Cumulative Incidences of Lung Cancer in Various Interstitial Lung Diseases

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Abstract

Background

Interstitial lung disease (ILD) patients often develop lung cancer. However, previous studies on the incidences of lung cancer in ILD patients focused on specific aetiologies, such as idiopathic pulmonary fibrosis (IPF). The lung cancer incidences in these patients have not been investigated, and thus, we aimed to evaluate them here.

Methods

ILD patients at our hospital were retrospectively reviewed. The cumulative incidences of lung cancer in patients with various ILDs were estimated with Kaplan-Meier curves and compared between ILD groups using log-rank tests. The association between several variables at initial diagnosis and lung cancer development was assessed with Cox proportional hazards regression analysis to identify predictors.

Results

In all, 606 ILD patients, including 161 with IPF, 133 with non-IPF idiopathic interstitial pneumonias, 160 with chronic hypersensitivity pneumonitis, 87 with connective tissue disease-related ILDs, 19 with pulmonary sarcoidosis, and 46 with other ILDs, were included. Twenty-eight patients developed lung cancer. The cumulative incidences of lung cancer at 1, 3, and 5 years were: 1.9, 5.7, and 12.3% with IPF, respectively; 0.8, 0.8, and 4.0% in non-IPF idiopathic interstitial pneumonias; 2.0, 4.6, and 11.0% in chronic hypersensitivity pneumonitis; and 1.1, 1.1, and 2.9% in connective tissue disease-related ILDs. IPF patients had a higher incidence of lung cancer than non-IPF idiopathic interstitial pneumonia patients ($p = 0.036$). A radiological usual interstitial pneumonia pattern, forced vital capacity value, and pack-years were associated with lung cancer development (hazard ratios 2.959, 1.031, 1.011; 95% confidence intervals 1.257–6.963, 1.006–1.057, 1.002–1.020, $p = 0.013$, 0.017, 0.020, respectively).

Conclusions

The lung cancer incidence is higher in IPF patients than in non-IPF idiopathic interstitial pneumonia patients and is equally high in patients with chronic hypersensitivity pneumonitis and IPF.

Background

Interstitial lung diseases (ILDs) are a group of diffuse parenchymal lung disorders with various forms. ILDs are mainly divided into two categories: ILDs with and without any known causes. The former include hypersensitivity pneumonitis (HP), connective tissue disease-related ILDs (CTD-ILDs), ILDs with anti-neutrophil cytoplasmic antibody-associated vasculitis, and drug-induced pneumonia. The latter are called

idiopathic interstitial pneumonias (IIPs), and the main subtype is idiopathic pulmonary fibrosis (IPF) [1]. In terms of the clinical course, ILDs can be acute or chronic [2]. The former include acute HP, acute eosinophilic pneumonia (EP), and acute or subacute IIPs, which consist of acute interstitial pneumonia, cryptogenic organizing pneumonia, nonspecific interstitial pneumonia (NSIP), and acute exacerbation of IPF or NSIP [3]. The latter are IPF, chronic HP, CTD-ILDs, chronic EP, pulmonary sarcoidosis, asbestosis, radiation pneumonitis, pulmonary alveolar proteinosis.

There are a number of common comorbidities of IPF, a specific form of chronic, progressive fibrosing ILD, including lung cancer (LC), pulmonary hypertension, chronic obstructive pulmonary disease (COPD)/emphysema, pulmonary embolism, and pulmonary infections [4–7]. Previous studies reported that patients with IPF are at high risk for developing LC [8, 9]. IPF patients with LC had a worse prognosis than those without LC [10–12]. Choi et al. reported that the incidence of LC in IPF patients was higher than those in IIP patients and COPD patients [13]. High incidences of LC in patients with CTD-ILDs [14, 15] and IIPs [13] have also been reported. The prevalence of LC in chronic HP patients has been reported, but the incidence has not yet [16].

The incidence of LC in patients with ILDs other than IPF, IIPs, and CTD-ILDs has not yet been revealed. The present study was performed to evaluate the cumulative incidences of LC in patients with ILDs with various aetiologies.

Methods

Patient selection

This study was a retrospective single-centre cohort study involving patients with ILDs. In this study, 672 ILD patients who were diagnosed between January 2008 and December 2012 at Tokyo Medical and Dental University Hospital and who visited their physician regularly were recruited. The exclusion criteria were as follows: (i) patients who had LC at the time of the initial ILD diagnosis, (ii) patients with acute ILDs, and (iii) patients whose high-resolution computed tomography (HRCT) images were not available in the medical records (Fig. 1). Patients with acute ILDs were excluded from this study because the activity of acute ILDs is temporary and does not cause chronic inflammation and fibrosis. Patients enrolled in this study were observed for up to five years because most chronic ILD patients, have a poor prognosis in general. This study was approved by the Institutional Review Board of Tokyo Medical and Dental University (approval number: M2019-087). Because of the retrospective nature of the study, written consent from the use of records was waived.

Definition of each ILD

The diagnosis of IPF was based on the clinical practice guidelines from the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) [17]. The diagnosis of IIPs was based on the ATS/ERS statement about the classification of IIPs [5]. IIPs other than IPF were defined as non-IPF IIPs in this study. The diagnosis of

chronic HP in this study was based on the criteria as previously described [18]. Connective tissue disease (CTD) comprises a group of chronic and systemic autoimmune disorders, such as rheumatoid arthritis, systemic sclerosis, polymyositis or dermatomyositis, Sjögren syndrome, and systemic lupus erythematosus [14]. Patients with CTD were diagnosed by rheumatologists and/or dermatologists in our hospital or fulfilled the criteria for a specific CTD [19-24]. The diagnosis of sarcoidosis was established based on the guidelines of the ATS/ERS/World Association for sarcoidosis and other granulomatous disorders [25]. Pulmonary sarcoidosis patients with radiographic stage II or higher were included [26].

Study design

The diagnosis of LC was based on histological and/or cytological findings of carcinoma. Metastatic disease of the lung was excluded. The eighth edition of the TNM classification system for LC was used in this study [27]. Sex, age, pack-years, and radiological usual interstitial pneumonia (UIP) pattern at the time of the initial ILD diagnosis were recorded. The forced vital capacity (FVC), forced expiratory volume in one second (FEV_1)/FVC values, and serum levels of Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) were recorded for the ILD patients within six months of the initial ILD diagnosis. The radiological UIP pattern was based on HRCT scanning patterns indicated in the clinical practice guidelines published by the ATS, ERS, JRS, and ALAT [17]. The cumulative incidences of LC in ILD patients, and the predictive factors were estimated. ILD patients who developed LC were reviewed for radiological characteristics as well as for LC stage and treatment at the time of LC diagnosis. The diagnosis criteria for emphysema was obtained from previous reports [9]. HRCT at the time of LC diagnosis was retrospectively interpreted by two pulmonary specialists (T.S., M.E.).

Statistical analysis

Data are represented as numbers or medians. Statistical analyses were performed using GraphPad Prism 8 software (GraphPad, San Diego, CA, USA) and EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan) [28]. Data are expressed as medians and ranges. One-way analysis of variance or the Kruskal-Wallis test was used as appropriate to compare the values between different groups. When significant differences between groups were observed, intergroup comparisons were assessed using Tukey's multiple comparisons test or Dunn's multiple comparisons test, as appropriate. The cumulative incidences of LC in ILD patients were evaluated with Kaplan-Meier curves and compared between groups with log-rank tests. Multiple adjustment was not performed. Cox proportional hazards regression analysis was used to identify the significant variables predicting the development of LC. Nine variables were examined for their association with the development of LC in patients with ILDs, namely, sex, age, pack-years, radiological UIP pattern on HRCT, FVC value, FEV_1/FVC value, serum KL-6 level, serum SP-D level, and aetiology. In univariate Cox proportional regression analysis, all available data were used for every variable. All reported p values were two-sided, and a value < 0.05 was considered to be statistically significant.

Results

Clinical characteristics of patients with ILDs

Of the 672 ILD patients, 66 were excluded: 55 patients had LC at the time of the initial diagnosis of an ILD, 8 patients had acute ILDs, and 3 patients did not have HRCT images available (Fig. 1). The 606 patients with ILDs were divided into 6 groups based on aetiology: 161 with IPF, 133 with non-IPF IIPs, 160 with chronic HP, 87 with CTD-ILDs, 19 with pulmonary sarcoidosis, and 46 with other ILDs. Among the 46 patients with other ILDs, 15 had ILDs with anti-neutrophil cytoplasmic antibody-associated vasculitis, 9 had suspected or diagnosed drug-induced ILDs, 7 had suspected or diagnosed asbestosis, 4 had suspected or diagnosed radiation pneumonitis, 3 had chronic EP, 3 had suspected but undiagnosed pulmonary sarcoidosis, 2 had pulmonary alveolar proteinosis, 2 had suspected but undiagnosed CTD-ILDs, and 1 had Castleman's disease.

The characteristics of the ILD patients are summarized in Table 1. The group of patients with CTD-ILDs had a higher proportion of female patients than IPF, non-IPF IIPs, chronic HP, and other ILDs. The group with non-IPF IIPs had a higher proportion of female patients than IPF. No differences were seen in age at the time of initial ILD diagnosis among the groups. The number of pack-years at the time of initial ILD diagnosis was higher in the group with IPF than non-IPF IIPs, chronic HP, CTD-ILDs, and pulmonary sarcoidosis. The IPF group had a higher proportion of patients with radiological UIP pattern at the time of initial diagnosis than any other groups, and the chronic HP group had the second highest proportion among the groups. The IPF, chronic HP, and CTD-ILD groups had lower FVC values than the non-IPF IIP and pulmonary sarcoidosis groups. The groups of chronic HP and CTD-ILD groups had lower FVC values than the group of other ILDs. The IPF and non-IPF IIP groups had lower FVC values than chronic HP groups. The other ILD group had a lower FEV_1/FVC value than the IPF, non-IPF IIP, and CTD-ILD group. The chronic HP group had a higher serum KL-6 and SP-D levels than any other groups.

Characteristics of ILD patients who developed LC

The characteristics of the ILD patients who developed LC are summarized in Table 2. The median observation period of ILD patients was 45 (range, 4-60) months. Of the 606 ILD patients, 28 developed LC during the observation period. The median interval between diagnosis and the development of LC was 32 (range, 4-60) months. Among the 28 ILD patients who developed LC, 12 had IPF, 10 had chronic HP, 3 had non-IPF IIPs, 2 had CTD-ILDs, and 1 had pulmonary sarcoidosis. Of the 28 ILD patients with LC development, 25 (89%) were male smokers. 24 patients (86%) had radiological UIP pattern at the diagnosis of ILDs, and 17 (71%) had LC lesion adjacent to honeycombing. Squamous cell carcinoma was the most frequent cell histological type (n = 13 [46%]), followed by adenocarcinoma (n = 17 [25%]). Of the 14 patients performed surgery on, all 11 excluding 3, whose pathological findings were not available, had pathological UIP pattern.

Cumulative incidences of LC in ILD patients

The cumulative incidences of LC at 1, 3, and 5 years were 1.9, 5.7, and 12.3% in the IPF group; 0.8, 0.8, and 4.0% in the non-IPF IIPs group; 2.0, 4.6, and 11.0% in the chronic HP group; and 1.1, 1.1, and 2.9% in

the CTD-ILD group (Fig. 2). As a result of comparing the four groups together, no significant difference was found in the cumulative incidence of LC among the IPF, non-IPF IIP, chronic HP, and CTD-ILD groups (p = 0.074). The incidence densities of LC in the IPF, non-IPF IIPs, chronic HP, and CTD-ILD groups were 2.36, 0.70, 1.98, and 0.64 per 100 person-years, respectively. When each two groups were compared, IPF patients had a higher incidence of LC than non-IPF IIP patients (p = 0.036) (Fig. 2). Cox proportional regression hazards models showed that IPF was also significantly associated with the development of LC compared to non-IPF IIPs (hazard ratios 6.042, 95% confidence interval [CI] 1.284-28.440, p = 0.023).

Factors predictive of LC development in ILD patients

To determine the factors in ILD patients that were predictive of LC development at the time of the initial ILD diagnosis, nine factors were first assessed with univariate Cox proportional regression hazards models. Male sex, pack-years, radiological UIP pattern, and FVC value were significantly associated with the development of LC (Table 3). Whereas, age, and serum KL-6 and SP-D levels were not associated with LC development. Multivariate Cox proportional regression hazards models, which included the factors that were significant in the univariate analysis, showed that a radiological UIP pattern, FVC value, and pack-years were independent predictive factors for the development of LC (Table 4). Focusing on the IPF and chronic HP groups, univariate Cox proportional regression hazards models showed that a FVC value and pack-years were significantly associated with the development of LC in IPF patients and in chronic HP patients, respectively (Tables 5 and 6).

Discussion

There were three main findings in the present study. First, the incidence of LC in IPF patients is higher than that in non-IPF IIP patients. The incidence densities of LC in IPF patients ranged from 0.81 to 4.71 per 100 person-years in previous reports [8–13, 29–35]. The incidence rate in this study was comparable with those in previous reports on IPF patients. The incidence densities of LC in patients with CTD-ILDs were also reported in two previous studies as 0.98 and 1.66 per 100 person-years [14, 15]. Thus, the incidence density of LC in CTD-ILD patients in this study was slightly lower than the values in previous reports [14, 15]. Moreover, Choi et al. reported that the incidence densities of LC in IPF and IIP patients were 3.81 and 1.57 per 100 person-years, respectively, and that the incidence of LC in IPF patients was higher than that in IIP patients based on data from the Korean national database [13]. Although the IIP patient group included the IPF patient group in the previous report, our result was consistent with theirs. Our study revealed that the incidence of LC is higher in IPF patients than in patients with IIPs other than IPF when diagnosed according to the strict criteria for each disease. Our results revealed that the number of pack-years was higher in IPF patients than in non-IPF IIP, chronic HP, CTD-ILD, and pulmonary sarcoidosis patients. Thus, a hypothesis that a history of smoking simply affects LC development in IPF patients might be considered. However, the median incidence of LC in IPF patients from 11 cohort studies was 2.07 per 100 person-years (95% CI, 1.46–2.67), which is obviously higher than the incidence rates of 0.2–0.7 per 100 person-years reported in LC screening trials in heavy smokers without ILD [36]. This suggests that IPF increases the risk of LC development beyond what would be expected in older

populations and in those with smoking history [36]. This suggest that IPF itself may participate in LC development more than non-IPF IIPs do.

Second, we determined the incidence of LC in chronic HP patients. A previous study on the association between chronic HP and LC revealed that the prevalence of LC in chronic HP patients was 10.3% [16]. In our study, the incidence density of LC in the chronic HP group (1.98 per person-years) was the second highest among groups and was not significantly different from the incidence density in the IPF group (2.36 per person-years). Since previous studies reported that the incidence densities of LC in IPF patients were 0.81 to 4.71 per 100 person-years [8, 9, 11–13, 29–35], the incidence density in chronic HP patients in our study was approximately equal to that in IPF patients in previous reports.

Third, in a multivariate proportional hazards model, a radiological UIP pattern, FVC value, and pack-years were predictive factors for the development of LC in ILD patients. K.J. Lee et al. revealed that most LCs were located in the fibrosis of IPF lesions, and suggested that fibrotic lesions of IPF may be involved in lung carcinogenesis [10]. In our study, all 11 patients who underwent surgery for LC except 3 lacking pathological data had pathological UIP pattern lesions. Therefore, that a radiological UIP pattern was one of predictive factors of LC development in ILD patients may indicate that radiological UIP lesions affect the development of LC. In the present study, a FVC value in ILD patients was also associated with LC development. ILD patients with LC had a higher FVC (90.4 [range, 52.4-115.1] vs. 78.1 [range, 22.0-126.8] %, $p = 0.003$) and a lower FEV_1/FVC value (79.2 [range, 69.9–91.5] vs. 83.2 [range, 31.0-100.0] %, $p = 0.002$) than ILD patients without LC, which supported the results of previous studies on the incidence of LC in IPF patients [8, 9]. Ozawa et al. showed that patients with IPF and emphysema had relatively higher FVC and lower FEV_1/FVC values than those with IPF without emphysema [8]. Then, in our study, ILD patients with LC were more likely to have emphysema than ILD patients without LC. A previous study revealed that emphysema is associated with LC development in IPF patients. [8]. Therefore, in ILD patients, a higher FVC value, linked to emphysema, might induce LC development. This helps to explain the result of univariate Cox proportional regression analysis in IPF patients. In our study, pack-years was identified as a predictive factor for LC in ILD patients, which agreed with the findings in previous reports revealing an association between IPF and LC development [9, 10]. This might elucidate the relation between pack-years and LC development in chronic HP patients in univariate Cox regression analysis.

This study had some limitations. First, this was a retrospective, single-institution cohort study with a limited sample size. Second, we specialize in HP, and patients with HP visit our hospital from all over the country. The proportion of HP patients among those with ILDs seems to be higher than that at other institutions. Future prospective and multicentre studies with including a larger series of ILD patients are needed.

Conclusions

The incidence of LC is higher in IPF patients than in non-IPF IIP patients and is comparatively high in patients with chronic HP and those with IPF. Moreover, a radiological UIP pattern, FVC value, and pack-

years might be associated with the development of LC in ILD patients.

Abbreviations

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; ALAT: Latin American Thoracic Association; ATS: American Thoracic Society; COPD: chronic obstructive pulmonary disease; CI: confidence interval; CTD: connective tissue disease; CTD-ILDs: connective tissue disease-related interstitial lung diseases; EP: eosinophilic pneumonia; ERS: European Respiratory Society; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HP: hypersensitivity pneumonitis; HRCT: high-resolution computed tomography; IIPs: idiopathic interstitial pneumonias; ILDs: interstitial lung diseases; IPF: idiopathic pulmonary fibrosis; JRS: Japanese Respiratory Society; KL-6: Krebs von den Lungen-6; LC: lung cancer; NSIP: nonspecific interstitial pneumonia; SP-D: surfactant protein D; UIP: usual interstitial pneumonia

Declarations

Ethics approval and consent to participate

The present study conformed to the Declaration of Helsinki and was approved by the Institutional Review Board of Tokyo Medical and Dental University (approval number: M2019-087). Informed consent was waved by the Institutional Review Board of Tokyo Medical and Dental University in view of the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

YM takes full responsibility for the content of this manuscript, including data and analysis. TS, HS, and TO contributed to the study design, analysis and interpretation of the data, and the writing of this manuscript. MA, TH contributed to data analysis and interpretation. ME and MI contributed to data analysis. All authors critically revised the manuscript for intellectual content, approved the final draft, and agreed to be accountable for all aspects of the work.

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Tables

Table 1 Characteristics of patients with each disease

	IPF	Non-IPF IIPs	Chronic HP	CTD-ILDs	Sarcoidosis	Other ILDs	p value
Number of patients	161	133	160	87	19	46	—
Sex, male/female	126/35	77/56	107/53	30/57	10/9	30/16	< 0.001
Age	69 (25–93)	69 (35–89)	68 (40–85)	66 (32–87)	65 (31–81)	65 (34–83)	0.070
Pack-years, number (%)	35.0 (0-162.0)	10.5 (0-105.0)	20.0 (0-154.0)	0.1 (0–80.0)	0 (0–51.0)	2.5 (0-135.0)	< 0.001
Radiological UIP pattern	126 (78)	0/ (0)	85 (53)	28 (32)	3 (16)	8 (17)	< 0.001
FVC, % predicted	76.7 (32.4-120.5)	86.0 (29.4-126.5)	75.6 (22.0-126.8)	74.0 (31.8–112.0)	92.5 (60.5-118.2)	85.8 (43.2-119.2)	< 0.001
FEV_1/FVC, %	83.1 (54.4–100.0)	79.7 (53.2–100.0)	85.3 (31.0-100.0)	82.8 (54.9–99.2)	79.3 (72.9–97.3)	77.0 (66.4–95.8)	< 0.001
KL-6, U/mL	805 (252–6518)	577 (161–5140)	1129 (273-10000)	818 (226–5591)	625 (202–1560)	632 (182–4881)	< 0.001
SP-D, ng/mL	199.0 (20.5–3070.0)	125.0 (17.2–1490.0)	237.5 (35.2–1660.0)	132.0 (17.2–640.0)	66.6 (17.2–357.0)	115.0 (17.2–341.0)	< 0.001

Data were presented as numbers or medians (percentages or ranges).

Abbreviations: CTD-ILDs connective tissue disease-related interstitial lung diseases, FEV_1 forced expiratory volume in one second, FVC forced vital capacity, HP hypersensitivity pneumonitis, IPF idiopathic pulmonary fibrosis, KL-6 Krebs von den Lungen-6, non-IPF IIPs non-idiopathic pulmonary fibrosis idiopathic interstitial pneumonias, SP-D surfactant protein D, UIP usual interstitial pneumonia

Table 2 Characteristics of ILD patients developing LC

Number of patients	28
Male sex	25 (89)
Age	69 (43-77)
Smokers	27 (96)
Pack-years	46.0 (0-154.0)
Etiology	
IPF	12 (43)
Chronic HP	10 (36)
non-IPF IIPs	3 (11)
CTD-ILDs	2 (7)
Sarcoidosis	1 (4)
Other ILDs	0 (0)
Emphysema at the initial diagnosis of ILDs	18 (64)
Radiological UIP pattern at the diagnosis of LC	24 (86)
Adjacent to honeycombing	17 (71)
Histological type	
Squamous cell carcinoma	13 (46)
Adenocarcinoma	7 (25)
Small cell carcinoma	4 (14)
Large cell carcinoma	1 (4)
Others	3 (11)
Location	
Upper lobes	12 (43)
Middle lobes	3 (11)
Lower lobes	13 (46)
Stage of LC	
I	11 (39)
II	2 (7)
IIIA	3 (11)

IIIB	2 (7)
IV	8 (29)
Unknown	2 (7)
Treatment for LC	
Operation	14 (50)
Chemotherapy	11 (39)
Best supportive care	2 (7)
Unknown	1 (4)

Data were presented as numbers (%) or medians (ranges).

Abbreviations: *CTD-ILDs* connective tissue disease-related interstitial lung diseases, *HP* hypersensitivity pneumonitis, *ILD* interstitial lung disease, *IPF* idiopathic pulmonary fibrosis, *LC* lung cancer; *non-IPF IIPs* non-idiopathic pulmonary fibrosis idiopathic interstitial pneumonias, *UIP* usual interstitial pneumonia

Table 3 Hazard ratios and 95% CIs of covariates in the univariate Cox proportional hazards model of LC in ILD patients

Variable	Hazard ratio	95% CI		p value
		Lower	Upper	
Male sex	5.327	1.608	17.65	0.006
Age	1.019	0.980	1.060	0.342
Pack-years	1.016	1.008	1.024	< 0.001
Radiological UIP pattern	2.989	1.377	6.490	0.006
FVC, % predicted	1.024	1.002	1.048	0.034
FEV_1/FVC, %	0.964	0.928	1.001	0.058
KL-6, U/mL	1.000	1.000	1.000	0.727
SP-D, ng/mL	1.000	0.999	1.002	0.757
Aetiology	—	—	—	0.267

Abbreviations: *CI* confidence interval, *FEV_1* forced expiratory volume in one second, *FVC* forced vital capacity, *ILD* interstitial lung disease, *KL-6* Krebs von den Lungen-6, *LC* lung cancer, *SP-D* surfactant protein D, *UIP* usual interstitial pneumonia

Table 4 Hazard ratios and 95% CIs of covariates in the multivariate Cox proportional hazards model of LC in ILD patients

Variable	Hazard ratio	95% CI		p value
		Lower	Upper	
Male sex	2.566	0.707	9.308	0.152
Pack-years	1.011	1.002	1.020	0.020
Radiological UIP pattern	2.959	1.257	6.963	0.013
FVC, % predicted	1.031	1.006	1.057	0.017
FEV_1/FVC, %	0.998	0.946	1.053	0.943
Abbreviations: *CI* confidence interval, *FEV_1* forced expiratory volume in one second, *FVC* forced vital capacity, *ILD* interstitial lung disease, *LC* lung cancer, *UIP* usual interstitial pneumonia				

Table 5 Hazard ratios and 95% CIs of covariates in the univariate Cox proportional hazards model of LC in IPF patients

Variable	Hazard ratio	95% CI		p value
		Lower	Upper	
Male sex	1.378	0.302	6.289	0.679
Age	1.010	0.950	1.074	0.756
Pack-years	1.000	0.985	1.016	0.958
Radiological UIP pattern	1.209	0.324	4.503	0.778
FVC, % predicted	1.061	1.020	1.105	0.004
FEV_1/FVC, %	0.966	0.910	1.025	0.252
KL-6, U/mL	0.999	0.998	1.000	0.200
SP-D, ng/mL	1.000	0.998	1.002	0.876
Abbreviations: *CI* confidence intervals, *FEV_1* forced expiratory volume in one second, *FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *KL-6* Krebs von den Lungen-6, *LC* lung cancer, *SP-D* surfactant protein D, *UIP* usual interstitial pneumonia				

Table 6 Hazard ratios and 95%CIs of covariates in the univariate Cox proportional hazards model of LC in chronic HP patients

Variable	Hazard ratio	95% CI		p value
		Lower	Upper	
Male sex	4.936	0.625	38.970	0.130
Age	1.013	0.939	1.093	0.739
Pack-years	1.019	1.006	1.032	0.004
Radiological UIP pattern	2.169	0.560	8.395	0.262
FVC, % predicted	1.003	0.967	1.040	0.864
FEV_1/FVC, %	0.968	0.919	1.019	0.215
KL-6, U/mL	1.000	1.000	1.000	0.695
SP-D, ng/mL	1.000	0.995	1.004	0.827

Abbreviations: *CI* confidence interval, *FEV_1* forced expiratory volume in one second, *FVC* forced vital capacity, *HP* hypersensitivity pneumonitis, *KL-6* Krebs von den Lungen-6, *LC* lung cancer, *SP-D* surfactant protein D, *UIP* usual interstitial pneumonia

Figures

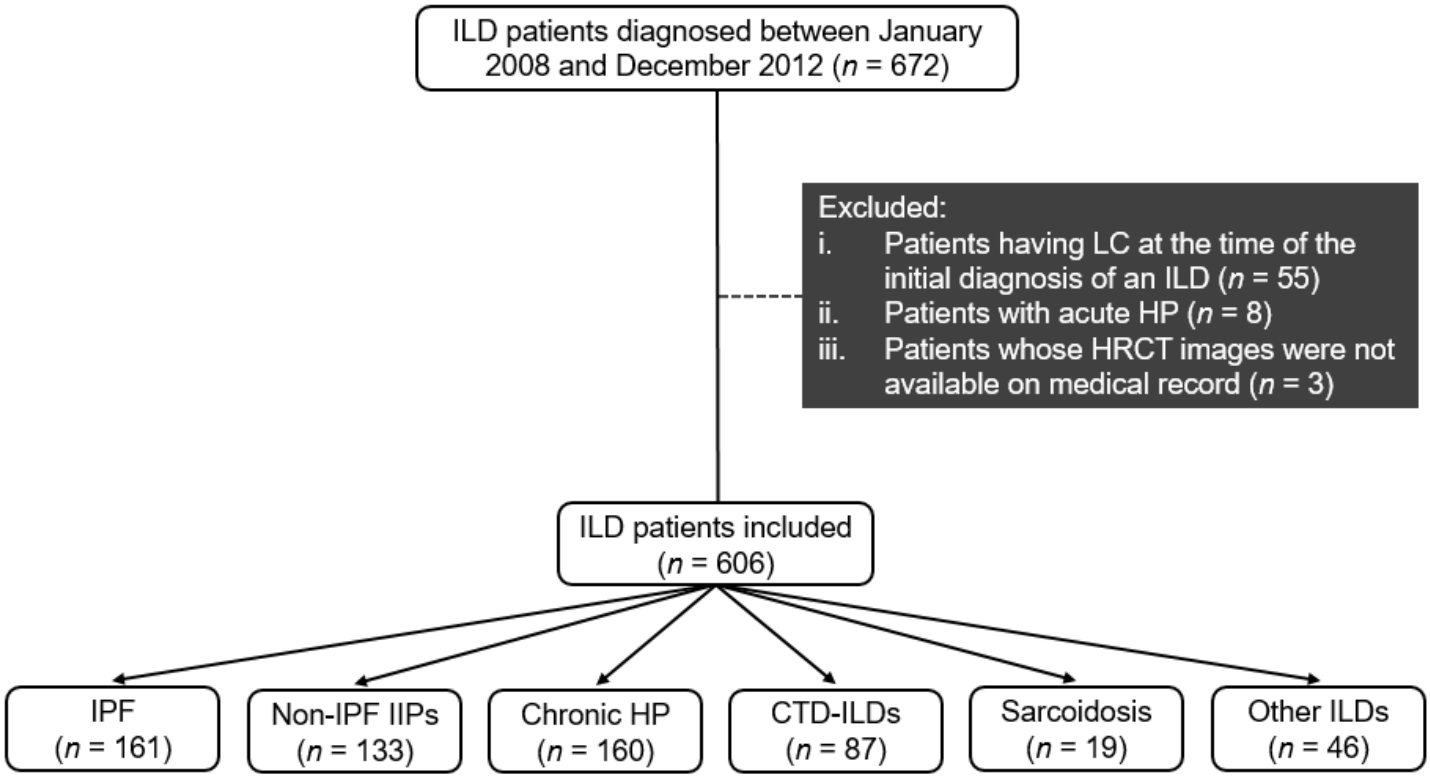
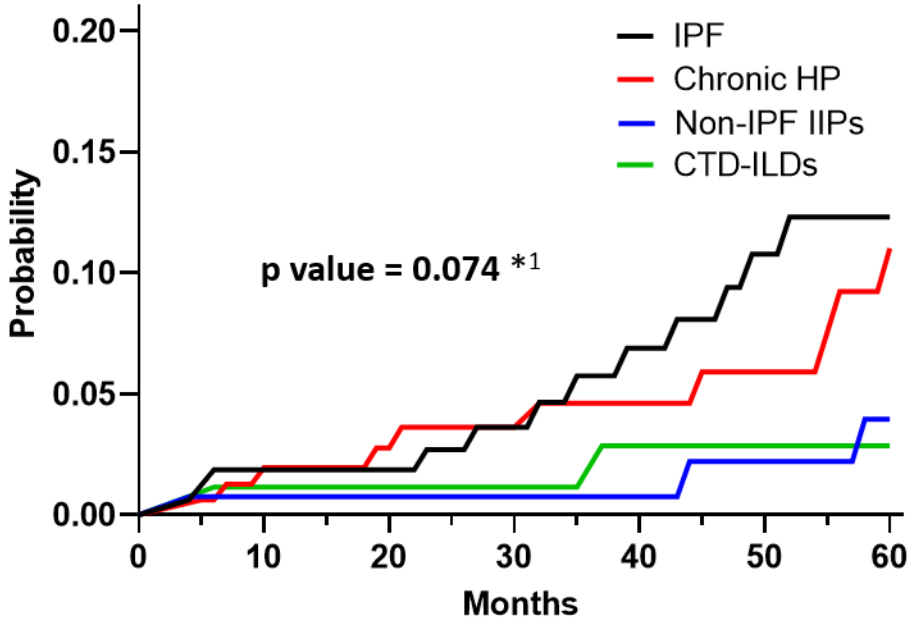


Figure 1

Patient selection flow chart for ILD patients. The 606 patients with ILDs were divided into 6 groups based on etiology: IPF, non-IPF IIPs, chronic HP, CTD-ILDs, pulmonary sarcoidosis, other ILDs. Abbreviations: CTD-ILDs, connective tissue disease-related interstitial lung diseases, HP, hypersensitivity pneumonitis, HRCT, high-resolution computed tomography, ILDs, interstitial lung diseases, IPF, idiopathic pulmonary fibrosis, LC, lung cancer, non-IPF IIPs, non-idiopathic pulmonary fibrosis idiopathic interstitial pneumonias



Comparisons of LC incidences between every two ILD groups

			p value *2
IPF	vs.	Chronic HP	0.657
IPF	vs.	Non-IPF IIPs	0.036
IPF	vs.	CTD-ILDs	0.060
Chronic HP	vs.	Non-IPF IIPs	0.081
Chronic HP	vs.	CTD-ILDs	0.113
Non-IPF IIPs	vs.	CTD-ILDs	0.921

Figure 2

Cumulative incidence curve of LC by Kaplan-Meier analysis, and comparison between every two ILD groups. IPF (black line), chronic HP (red line), non-IPF IIPs (blue line), and CTD-ILDs (green line). Abbreviations: CTD-ILDs, connective tissue disease-related interstitial lung diseases, HP, hypersensitivity pneumonitis, IPF, idiopathic pulmonary fibrosis, LC, lung cancer, non-IPF IIPs, non-idiopathic pulmonary fibrosis idiopathic interstitial pneumonias *1, comparing four groups at once using Log rank test, *2, comparing every two groups using Log rank test