IPF and lung cancer share many pathological similarities, including abnormal activation of Wnt/β-catenin and PI3K/AKT signaling pathways [25], which could be incorporated into diagnostic models. This model can be further optimized by integrating imaging data, such as CT features. Tsuchiya et al. [26] showed that pulmonary hemodynamic parameters, assessed by phase-contrast MRI, particularly decreased right heart output and reduced relative pulmonary artery area change, can predict short-term mortality in ILD patients.

Serum markers offer significant advantages over pulmonary function parameters in diagnosis, particularly due to the non-invasive nature and easy operability. Satoh et al. [27] showed that proteomic analysis can help identify primary tumor sites in patients with elevated CEA, thus distinguishing false-positive results. In

Table 10. Competing risk model analysis of lung cancer-related death vs. non-lung cancer-related death in PF+LC patients

Variable	Univariate Analysis			Multivariate Analysis		
	β	*P* Value	sHR (CI)	β	*P* Value	sHR (CI)
Cyfra21-1	0.236	<0.001	1.266 (1.162-1.379)	0.263	<0.001	1.301 (1.164-1.454)
CEA	-0.005	0.820	0.995 (0.949-1.042)			
NSE	-0.010	0.470	0.990 (0.965-1.017)			
SCC	1.275	0.540	3.578 (0.062-205.101)			
PO_2	0.005	0.430	1.005 (0.993-1.016)			
FVC	-0.032	<0.001	0.969 (0.956-0.981)	-0.029	<0.001	0.971 (0.958-0.985)
DLCO	-0.024	0.002	0.976 (0.961-0.991)	-0.012	0.076	0.988 (0.975-1.001)
DLCO/VA	-0.004	0.510	0.996 (0.983-1.009)			
Lung Reserve Rate	0.006	0.490	1.006 (0.989-1.023)			
Age						
<65 years						
≥65 years	0.248	0.260	1.282 (0.831-1.977)			
Gender						
Female						
Male	0.309	0.210	1.363 (0.844-2.199)			
BMI						
<25 kg/m^2						
≥25 kg/m^2	0.175	0.490	1.192 (0.721-1.970)			
Diabetes History						
No						
Yes	-0.127	0.720	0.880 (0.439-1.764)			
Hypertension History						
No						
Yes	-0.160	0.520	0.852 (0.521-1.394)			
Smoking History						
No						
Yes	0.096	0.670	1.101 (0.709-1.712)			
Alcohol History						
No						
Yes	-0.074	0.790	0.929 (0.538-1.606)			
Fibrosis Type						
Other						
Idiopathic fibrosis	0.501	0.026	1.651 (1.061-2.568)	1.078	<0.001	2.939 (1.717-5.030)
Tumor Type						
Squamous carcinoma						
Adenocarcinoma	-0.394	0.080	0.674 (0.434-1.048)			
T Stage						
T3+T4						
T1+T2	-0.236	0.290	0.790 (0.511-1.220)			
N Stage						
N0						
N1-3	0.594	0.039	1.811 (1.031-3.181)	0.404	0.150	1.497 (0.863-2.597)
M Stage						
M0						
M1	0.543	0.024	1.721 (1.073-2.762)	0.643	0.010	1.902 (1.168-3.096)
Pirfenidone treatment						
No						
Yes	-1.259	<0.001	0.284 (0.163-0.494)	-1.051	<0.001	0.350 (0.192-0.635)

Note: sHR: Subdistribution Hazard Ratio, CI: Confidence Interval, Cyfra21-1: Cytokeratin 19 fragment, CEA: Carcinoembryonic Antigen, NSE: Neuron-Specific Enolase, SCC: Squamous Cell Carcinoma antigen, PO_2: Partial Pressure of Oxygen, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity for Carbon Monoxide, DLCO/VA: DLCO adjusted for alveolar volume, BMI: Body Mass Index.


A
Overall Cumulative Incidence Function
LC-Death
No-LC-Death
Cumulative Incidence (%)
Time (months)
Number at risk
1 187 182 116 96 72
B
CIF by M Stage - LC-Death
M0
M1
P = 0.021
Cumulative Incidence of LC-Death (%)
M1 49 47 20 9 9
M0 138 135 96 87 63
C
CIF by M Stage - No-LC-Death
M0
M1
P = 0.201
Cumulative Incidence of No-LC-Death (%)
M1 49 47 20 9 9
M0 138 135 96 87 63
D
CIF by N Stage - LC-Death
N0
N1-3
P = 0.039
Cumulative Incidence of LC-Death (%)
N1-3 143 138 79 68 49
N0 44 44 37 28 23
E
CIF by N Stage - No-LC-Death
N0
N1-3
P = 0.907
Cumulative Incidence of No-LC-Death (%)
N1-3 143 138 79 68 49
N0 44 44 37 28 23
F
CIF by Fibrosis Type - LC-Death
IPF
Other
P = 0.026
Cumulative Incidence of LC-Death (%)
Other 96 94 66 56 47
IPF 91 88 50 40 25
G
CIF by Fibrosis Type - No-LC-Death
IPF
Other
P < 0.001
Cumulative Incidence of No-LC-Death (%)
Other 96 94 66 56 47
IPF 91 88 50 40 25
H
CIF by Cyfra21.1 - LC-Death
<3.42
≥3.42
P < 0.001
Cumulative Incidence of LC-Death (%)
≥3.42 144 139 73 55 38
<3.42 43 43 43 41 34
I
CIF by Cyfra21.1 - No-LC-Death
<3.42
≥3.42
P = 0.012
Cumulative Incidence of No-LC-Death (%)
≥3.42 144 139 73 55 38
<3.42 43 43 43 41 34
J
CIF by FVC - LC-Death
<60.9
≥60.9
P < 0.001
Cumulative Incidence of LC-Death (%)
≥60.9 115 112 81 72 67
<60.9 72 70 35 24 5
K
CIF by FVC - No-LC-Death
<60.9
≥60.9
P < 0.001
Cumulative Incidence of No-LC-Death (%)
≥60.9 115 112 81 72 67
<60.9 72 70 35 24 5
L
CIF by DLCO - LC-Death
<47.6
≥47.6
P < 0.001
Cumulative Incidence of LC-Death (%)
≥47.6 108 105 70 66 59
<47.6 79 77 46 30 13
Time (months)
Number at risk

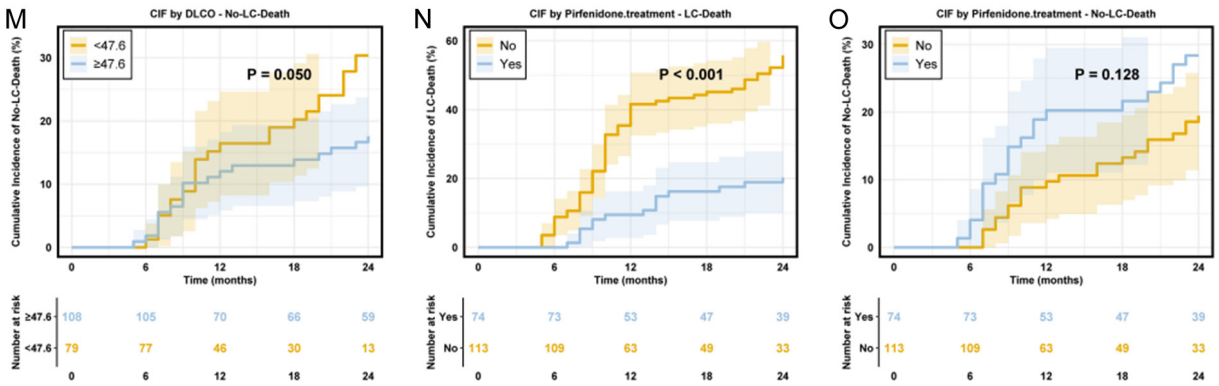


Figure 7. Cumulative incidence curves for PF+LC patients stratified using different variables (Competing Risk Model). A. Overall mortality cumulative incidence rate; B. Cumulative incidence rate of lung cancer-related death stratified by M stage; C. Cumulative incidence rate of non-lung cancer-related death stratified by M stage; D. Cumulative incidence rate of lung cancer-related death stratified by N stage; E. Cumulative incidence rate of non-lung cancer-related death stratified by N stage; F. Cumulative incidence rate of lung cancer-related death stratified by fibrosis type; G. Cumulative incidence rate of non-lung cancer-related death stratified by fibrosis type; H. Cumulative incidence rate of lung cancer-related death stratified by Cyfra21-1 level; I. Lung cancer death cumulative incidence rate stratified by FVC level; J. Cumulative incidence rate of lung cancer-related death stratified by FVC level; K. Lung cancer death cumulative incidence rate stratified by FVC level; L. Cumulative incidence rate of lung cancer-related death stratified by DLCO level; M. Cumulative incidence of lung cancer mortality stratified by DLCO level; N. Cumulative incidence rate of lung cancer-related death stratified by Pirfenidone treatment; O. Cumulative incidence rate of non-lung cancer-related death stratified by Pirfenidone treatment. Note: Cyfra21-1: Cytokeratin 19 fragment, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity for Carbon Monoxide, PF: Pulmonary Fibrosis, LC: Lung Cancer.

contrast, pulmonary function testing depends on professional equipment and patient cooperation, which can be limited by technical differences or patient conditions. However, the diagnostic value of lung reserve rate and PO_2 suggests that pulmonary function parameters still play an essential role, particularly when monitoring disease progression or evaluating treatment effects. Literature indicates [28] that in large clinical practice database analyses, the incidence of PF diagnosis among lung cancer patients was significantly higher compared to controls, with worse survival rates in PF patients. Compared to existing lung cancer screening methods such as low-dose CT, serum markers have the advantages of lower costs and no radiation exposure, making them suitable for screening high-risk PF patients.

In PF patients, Cyfra21-1, FVC, DLCO, age, and idiopathic fibrosis were significant predictors of survival outcomes. The elevation of Cyfra21-1 may reflect epithelial cell damage or abnormal proliferation during the progression of lung tissue fibrosis, suggesting that it is not only a lung cancer marker but also associated with PF pathological progression. A decline in FVC and DLCO indicates severe impairment of lung capacity and gas exchange, which are closely related to shortened survival. Patients with idiopathic fibrosis have particularly poor prognosis, possibly due to the rapid progression of the disease and the potential for cancerous transformation. Dobkin et al. [29] showed that imaging Usual Interstitial Pneumonia (UIP) pattern is an independent risk factor for PF patients with concurrent lung cancer. Elderly patients also face increased survival risk, possibly due to comorbidity burden or decreased physiological reserve. Platenburg et al. [30] found that a substantial proportion of non-IPF patients met PPF criteria, and these patients had significantly shorter median transplant-free survival compared to those without PPF, with FVC and DLCO as independent risk factors for PPF. Further literature indicates [31] that in IPF patients, CA15-3 levels are significantly correlated with disease severity and survival, with marker levels significantly decreasing after lung transplantation. These findings are consistent with previous studies, but our study is the first to clarify Cyfra21-1's independent role in PF prognosis. Future research can deeply investigate Cyfra21-1's molecular mechanisms in the fibrotic microenvironment, such as its interactions with inflammatory factors or fibrotic signaling pathways, providing basis for the development of new therapeutic targets.

In PF+LC patients, Cyfra21-1, FVC, DLCO, age, and tumor staging (N stage, M stage) significantly influenced survival outcomes. The significant role of M stage highlights that distant metastasis is a key factor driving prognostic deterioration, underscoring the devastating impact of tumor spread in these patients. The prognostic value of Cyfra21-1 is likely related to its reflection of both tumor burden and the fibrosis-tumor interactions. Karampitsakos et al. [32] found that, in a European multicenter study, IPF patients with lung cancer had a significantly increased all-cause mortality risk, with monocyte count and anti-fibrotic treatment identified as important prognostic factors. A decline in FVC and DLCO further worsened survival risk, suggesting that pulmonary function deterioration remains a core element to prognostic assessment in comorbid conditions. Motono et al. [33] found that ILD was an independent risk factor for disease-free survival in pathological stage IA NSCLC patients, with elevated CEA levels also significantly affecting patient prognosis. Compared to simple lung cancer studies, PF+LC patients' prognosis is affected by synergistic effects of both fibrosis and tumor pathology, presenting more complex clinical characteristics. Literature [34] indicates that HRCT patterns, reclassified according to IPF guidelines, show UIP and possible UIP patterns as independent risk factors for severe postoperative acute exacerbation and death. The prognostic role of idiopathic fibrosis in PF+LC patients was less significant than in PF patients, possibly because tumor-related factors such as staging play a dominant role. Notably, pirfenidone treatment did not reach statistical significance in the multivariable Cox regression analysis, suggesting that its protective effect on OS in PF+LC patients may be masked by other key factors, such as tumor progression. This contrasts with previous studies showing survival benefits of pirfenidone in patients with isolated IPF, potentially reflecting the dominant role of tumor-related mortality risk in the PF+LC disease state, which could weaken the overall prognostic improvement provided by antifibrotic therapy.

Competing risk model analysis revealed the key roles of Cyfra21-1, FVC, DLCO, idiopathic fibrosis, and M stage in predicting lung cancer-specific mortality in PF+LC patients. Compared to traditional Cox proportional hazards regression models, Fine-Gray competing risk models provide a more nuanced approach by distinguishing lung cancer-related deaths from non-tumor-related deaths, thereby avoiding prognostic estimation bias caused by neglecting other causes of death, particularly suitable for PF+LC populations, which have complex death mechanisms [35]. Our study found that Cyfra21-1 is an important predictor of lung cancer-specific death, demonstrating importance in both competing risk and Cox models. Literature indicates [36] that CA19-9 levels are negatively correlated with functional decline in ILD patients, particularly in IPF rapid progressors, suggesting its potential as a disease severity marker. This suggests that Cyfra21-1 may play multiple roles in PF+LC disease progression, both reflecting tumor burden and possibly contributing to synergistic fibrosis-tumor progression through epithelial cell damage, inflammatory responses, or epithelial-mesenchymal transition (EMT). Pulmonary function parameters, such as FVC and DLCO, showed robust prognostic value in both models. These parameters reflect lung capacity and gas exchange function, respectively, and their decline indicates significantly impaired pulmonary function reserve in PF+LC patients under the dual impact of fibrosis and tumor. Enokida et al. [37] showed that CT diffuse lesion patterns combined with severe respiratory failure were the strongest predictors of short-term mortality in acute exacerbation of idiopathic chronic fibrosing interstitial pneumonia. This finding not only suggests a poorer overall prognosis but also highlights a strong association with an increased risk of lung cancer-related mortality.

As a subtype of PF, IPF demonstrated significant predictive value for lung cancer-specific death in the competing risk model, although its impact on overall mortality in PF+LC patients was not statistically significant in the Cox model. Yoon et al. [38] conducted a nationwide study and found that pirfenidone treatment was significantly associated with a reduced risk of lung cancer in IPF patients, further suggesting that antifibrotic therapy may have antitumor effects. Similarly, a Thorax article [39] demonstrated that IPF patients receiving antifibrotic therapy had a significantly lower incidence of lung cancer and lung cancer-related mortality, which aligns with the results of our competing risk model. Moreover, a real-world study by Lee et al. [40] found that even low-dose pirfenidone could improve survival and slow lung function decline in IPF patients, indicating that its potential benefits extend beyond antifibrotic effects and may also reduce lung cancer risk by improving pulmonary function. In addition, evidence [41] shows that pirfenidone can inhibit TGF-β1 - mediated metabolic reprogramming and EMT in NSCLC, conferring direct antitumor potential. Similarly, Wang et al. [42] reported that pirfenidone delays renal cancer progression by suppressing TGF-β signaling and improving the tumor immune microenvironment, a mechanism that may also apply to the special population with pulmonary fibrosis combined with lung cancer. The competing risk model effectively uncovered these relationships, enhancing the precision of clinical risk stratification.

Among tumor-related variables, M stage - an indicator of distant metastasis - emerged as a robust prognostic factor in both models, underscoring that systemic tumor progression is a key driver of mortality in PF+LC. Interestingly, pirfenidone therapy showed a marked protective effect in the competing risk model but did not reach statistical significance in the Cox model. This discrepancy highlights the unique value of the competing risk analysis: pirfenidone may specifically lower lung cancer-related mortality by slowing fibrosis progression, suppressing inflammation, or modulating the fibrosis - tumor microenvironment interplay - effects that could be obscured in conventional survival analyses by non-cancer-related deaths. Collectively, these findings support the view that antifibrotic therapy in PF+LC patients may provide dual benefits: delaying fibrosis progression while reducing cancer-related mortality risk, thereby offering an important therapeutic option for this high-risk population.

Study limitations include the potential for selection bias inherent to the retrospective design, possible interference with the specificity of CEA and NSE by co-morbid conditions, variability in pulmonary function test standardization over time, and the short 2-year follow-up that may underrepresent long-term outcomes. In addi-

tion, the single-center nature of our cohort restricts external validity and generalizability.

Treatment-related confounders, such as chemotherapy, radiotherapy, or targeted therapy in PF+LC patients, were not adjusted for, which may have influenced OS and lung cancer - specific mortality estimates. Although the calculation method for lung reserve rate and the detailed arterial blood gas procedures have been clarified in the revision, residual confounding from unmeasured variables (e.g., imaging features, molecular alterations, treatment intensity) cannot be fully excluded. Future research should prioritize multicenter, prospective studies with standardized pulmonary function protocols and systematic treatment data collection. Developing integrated biomarker - function - imaging prognostic models, potentially enhanced by machine learning, along with external validation, would provide more robust and generalizable results. Additionally, further exploration of the mechanistic links between Cyfra21-1, CEA, and the PF-LC microenvironment and investigation of the effects of antifibrotic agents and immuno-oncology therapies on biomarker dynamics and patient outcomes are warranted.

Conclusions

This study demonstrates that CEA and NSE are effective non-invasive markers for distinguishing PF from PF+LC, with lung reserve rate and PO_2 providing valuable supplementary information. Cyfra21-1, FVC, DLCO, age, and tumor staging play key roles in predicting survival outcomes and lung cancer-specific mortality.

Disclosure of conflict of interest

None.

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Table S1. Delong test was used to analyze the efficacy of tumor markers and pulmonary function indexes in the diagnosis of ILD and ILC+LC patients

Marker1	Marker2	Z_value	*P*_value	AUC_difference	CI_lower_upper
Cyfra21-1	CEA	-3.395	<0.001	-0.116	-0.183 - -0.049
Cyfra21-1	NSE	-0.921	0.357	-0.034	-0.107 - 0.039
Cyfra21-1	SCC	3.378	<0.001	0.122	0.051 - 0.192
Cyfra21-1	PO2	-0.02	0.984	-0.001	-0.066 - 0.065
Cyfra21-1	FVC	3.573	<0.001	0.104	0.047 - 0.161
Cyfra21-1	DLCO	4.386	<0.001	0.142	0.079 - 0.206
Cyfra21-1	DLCO/VA	2.074	0.038	0.072	0.004 - 0.139
Cyfra21-1	Lung Reserve Rate	-0.366	0.715	-0.012	-0.076 - 0.052
CEA	NSE	2.396	0.017	0.082	0.015 - 0.148
CEA	SCC	7.123	<0.001	0.237	0.172 - 0.303
CEA	PO2	3.442	<0.001	0.115	0.050 - 0.181
CEA	FVC	6.732	<0.001	0.22	0.156 - 0.284
CEA	DLCO	8.048	<0.001	0.258	0.195 - 0.321
CEA	DLCO/VA	5.548	<0.001	0.187	0.121 - 0.254
CEA	Lung Reserve Rate	3.393	<0.001	0.104	0.044 - 0.164
NSE	SCC	4.319	<0.001	0.156	0.085 - 0.226
NSE	PO2	1.01	0.313	0.034	-0.032 - 0.099
NSE	FVC	3.866	<0.001	0.138	0.068 - 0.208
NSE	DLCO	5.103	<0.001	0.176	0.109 - 0.244
NSE	DLCO/VA	3.035	0.002	0.106	0.037 - 0.174
NSE	Lung Reserve Rate	0.663	0.508	0.022	-0.043 - 0.088
SCC	PO2	-3.552	<0.001	-0.122	-0.190 - -0.055
SCC	FVC	-0.496	0.62	-0.018	-0.087 - 0.052
SCC	DLCO	0.584	0.559	0.021	-0.049 - 0.090
SCC	DLCO/VA	-1.402	0.161	-0.05	-0.120 - 0.020
SCC	Lung Reserve Rate	-4.138	<0.001	-0.134	-0.197 - -0.070
PO2	FVC	3.366	<0.001	0.105	0.044 - 0.165
PO2	DLCO	4.478	<0.001	0.143	0.080 - 0.205
PO2	DLCO/VA	2.241	0.025	0.072	0.009 - 0.136
PO2	Lung Reserve Rate	-0.357	0.721	-0.011	-0.074 - 0.051
FVC	DLCO	1.328	0.184	0.038	-0.018 - 0.095
FVC	DLCO/VA	-0.946	0.344	-0.032	-0.099 - 0.035
FVC	Lung Reserve Rate	-3.675	<0.001	-0.116	-0.178 - -0.054
DLCO	DLCO/VA	-1.991	0.046	-0.071	-0.140 - -0.001
DLCO	Lung Reserve Rate	-4.651	<0.001	-0.154	-0.219 - -0.089
DLCO/VA	Lung Reserve Rate	-2.732	0.006	-0.084	-0.144 - -0.024

Note: Cytokeratin 19 fragment (Cyfra21-1), Carcinoembryonic Antigen (CEA), Neuron-Specific Enolase (NSE), Squamous Cell Carcinoma antigen (SCC), Partial Pressure of Oxygen (PO2), Forced Vital Capacity (FVC), Diffusing Capacity for Carbon Monoxide (DLCO), DLCO adjusted for alveolar volume (DLCO/VA), Area Under the Curve (AUC), Confidence Interval (CI).