의학석사 학위논문

섬유화 간질성 폐질환 환자에서 폐암의 임상적 특징과 예후

Clinical characteristics and outcome of lung cancer in patients with fibrosing interstitial lung disease

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이 논문을 의학석사 학위 논문으로 제출함

2024 년 2 월

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ABSTRACT

Background Lung cancer (LC) is an important comorbidity of interstitial lung disease (ILD) and associated with poor prognosis. The comparison of clinical characteristics and outcome of each ILD subtype in LC patients are not well known. Therefore, in this study, we evaluated the difference between IPF and non-IPF ILD and prognostic factors in patients with ILD-LC.

Methods The medical records of 163 patients diagnosed with ILD-LC at Asan Medical Center from January 2018 and May 2023 were retrospectively reviewed. Baseline characteristics and clinical outcome between IPF-LC and non IPF ILD-LC groups were compared and prognostic factors were analyzed by Cox proportional hazard model.

Results The median follow-up period was 11 months after cancer diagnosis. There were no statistically significant differences in clinical characteristics between IPF and non-IPF ILD-LC groups, and even no difference in mortality (Median survival: 26 vs. 20 months, $p = 0.530$). Higher level of KL-6 (≥ 1000U/mL, hazard ratio [HR], 1.970; 95% confidence interval [CI]: 1.026-3.783; $p = 0.025$) and advanced clinical stage of LC (HR 3.876 for stage II, $p = 0.025$, HR 5.092 for stage III, $p = 0.002$ and HR 5.626 for stage IV, compared to stage I, $p = 0.002$) were independent prognostic factors in patients with ILD-LC. In aspect of treatment, surgery was the significant factor for survival (HR, 0.235; 95% CI: 0.106-0.520; $p < 0.001$).

Conclusion There was no survival difference between IPF-LC and non-IPF ILD-LC. KL-6 might be act as a prognostic marker in patient ILD-LC.

Contents

INTRODUCTION

Interstitial lung diseases (ILD) are a group of diffuse parenchymal lung disorders[1], which affect the pulmonary interstitial space[2]. It is estimated that more than 200 diseases have been reported to belong to ILD. The most common type of fibrosing interstitial lung disease, Idiopathic pulmonary fibrosis (IPF)[3], is a form of chronic and progressive disease of unknown cause with a median survival of 3-5 years from the time of diagnosis[4]. Patients with IPF have several comorbidities including pulmonary hypertension, emphysema, and lung cancer (LC)[5]. Among various comorbidities, especially the prevalence of lung cancer (LC) in patients with IPF has been reported approximately 20%[6], which is a higher compared to the general population[7]. Moreover, among patients with IPF, the mean survival time was shorter (1.6-1.7 years) in those who had LC than in those who had no LC[8]. Recently, there has also been a suggestion that IPF and LC may share common genetic and pathogenic mechanisms[9]. It has been reported that pulmonary fibroblasts share similar characteristics with cancer cells, such as unregulated cell proliferation, resistance to apoptosis, and telomere shortening[10-12].

Although IPF is the most common type of ILD, it accounts only for 17-37% of all ILD diagnoses[13]. Recently, it has been reported that LC is also an important comorbidity in patients with ILD other than IPF[14-16]. In addition, several previous studies have reported that the prevalence of LC in patients with non-IPF ILD is also higher than in the general population[17, 18]. However, in patients with ILD and LC, the comparison of clinical characteristics according to ILD subtype has not been well elucidated. Therefore, in this study, we evaluated the clinical and prognostic differences between IPF and non-IPF in patients with LC and factors affecting prognosis in all fibrosing interstitial lung diseases.

METHODS

Study population

This retrospective single-center study reviewed 163 consecutive patients diagnosed with ILD and LC between January 2018 and May 2023 at the Asan Medical Center in South Korea. The types of ILD were divided into IPF and non-IPF. The diagnosis of IPF was made by the diagnostic criteria of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Association in 2018[19]. The non-IPF type includes

hypersensitivity pneumonitis, nonspecific interstitial pneumonia (NSIP), smoking-related ILD, connective tissue disease-related ILD (CTD-ILD), and unclassified ILD. CTD was diagnosed by rheumatologists using specific criteria[20-25]. We diagnosed LC based on the histological results, which were confirmed by pathologists at our center. LC was classified according to the World Health Organization tumor classification, and staging of LC was performed using the 8th edition of the TNM classification of malignant tumors[26]. This study was conducted in compliance with the Declaration of Helsinki. The study protocol was endorsed by the Institutional Review Board of Asan Medical Center (IRB number: 2023-1078). Informed consent was waived because of the retrospective study design and anonymity of clinical data.

Clinical data

We obtained the baseline characteristics, including age, sex, body mass index (BMI), smoking history, pulmonary function test results, laboratory data, and profiles of ILD and LC, from the electronic medical records. Data obtained from medical records or the National Insurance Corporation was used for the purpose of examining mortality rates. Consistent with the recommendations of the ERS/ATS, spirometry was performed to evaluate pulmonary function and measure total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLco)[27, 28]. The profile of ILD encompassed the type, imaging and histological findings, and treatment for ILD at the time of LC diagnosis. The initial treatment for LC was categorized into four 4 main modalities: surgery, radiotherapy, chemotherapy, and concurrent chemoradiation therapy.

Statistical analysis

Categorical variables were reported using numbers and percentages, while continuous variables were presented as medians with interquartile ranges (IQR). To compare the variables between the two groups, either the Chi-squared test or Fisher's exact test was used for categorical variables. The Kaplan-Meier-methods was used for time-to-event analysis for all-cause mortality. Univariable and multivariable Cox proportional hazards regression models were utilized to identify risk factors associated all-cause mortality. The results were reported as hazard ratio (HR) with 95% confidence interval (CI). Significance was determined by two-sided *p* values less than

0.05. Survival analysis was conducted using the Kaplan-Meier estimator. All statistical analyses were performed using SPSS version 27.0 software (IBM Corporation, Armonk, NY).

RESULTS

Baseline patient characteristics

Among the 163 patients, the ILD type was IPF in 92 (56.4%) patients and non-IPF in 71 (43.6%) patients. The median follow-up period after lung cancer diagnosis was 11 months. The non-IPF group included unclassified ILD (n=54), CTD-ILD (n=14), NSIP (n=2), and chronic HP (n=1). The baseline characteristics of all patients at the time of diagnostic LC were summarized in Table 1. The mean age of patients was 70.4 years, 92.6% were males, and 91.4% were ever-smokers. Out of a total of 163 patients, 141 (86.5%) were diagnosed with non-small cell lung cancer (NSCLC) and 22 (13.5%) were diagnosed with small cell lung cancer (SCLC). The most common histologic subtype of NSCLC was adenocarcinoma (52.5%), followed by squamous cell carcinoma (45.4%) and others (2.1%). There were no statistically significant differences in the baseline characteristics, including age, sex, and baseline pulmonary function test results between the IPF and non-IPF groups.

Table 1. Baseline characteristics of patients with interstitial lung disease and lung cancer at lung cancer diagnosis

Characteristic	Total (n = 163)	IPF-LC(n=92)	Non IPF-LC (n = 71)	*p*-value
Type of ILD				
IPF	92 (56.4)	92 (100.0)	0 (0.0)	
Unclassifiable	54 (33.1)	0 (0.0)	54 (76.1)	
CTD-ILD	0 (0.0)	0 (0.0)	14 (82.4)	
NSIP	0 (0.0)	0 (0.0)	2 (11.8)	
Chronic HP	0 (0.0)	0 (0.0)	1 (5.89)	
Age, years	70.4 ± 7.3	70.5 ± 7.4	70.2 ± 7.2	0.827
Male	151 (92.6)	85 (92.4)	66 (93.0)	0.899
BMI, kg/m^2	24.4 ± 3.1	24.4 ± 2.8	24.4 ± 3.5	0.956
Ever-smoker	149 (91.4)	84 (91.3)	65 (91.5)	0.827
Pulmonary function test				
FVC (predicted), % (n = 161)	76.6 ± 16.8	76.5 ± 16.4	76.9 ± 17.5	0.884
FEV1 (predicted), % (n = 161)	81.2 ± 15.8	80.9 ± 15.2	81.5 ± 16.7	0.812
TLC (predicted), % (n = 81)	79.6 ± 13.4	79.3 ± +12.8	80.10 ± 14.47	0.800
DLco (predicted), % (n = 150)	55.7 ± 17.6	54.5 ± 17.7	57.39 ± 17.45	0.319
Laboratory data				
KL-6 ≥ 1000 U/mL (n = 117)	32 (27.4)	20 (28.6)	12 (25.5)	0.718
Type of LC				
NSCLC	141 (86.5)	81 (88.0)	60 (84.5)	0.512
Adenocarcinoma	74 (52.5)	43 (53.1)	31 (51.7)	0.867
Squamous cell carcinoma	64 (45.4)	35 (43.2)	29 (48.3)	0.546
Others*	3 (2.1)	3 (3.7)	0 (0.0)	0.261
SCLC	22 (13.5)	11 (12.0)	11 (15.5)	0.512

Data are reported as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. ILD, interstitial lung disease; IPF, idiopathic progressive fibrosis; CTD, connective tissue disease; HP, hypersensitivity pneumonitis; NSIP, nonspecific interstitial pneumonia BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; TLC, total lung capacity; DLco, diffusing capacity for carbon monoxide; KL-6, krebs von den lungen-6; IS, Immunosuppressants, LC; lung cancer, NSCLC; non-small cell lung cancer, SCLC; small cell lung cancer
* Other histologic types include large cell carcinoma.

Clinical characteristics and management of patients

In NSCLC patients, 32.9% of patients were classified as stage I, 14.3% as stage II, stage III as 27.1% and 25.7% as stage IV, as shown in Table 2. Among NSCLC patients, the proportions of patients who received surgery, chemotherapy, radiotherapy and concurrent chemoradiation therapy (CCRT) were 32.6%, 22.7%, 22.0%, and 5.0% respectively. The percentage of CCRT was higher in the non-IPF group (1.2% vs. 10.0%, $p = 0.042$). In aspects of ILD among NSCLC patients, compared with the non-IPF group, the IPF group had higher proportion of patients received antifibrotic agents (pirfenidone or nintedanib, 80.2% vs. 8.3%, $p < 0.001$) but had lower proportion of patients who received steroids and immunosuppressants for initial treatment of ILD (6.2% vs. 20.0%, $p < 0.013$) (Table 2). There was no statistically significant difference in the incidence of AE following the treatment of LC (28.4% vs. 20.0%, $p = 0.254$). Additionally, there was no significant difference in mortality rates between two groups (42.0% vs. 38.3%, $p = 0.663$). The clinical characteristics and treatment of patients with small cell lung cancer (SCLC) are summarized in e-Table 1. There were no significant differences in stage, treatment for lung cancer, and mortality between the IPF and non-IPF groups.

Table 2. Comparison of the clinical characteristics and management of NSCLC patients according to the type of ILD

Characteristic	Total (n = 141)	IPF-LC (n = 81)	Non-IPF-LC (n = 60)	*p*-value
Clinical stage of NSCLC				0.337
I	46 (32.9)	31 (38.3)	15 (25.0)	
II	20 (14.3)	9 (11.1)	11 (18.3)	
III	38 (27.1)	21 (25.9)	17 (28.3)	
IV	36 (25.7)	10 (24.7)	17 (28.3)	
Initial treatment for NSCLC				
Surgery	46 (32.6)	30 (37.0)	16 (26.7)	0.194
Lobar resection	29 (63.0)	14 (46.7)	15 (93.8)	
Sublobar resection	17 (37.0)	16 (53.3)	1 (6.3)	
Chemotherapy	32 (22.7)	15 (18.5)	17 (28.3)	0.169
Radiotherapy	31 (22.0)	19 (23.5)	12 (20.0)	0.624
CCRT	7 (5.0)	1 (1.2)	6 (10.0)	0.042
Best supportive care	25 (17.7)	16 (19.8)	9 (15.0)	0.465
Treatment of ILD				
Antifibrotic agent	70 (49.6)	65 (80.2)	5 (8.3)	<0.001
Corticosteroid ± IS	54 (38.3)	29 (35.8)*	25 (41.7)**	0.479
Initial treatment	17 (12.1)	5 (6.2)	12 (20.0)	0.013
Acute exacerbation	37 (26.2)	25 (30.9)	12 (20.0)	0.147
RT pneumonitis	5 (3.5)	2 (2.5)	3 (5.0)	0.651
Acute exacerbation	37 (26.2)	25 (30.9)	12 (20.0)	0.147
Overall mortality	57 (40.4)	34 (42.0)	23 (38.3)	0.663
AE related death	21 (36.8)	14 (41.2)	7 (30.4)	0.409
Infection related death	15 (26.3)	7 (20.6)	8 (34.8)	0.232
Unknown	21 (36.8)	14 (41.2)	7 (30.4)	0.409

Data are reported as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. NSCLC, non-small cell lung cancer; CCRT, concurrent chemoradiation therapy; ILD, interstitial lung disease; IS, Immunosuppressants; SCLC, small cell lung cancer; AE, acute exacerbation

* 3 patients were treated with steroid as initial treatment and during acute exacerbation

** 2 patients were treated with steroid as initial treatment and during acute exacerbation

Prognostic factor in patients with NSCLC

The Cox regression analysis of risk factors associated with mortality in NSCLC patients based on their baseline characteristics is summarized in Table 3. The result of the univariate Cox analysis showed that decreased FVC (hazard ratio [HR], 0.983; 95% confidence interval [CI], 0.968-0.998; p = 0.023), and decreased TLC (HR, 0.961; CI, 0.934–0.988; p = 0.005) were significantly correlated with mortality. The higher level of KL-6 (≥1000) (HR, 2.554; CI, 1.378-4.734; p = 0.003) and advanced clinical lung cancer stage were associated with a higher risk of mortality. However, subtype of ILD (IPF versus non-IPF ILD) was not a significant factor for mortality in the univariate analysis (HR, 0.892; CI, 0.516-1.542; p = 0.682). In multivariate analysis, higher levels of KL-6 were independently associated with increased mortality (HR, 1.970; CI, 1.026–3.783; p = 0.042) after adjusting for other risk factors. Clinical stage was also identified as an independent risk factor for mortality (HR 3.876 for stage II, p = 0.025; HR 5.092 for stage III, p = 0.002; and HR 5.626 for stage IV, compared to stage I, p = 0.002).

Table 4 showed the risk factors for all-cause mortality based on the treatment factor of patients. In the univariate analysis, the use of steroids and/or immunosuppressants (HR, 2.058; CI, 1.218-3.476; p = 0.007) and acute exacerbation (HR, 2.094; CI, 1.224-3.581; p = 0.007) were associated with mortality. Although surgery for lung cancer was associated with lower mortality (HR, 0.198; CI, 0.092-0.423; p < 0.001), chemotherapy was associated with a poor prognosis (HR, 2.334; CI, 1.276-4.269; p = 0.006) in univariate analysis. In the multivariate analysis, only surgery was independently associated with lower mortality (HR, 0.235; CI, 0.106-0.520; p < 0.001), after adjusting for other variables.

Table 3. Predicting baseline factor for mortality in patients with ILD and NSCLC assessed by Cox proportional hazard model

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.006	0.971-1.043	0.736			
Male	3.426	0.832-14.111	0.088			
Ever-smoker	1.139	0.486-2.671	0.765			
IPF (vs. non-IPF ILD)	0.963	0.563-1.649	0.892			
SqCC (vs. ADC)	1.039	0.613-1.759	0.888			
Pulmonary function test						
FVC (predicted), %	**0.983**	**0.968-0.998**	**0.023**	0.992	0.974-1.011	0.411
FEV1 (predicted), %	0.989	0.972-1.006	0.189			
TLC (predicted), %	**0.961**	**0.934-0.988**	**0.005**			
DLco (predicted), %	0.986	0.973-1.000	0.051			
KL-6 ≥ 1000 U/mL	**2.554**	**1.378-4.734**	**0.003**	**1.970**	**1.026-3.783**	**0.042**
Lung cancer stage						
Stage I (ref)						
Stage II	**4.476**	**1.778-11.271**	**0.001**	**3.876**	**1.187-12.660**	**0.025**
Stage III	**3.722**	**1.612-8.594**	**0.002**	**5.092**	**1.801-14.401**	**0.002**
Stage IV	**8.717**	**3.630-20.936**	**<0.001**	**5.626**	**1.889-16.757**	**0.002**

HR, hazard ratio; CI, confidence interval; SqCC, Squamous cell carcinoma; ADC, adenocarcinoma; TLC, total lung capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLco, diffusing capacity for carbon monoxide; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; KL-6, krebs von den lungen-6; IS, immunosuppressant; CCRT, concurrent chemoradiation therapy.

TLC was not included in the multivariate analysis due to its high correlation with FVC ($r = 0.853$, $p < 0.001$).

Table 4. Predicting treatment factor for mortality in patients with ILD and NSCLC assessed by Cox proportional hazard model

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
ILD treatment						
Antifibrotics	0.714	0.420-1.214	0.214			
Corticosteroid ± IS	**2.058**	**1.218-3.476**	**0.007**	1.162	0.503-2.685	0.726
Acute exacerbation	**2.124**	**1.147-3.931**	**0.017**	1.282	0.542-3.034	0.572
Initial treatment for LC						
Surgery	**0.198**	**0.092-0.423**	**<0.001**	**0.235**	**0.106-0.522**	**<0.001**
Chemotherapy	**2.334**	**1.276-4.269**	**0.006**	1.290	0.682-2.439	0.434
Radiotherapy	0.781	0.412-1.480	0.449			
CCRT	0.916	0.222-3.776	0.904			

HR, hazard ratio; CI, confidence interval; SqCC, Squamous cell carcinoma; ADC, adenocarcinoma; TLC, total lung capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLco, diffusing capacity for carbon monoxide; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; KL-6, krebs von den lungen-6; IS, immunosuppressant; LC, lung cancer; CCRT, concurrent chemoradiation therapy.

Comparison of clinical characteristics and clinical course according to baseline KL-6 levels

Since KL-6 was independently associated with mortality in NSCLC patients, a comparison of clinical characteristics according to KL-6 level was presented in Table 5. There were no significant differences in the proportion of ILD subtypes, sex, BMI, and smoking history between the two groups. The mean age was significantly lower in the higher KL-6 group (67.5 vs 71.1 years, $p = 0.030$). Patients with higher KL-6 levels had lower predicted FVC values (72.9% vs. 83.4%, $p = 0.004$) and DLco (46.1% vs. 58.7%, $p = 0.001$) compared to patients with lower KL-6 levels. There were no differences between the two groups in the histologic type and stage of LC. In aspect of treatment of ILD and LC, the usage of steroid and/or immunosuppressants was more common in the patients of higher KL-6 level (69.0 vs. 27.5%, $p < 0.001$) than patients with lower KL-6. The incidence of AE (51.7% vs. 20.3%, $p = 0.002$) and mortality (65.5% vs. 31.9%, $p = 0.002$) was higher in the group with a higher KL-6 level compared to the group with a lower KL-6 level.

Table 5. Comparison of clinical characteristics in NSCLC patients with fibrosing ILD according to KL-6

Characteristic	KL-6 ≥ 1,000 (n = 29)	KL-6 < 1,000 (n = 69)	*p*-value
Type of ILD			0.807
IPF	18 (62.1)	41 (59.4)	
Non-IPF ILD	11 (37.9)	28 (40.6)	
Age, years	67.5 ± 7.1	71.1 ± 6.9	0.030
Male	91 (92.9)	27 (93.1)	0.951
BMI, kg/m^2	24.0 ± 3.58	24.7 ± 3.2	0.899
Ever-smoker	27 (93.1)	64 (92.8)	0.516
Pulmonary function test			
FVC (predicted). % (n = 97)	68.3 ± 17.3	79.0 ± 16.0	0.007
FEV1 (predicted), % (n = 97)	72.9 ± 15.6	83.4 ± 15.5	0.004
TLC (predicted), % (n = 93)	72.5 ± 13.9	83.6 ± 11.2	0.003
DLco (predicted), % (n = 56)	46.1 ± 16.5	58.7 ± 16.0	0.001
Type of NSCLC			0.668
Adenocarcinoma	17 (58.6)	34 (49.3)	
Squamous cell carcinoma	11 (37.9)	34 (49.3)	
Others	1 (3.5)	1 (1.4)	
Stage of NSCLC			0.120
I	5 (17.2)	28 (40.6)	
II	7 (24.1)	9 (13.0)	
III	7 (24.1)	16 (23.2)	
IV	10 (34.5)	16 (23.2)	
Initial treatment for lung cancer			
Surgery	6 (20.7)	26 (37.7	0.102
Chemotherapy	9 (31.0)	14 (20.3)	0.252
Radiotherapy	5 (17.2)	17 (24.6)	0.423
CCRT	1 (3.4)	3 (4.3)	0.837
Best supportive care	8 (27.6)	9 (13.0)	0.083
ILD treatment			
Antifibrotics	16 (55.2)	40 (58.0)	0.798
Corticosteroid ± IS	20 (69.0)*	25 (36.2)**	0.003
Initial treatment	8 (27.6)	7 (10.1)	0.029
Acute exacerbation	15 (51.7)	16 (23.2)	0.006
RT pneumonitis	0 (0.0)	3 (4.3)	0.254

Acute exacerbation	15 (51.7)	14 (20.3)	0.002
Overall mortality	19 (65.5)	22 (31.9)	0.002
AE related death	11 (57.9)	6 (27.3)	0.047
Infection related death	2 (10.5)	6 (27.3)	0.249
Unknown	6 (31.6)	10 (45.5)	0.364

Data are reported as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. KL-6, krebs von den lungen-6; ILD, interstitial lung disease; IS, immunosuppressants; BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; TLC, total lung capacity; DLco, diffusing capacity for carbon monoxide; NSCLC, non-small cell lung cancer; LC, lung cancer; CCRT, concurrent chemoradiation therapy.

*3 patients were treated with steroid as initial treatment and during acute exacerbation

**1 patients were treated with steroid as initial treatment and during acute exacerbation

Survival analysis

Figure 1 showed a comparison of survival curves between the IPF and non-IPF patients with LC. There was no statistically significant difference in mortality between the two groups (median survival: 26 vs. 20 months, $p = 0.530$, Figure 1). A comparison of survival curves based on the KL-6 level is shown in Figure 2. The median survival of patients with a higher level of KL-6 (≥1000) was shorter (15 vs. 31 months, respectively, $p = 0.002$) than patients with a lower level of KL-6 (<1000).

Figure 1. Comparison of survival curves between the IPF and non-IPF ILD in patients with lung cancer

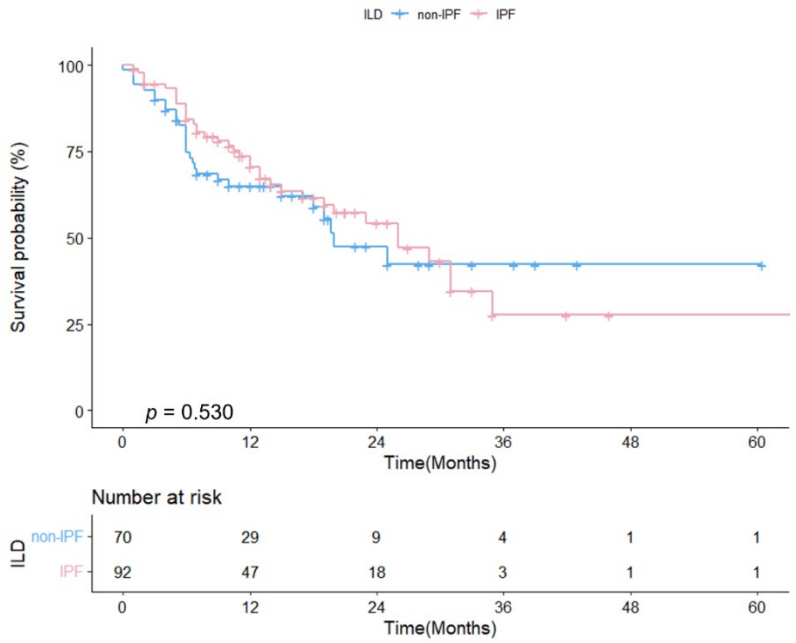
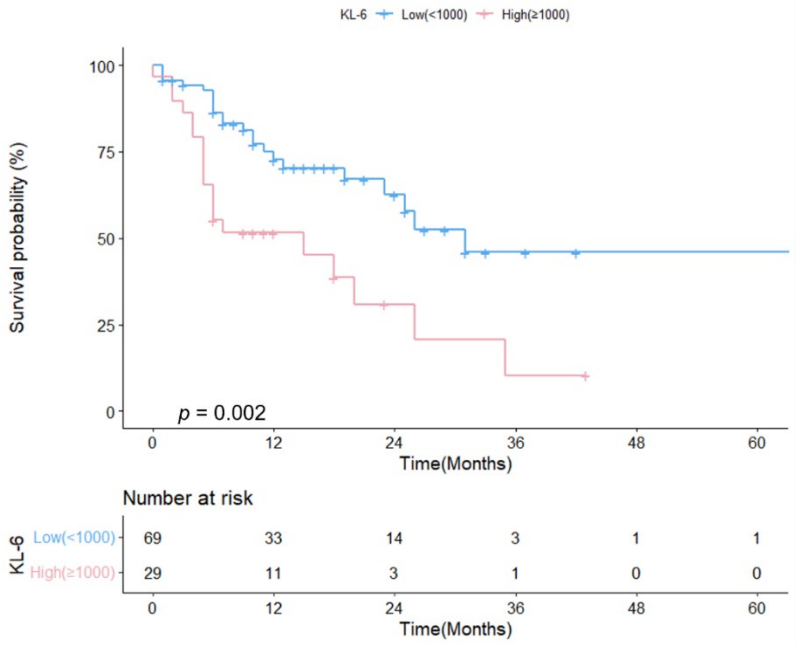


Figure 2. Comparison of survival curves between higher (≥1000U/mL) and lower (<1000U/mL) KL-6 groups in patients with NSCLC



DISCUSSION

In our current study, we found no significant differences in the frequency of acute exacerbation and prognosis between IPF and non-IPF ILD in patients with LC. Higher level of KL-6 (≥1000) was independently associated with mortality in LC patients with fibrosing ILD, along with clinical stage of lung cancer. Moreover, patients with higher level of KL-6 showed poorer survivor compared to the others.

There was no difference in the prognosis between IPF and non-IPF ILD in patients with LC and when LC developed in our current study. In general, although IPF showed a poorer prognosis than non-IPF ILD[29, 30], there are few previous studies that have focused on the prognosis according to the ILD subtype in patients with ILD-LC. In a previous study reported by Yoon et al., it was reported that lung cancer with IPF had higher mortality compared to lung cancer in non IPF ILD (HR, 6.2; p = 0.001) among 31 IPF-LC patients and 16 non-IPF ILD-LC patients. However, it was difficult to make a meaningful comparison between the groups due to the small sample size and difference in cancer subtypes; despite statistically insignificant, the IPF group comprised of 41% SqCC patients and 26% ADC patients, while the non-IPF ILD group comprised of 19% SqCC and 63% ADC[31]. Additionally, other studies have demonstrated that LC patients with non-IPF ILD are associated with a poorer prognosis compared to non-IPF ILD patients without LC[32, 33]. These previous results suggested that even in non-IPF ILD, the development of LC may lead to a poor prognosis, which is consistent with the results of our study. In addition to IPF, there are subtype of ILDs such as progressive fibrosing interstitial lung disease (PF-ILD) or progressive pulmonary fibrosis (PPF) that exhibit a progressive course[34, 35]. As it is possible that some patients with PPF were included in the non-IPF ILD group, this could be an additional factor contributing to the absence of prognostic differences between the IPF and non-IPF groups. Additionally, there is a possibility that there may be no difference in prognosis due to the effects of anti-fibrotic agents that are more commonly used in IPF[36]. The antifibrotic agents have been shown to effectively decelerating the progression of fibrosis and an effect; though limited, of anti-tumor properties. Although there is still no well-established research[37, 38], it might be considered that the effects of medication may have contributed to the improved survival rates of the IPF group. Another possible explanation for the absence of prognostic differences between IPF and non-IPF LC is the occurrence of AE in both IPF and non-IPF ILDs[39-41], which have been associated with poor clinical outcomes. In our study, AE was observed to occur at a similar

rate of 30.9% in patients with IPF and 20.0% in patients with non-IPF (p = 0.147) in NSCLC patients.

In our present study, we observed an independent association between KL-6 and poor prognosis in patients with fibrosing ILD who also have LC. KL-6 is a high-molecular-weight glycoprotein encoded by the MUC1 gene and distributed mainly on the surface of type II alveolar epithelial cells (AECs) covering bronchioles and alveoli[42]. When there is injury, cell proliferation and inflammation, AECs is disrupted and then KL-6 may diffuse into the pulmonary epithelial lining fluid and blood flow[43]. KL-6 has been suggested as a diagnostic and prognostic indicator not only in IPF but also in non-IPF ILD[44, 45]. Previous studies have showed that the baseline serum KL-6 level might be act as a sensitive predictor for the onset of AE in IPF[46] and elevated KL-6 level has been associated with more severe, progressive and poor outcomes of ILD[47, 48]. In addition, previous studies showed that high level of KL-6 was associated with poor clinical outcome in NSCLC patients who underwent surgery or received tyrosine kinase inhibitor (TKI) treatment[49-51]. Recently, there have also been studies presenting KL-6 as a prognostic factor in LC patients treated with immune checkpoint inhibitors (ICIs)[52]. Considering these previous reports, KL-6 might serve as a significant biomarker in LC patients accompanying ILD. Tomita et al., in 14 ILD patients with NSCLC, reported that a high KL-6 level showed a trend indicating a worse prognosis compared to those with lower levels (p = 0.063)[53]. However, Miyazaki et al., in 273 LC patients with and without ILD, reported that KL-6 was higher in ILD group but, there was no significant difference in prognosis based on KL-6 levels; however, this could be due to a low cutoff value (500U/mL) and the small sample size (n=68)[54]. Otherwise, the group with higher KL-6 levels (≥1000U/mL) showed the higher mortality in LC patients with fibrosing ILD in our study. These findings suggest that KL-6 with an appropriate cutoff might be a potent prognostic biomarker in these patients.

In this study, the stage of LC and surgery performed for LC were the independent prognostic factors in patients with NSCLC, respectively. Even in LC in ILD patients, it is relatively well known that the clinical stage of LC is the one of prognostic factors in these patients[55]. Sato et al. reported that the 5-year survivals rates following after surgical resection in lung cancers in patients with ILD were 59%, 42%, 43%, 29%, 25%, 17% and 16% for patients with stage(TNM stage, 6th edition) Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, respectively[56]. Alomaish et al., in 146 patient with lung cancer and ILD, reported that patients with stage IA, IB, IIB, and IIIA had a significantly

lower hazard of death or higher survival as compared to patients with stage IV based on the 7th edition of the TNM system (HR 0.121, 0.270, 0.273, 0.362, respectively)[57]. In our study, the stage of LC was an independent prognostic factor, as well. Moreover, surgery was independently associated with a favorable outcome in our study. Likewise, Han et al., in 160 patients diagnosed with LC and IPF, divided the patients were categorized into GAP stage and LC clinical stage, and showed the that in GAP stage I, surgery significantly improved the survival in both early and advanced LC stages ($p = 0.023$ and $p = 0.019$)[58]. In one survey, 78.2% of physicians responded that they consider surgery in patient with IPF of mild to moderate functional impairment (FVC>50%, DLCO>35%) with operable NSCLC (TNM stage I-II)[59]. Although there is a risk of acute exacerbation in about 10% of patients who received surgery for LC[60], and the surgery is feasible in selective patients with early stage of LC and relatively preserved pulmonary function[61].

There were some limitations to this study. First, our study was a single-center, retrospective study, which might have resulted in selection bias. Second, our study focused on only ILD patients diagnosed with LC, and there may be limitations in presenting cancer prevalence among ILD subtypes. Third, the follow-up periods were relatively short, with a median follow-up of 11 months after cancer diagnosis. However, considering the poor prognosis of patients with ILD-LC, it is believed that a meaningful analysis was possible. Despite these limitations, we considered that presenting lung cancer characteristics and clinical course based on ILD subtypes is a strength of our study.

Conclusion

In patients with lung cancer, there were no statistically significant differences in clinical characteristic s and mortality between IPF and non-IPF ILD. This finding suggests that the diagnosis and management of LC are important in non-IPF ILD patients as well as patients with IPF. Additionally, KL-6 might be served as a prognostic marker in lung cancer with fibrosing ILD.

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Supplemental Material

e-Table 1. Comparison of lung cancer characteristics in ILD patients with SCLC according to the type of ILD.

Characteristic	All (n = 22)	IPF-LC (n = 11)	Non-IPF-LC (n = 11)	*p*-value
Clinical stage				>0.999
Limited	12 (54.5)	6 (54.5)	6 (54.5)	
Extensive	10 (45.5)	5 (45.5)	5 (45.5)	
Initial treatment for lung cancer				
Surgery	1 (4.5)	1 (9.1)	0 (0.0)	>0.999
Chemotherapy	13 (59.1)	7 (63.6)	6 (54.5)	>0.999
Radiotherapy	2 (9.1)	1 (9.1)	1 (9.1)	>0.999
Concurrent chemoradiation therapy	4 (18.2)	1 (9.1)	3 (27.3)	0.586
Best supportive care	2 (9.1)	1 (9.1)	1 (9.1)	>0.999
Treatment of ILD				
Antifibrotic agent	11 (50.0)	10 (90.9)	1 (9.1)	<0.001
Corticosteroid ± IS	10 (45.5)	5 (45.5)	5 (45.5)	>0.999
Initial treatment	4 (18.2)	0 (0.0)	4 (36.4)	0.090
Acute exacerbation	9 (40.9)	5 (45.5)	4 (36.4)	>0.999
Acute exacerbation	9 (40.9)	5 (45.5)	4 (36.4)	>0.999
Overall mortality	11 (50.0)	4 (36.4)	7 (63.6)	0.201
AE-related death	2 (18.2)	2 (50.0)	0 (0.0)	0.109
Infection-related death	2 (18.2)	0 (0.0)	2 (18.2)	0.491
Unknown	7 (63.6)	2 (50.0)	5 (71.4)	0.576

Data are expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. ILD, interstitial lung disease; SCLC, small cell lung cancer; IS, immunosuppressants; AE, acute exacerbation

국문요약

연구배경: 간질성 폐질환에서 폐암은 중요한 동반 질환이며 불량한 예후와 관련되어 있다. 간질성 폐질환에서 폐암이 발생한 환자들에서 간질성 폐질환의 아형별로 임상적인 특징과 예후에 대한 비교는 아직 많이 연구되지 않았다. 이 연구는 후향적 연구로 폐암 환자에서 특발성 폐 섬유화증과 특발성 폐 섬유화증 이외의 간질성 폐질환 환자에서를 비교해보고, 간질성 폐질환과 폐암이 같이 있는 환자에서 예후에 영향을 미치는 인자를 분석해보고자 하였다.

연구방법: 2018 년 1 월부터 2023 년 5 월까지 서울아산병원에서 간질성 폐질환과 폐암을 진단받은 163 명의 환자들의 의무기록을 후향적으로 분석하였다. 특발성 폐 섬유화증 환자와 특발성 폐 섬유화증이 아닌 간질성 폐질환 환자들 간의 임상적 특성과 예후를 비교하였고 콕스 비례 위험 모델에 의해 예후인자를 분석하였다.

연구결과: 중앙 추적관찰 기간은 폐암 진단 이후 11 개월이었다. 특발성 폐 섬유화증과 특발성 폐 섬유화증이 아닌 간질성 폐질환 환자들에서 임상적 특징과 사망률에서 통계적으로 유의미한 차이가 없었다 (중앙 생존 기간: 26 개월 vs. 20 개월, p = 0.530). KL-6 수치가 높은 경우 (≥1000U/mL, 위험비, 1.970; 95% 신뢰구간, 1.026-3.783, p = 0.025)와 폐암의 병기는 (1 기와 비교하여, 2 기의 경우 위험비, 3.876, p = 0.025, 3 기 위험비 5.092, p = 0.002, 4 기 위험비 5.626, p = 0.002) 간질성 폐질환을 동반한 폐암 환자에서 독립적인 예후 인자였다. 폐암의 치료 측면에서 수술은 중요한 예후 인자였다 (위험비, 0.235; 95% 신뢰구간, 0.106 - 0.520; p < 0.001)

연구결론: 간질성 폐질환에 동반된 폐암 환자에서 특발성 폐 섬유화증과 이외의 간질성 폐질환 환자에서 임상적 특징과 예후 차이는 없었다. KL-6 가 간질성 폐질환에 동반된 폐암에서 예후를 예측하는데 유용한 인자로 활용될 수 있다.