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Abstract	Abstract

Background: The interstitial lung disease-gender-age-physiology (ILD-GAP) index and staging system have been reported as a clinical prognostic factor for ILD, including all ILD subtypes. **Objectives:** The purpose of this study was to clarify the association of various prognostic indices, including the ILD-GAP index, with the prognosis, the incidence of acute exacerbations of ILD (ILD-AE), and the use of long-term oxygen therapy (LTOT) after surgery in surgically resected patients with ILD and concomitant lung cancer, to provide additional information when considering whether it is safe to perform surgery. **Methods:** The medical records of patients

with ILD and concomitant lung cancer who had undergone surgery at Shinshu University Hospital between August 2001 and September 2016 were retrospectively analyzed. **Results:** There were significant differences in survival between the ILD-GAP index: 0–1 and ≥4 groups (p = 0.0001) and between the ILD-GAP index: 2–3 and ≥4 groups (p = 0.0236). A higher ILD-GAP index was independently associated with the risk of death (hazard ratio [HR] 1.32030; p = 0.0059). A higher body mass index (BMI) and a higher serum C-reactive protein (CRP) level were independently associated with the incidence of ILD-AE (HR 1.28336; p = 0.0206 and HR 26.3943; p = 0.0165, respectively). A higher severity of ILD on chest high-resolution computed tomography (HRCT) was independently associated with the use of LTOT (HR 2.78670; p = 0.0313). **Conclusions:** The ILD-GAP index can predict the prognosis in surgically resected patients with ILD and concomitant lung cancer. The BMI and serum CRP levels were independent determinants that predicted the incidence of ILD-AE. The severity of ILD on chest HRCT was an independent determinant that predicted the use of LTOT.

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Introduction

Lung cancer patients who have interstitial lung disease (ILD) have a high risk of complications and mortality. Although there are some reports limited to idiopathic pulmonary fibrosis (IPF) [1–5], the extent to which ILD (including its various subtypes), as a comorbidity of lung cancer, influences morbidity, mortality, and long-term survival after pulmonary resection for lung cancer has not been well studied. Sato et al. [6] reported that 2,418 of 41,742 patients (5.8%) who had undergone pulmonary resection for lung cancer presented with a clinical diagnosis of ILD.

Ley et al. [7] reported that the gender-age-physiology (GAP) index was useful for predicting mortality in patients with IPF. The GAP index is calculated based on GAP. Ryerson et al. [8] subsequently reported that the modified GAP model, named the ILD-GAP model, predicted the risk of death in all ILD subtypes. They developed this model including the following 4 subtypes; IPF, chronic hypersensitivity pneumonitis, connective tissue disease-associated ILD, and idiopathic nonspecific interstitial pneumonia (NSIP). They suggested that the ILD-GAP index was useful in all ILD subtypes and remained useful for all stages of disease severity and during follow-up evaluations.

Recently, prognostic indices that are indicative of the nutritional and immunological status have been found to be associated with recurrence and the prognosis in lung cancer patients, as stated below. The preoperative prognostic nutritional index (PNI), which is calculated based on serum albumin levels and total lymphocyte counts in the peripheral blood, was a predictor of recurrence [9] or a poor prognosis [10, 11] in non-small-cell lung cancer (NSCLC) patients who have undergone surgery. An elevated neutrophil-to-lymphocyte ratio (NLR) [12] and an elevated platelet-to-lymphocyte ratio (PLR) [13] were associated with the prognosis in lung cancer patients. In addition, systemic inflammatory response indices have also received attention. The modified Glasgow Prognostic Score (mGPS) [14], which is calculated based on serum albumin levels and serum C-reactive protein (CRP) levels, may also be a prognostic factor in patients with small-cell lung cancer. The prognostic index (PI) [15], which is calculated based on serum

CRP levels and white blood cell counts, may be correlated with both the response to chemotherapy and the survival rate of the patients with advanced NSCLC.

However, there continues to be a lack of information on the prognostic determinants in patients with ILD and concomitant lung cancer who have undergone surgery. We sought to clarify the association of these prognostic indices, including the ILD-GAP index, PNI, NLR, PLR mGPS, and PI, with the prognosis in such patients in a single academic institution. As a secondary objective, we sought to clarify the association of these prognostic indices with the incidence of acute exacerbations of ILD (ILD-AE) and the use of long-term oxygen therapy (LTOT) after surgery in the same population, in order to provide additional information to guide therapeutic decision-making when considering whether it is safe to perform surgery.

Materials and Methods

We retrospectively reviewed the medical records of all patients with lung cancer who had undergone pulmonary resection for primary lung cancer at Shinshu University Hospital between August 2001 and September 2016. Of these patients, those who presented with ILD were included in the present study. We obtained clinical data including the results of preoperative pulmonary function tests and laboratory examinations, chest high-resolution computed tomography (HRCT), the pathological stage of lung cancer, postoperative respiratory complications, and the survival. The tumor, nodes, and metastasis stage was evaluated based on the 7th edition of the tumor, nodes, and metastasis classification of lung cancer [16]. In the present study, ILD was defined as chronic, progressive fibrosing interstitial pneumonia of unknown cause occurring primarily in older adults or associated with connective tissue disease and occupation and was then classified based on the official statement of the American Thoracic Society and the European Respiratory Society [17]. ILD-AE was defined as any acute

respiratory event characterized by new bilateral ground glass-opacification/consolidation that was not completely explained by infectious disease and cardiac failure or fluid overload [18].

The visual HRCT assessment was performed based on our previous reports [19–24]. The extent of ILD was scored visually to grade the severity as previously described [25] and was classified into a 3-grade scale, as follows: 1, Minimum; 2, Moderate; and 3, Severe. There were some patients with ILD and concomitant emphysema. Thus, we also scored emphysema visually, based on the identification of low attenuation areas (LAA) in the bilateral upper, middle, and lower lung fields according to the methods of Goddard et al. [26] as follows: score 0, %LAA<5%; score 1, 5%≤%LAA<25%; score 2, 25%≤%LAA<50%; score 3, 50%≤%LAA<75%; and score 4, 75%≤%LAA. The visual score of the LAA was calculated as the sum of the scores of the 6 lung fields. The CT images were reviewed independently by 2 pulmonologists (F.U. and Y.K.) with no knowledge of the patients' clinical data.

All patients underwent spirometry and measurements of the diffusion capacity for carbon monoxide (DLco), the functional residual capacity, the total lung capacity, and the residual volume using a pulmonary function testing system (Chestac-8900®; Chest Co., Ltd., Tokyo, Japan) as previously described [19–24].

The diagnostic criteria for the ILD subtypes were based on the official statement of American Thoracic Society and the European Respiratory Society [17]. The diagnosis of ILD subtypes were made based on a multidisciplinary team discussion at our institution or by reviewing histology. The ILD-GAP index was calculated based on the ILD subtypes (IPF and unclassifiable ILD, 0; non-IPF, -2), gender (female, 0; male, 1), age (years; ≤60, 0; 61–65, 1; >65, 2), percent predicted forced vital capacity (%FVC; ≥75%, 0; 50%–75%, 1; <50%, 2), and percent predicted diffusion lung capacity for carbon monoxide (%DLCO; >55%, 0; 36%–55%, 1; ≤35%, 2) [8]. Patients were categorized into 3 groups based on their total scores as follows: ILD-GAP index: 0–1; ILD-GAP index: 2–3; and ILD-GAP index: ≥4. The PNI, NLR, PLR, mGPS,

and PI, which had previously been reported to be prognostic determinants for lung cancer [9–15], were calculated based on the laboratory data.

We retrospectively assessed the association of the clinical data and prognostic indices with the risk of death in patients with ILD and concomitant lung cancer who had undergone surgery. Second, we assessed the association of the clinical data and prognostic indices with the incidence of ILD-AE and the use of LTOT after surgery in the same population. Our institutional review board approved this retrospective study and provided all of the necessary ethical permissions (permission No. 3,932).

The data are presented as the mean ± SE or ratios with percentages, as appropriate. A univariate Cox proportional hazards regression analysis followed by a multivariate analysis was used to identify determinants associated with the risk of death. A logistic regression analysis was performed to identify determinants associated with the incidence of ILD-AE and the use of LTOT after surgery. In order to avoid multicollinearity, Pearson's correlation analysis was performed to identify variables that were highly correlated. If the Pearson's correlation coefficient (r) was ≥0.60, only one of the variables was included in the multivariate analysis. Variables with p values <0.05 in the univariate analyses were considered for inclusion in the multivariate analysis. Survival in each group was estimated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. The clinical characteristics of the 2 groups were compared using an unpaired t test. Categorical variables in 2 groups were evaluated using Fisher's exact test. All statistical analyses were performed using the StatFlex software program (version 6; Artech Co. Ltd, Osaka, Japan). p values <0.05 were considered to indicate statistical significance in all the statistical analyses.

Results

A total of 1,449 patients had undergone pulmonary resection for primary lung cancer at our institution during the study period. One hundred twenty-five of these patients (8.6%) also had ILD on chest HRCT. Twenty-three of the 125 patients were excluded from the study because of insufficient pulmonary function data. The data on the remaining 102 patients were analyzed in this study. Table 1 shows the clinical characteristics of the 102 patients with ILD and concomitant lung cancer who had undergone surgery, which included 44 patients with IPF, 52 patients with idiopathic NSIP, 5 patients with CTD-ILD, and 1 with unclassifiable ILD. There were no patients with hypersensitivity pneumonitis-ILD. There were no patients with pulmonary hypertension (PH), which is well known to have a negative impact on the prognosis of chronic lung disease like ILD [27, 28], as PH is considered to be a contraindication for lung cancer resection at our institution (the presence of PH was evaluated using an echocardiogram and was diagnosed by cardiologists for all patients before surgery). Some patients had received adjuvant chemotherapy after surgery for lung cancer and/or chemotherapy after developing recurrence (Table 1). However, there was no significant difference in the proportions of these patients among the 3 ILD-GAP index groups. No patients received radiotherapy. No patients received LTOT before surgery.

In addition, all subjects were divided into “the IPF group” and “the non-IPF group,” which included NSIP and other ILD subtypes, in order to compare clinical characteristics between the 2 groups (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000502849). The proportion of patients with advanced-stage lung cancer, the serum KL-6 level, the severity of emphysema and ILD on chest HRCT, the ILD-GAP index, and the incidence of postoperative hypoxemia and chemotherapy-related acute exacerbation were significantly higher and the parameters of diffusion lung capacity significantly lower in the IPF group than in the non-IPF group.

Figure 1 shows the Kaplan-Meier curve for the overall survival of these patients. The median survival time was 3.48 years. In addition, 102 patients were categorized into ILD-GAP

index: 0–1 (n = 46), ILD-GAP index: 2–3 (n = 32), and ILD-GAP index: ≥4 (n = 24). In the Kaplan-Meier analysis, the log-rank test showed that there were significant differences in survival between the ILD-GAP index: 0–1 and the ILD-GAP index: ≥4 groups (p = 0.0001) and between the ILD-GAP index: 2–3 and the ILD-GAP index: ≥4 groups (p = 0.0236; Fig. 2). A difference in survival was observed between the ILD-GAP index: 0–1 and the ILD-GAP index: 2–3 groups (p = 0.0637); however, it was not statistically significant (Fig. 2). Online supplementary Figure 1 shows the Kaplan-Meier curves of analyses between the IPF (n = 44) and the non-IPF (n = 58) groups. In the Kaplan-Meier analysis, the log-rank test showed that there was significant difference in survival between the IPF and the non-IPF groups (p < 0.0001).

The univariate Cox proportional hazards regression analysis showed that a higher Brinkman index, a higher severity of ILD on chest HRCT, a higher pathological stage of lung cancer, a lower serum albumin level, and a higher ILD-GAP index were associated with the risk of death (Table 2). The multivariate analysis showed that a higher pathological stage of lung cancer and a higher ILD-GAP index were independently associated with the risk of death (Table 3). In contrast, prognostic indices that are indicative of the nutritional, immunological status and systemic inflammation (e.g., the PNI, NLR, PLR, mGPS, and PI) were not associated with the risk of death.

The univariate logistic regression analysis also showed that a higher body mass index (BMI), a higher serum CRP level, a higher mGPS, and a higher PI were associated with the incidence of ILD-AE after surgery (Table 4). The multivariate analysis showed that a higher BMI and a higher serum CRP level were independently associated with the incidence of ILD-AE after surgery (Table 5). The PI was excluded as a candidate to avoid multicollinearity because the variable was highly correlated with the mGPS score (Pearson's r = 0.9210).

The univariate logistic regression analysis showed that a higher BMI, a higher severity of ILD on chest HRCT, a higher serum KL-6 level, and a higher ILD-GAP index were associated with the use of LTOT after surgery (Table 6). The multivariate analysis showed that a higher

severity of ILD on chest HRCT was independently associated with the use of LTOT after surgery (Table 7).

Discussion/Conclusion

The main purpose of the present study was to clarify the association of various prognostic indices including the ILD-GAP index, with the prognosis in patients with ILD and concomitant lung cancer who had undergone surgery, as the ILD-GAP index and staging system have been reported as clinical prognostic factors for ILD (including all ILD subtypes) [8]. The secondary objective was to clarify the association of various prognostic indices, including the ILD-GAP index, with the incidence of ILD-AE and the use of LTOT after surgery in the same population.

Recently, the ILD-GAP index has been widely utilized to evaluate disease severity and predict the prognosis in patients with all ILD subtypes. The ILD-GAP index could help determine the appropriate timing for lung transplantation. For example, patients with ILD-GAP index scores of more than 4 have a substantially higher mortality risk and should be considered for lung transplantation, if appropriate [8]. A modified ILD-GAP index may predict the incidence of ILD-AE and the prognosis in patients with ILD and NSCLC who had received chemotherapy [29, 30]. In addition, the present study revealed that the ILD-GAP index is also useful for predicting the prognosis in patients with ILD and concomitant lung cancer who had undergone surgery. These findings suggest that the ILD-GAP index can be widely useful for identifying the individual mortality risk in not only patients with all ILD subtypes but also such patients with concomitant lung cancer. On the other hand, previous studies reported that the PNI, NLR, and PLR were predictors of the prognosis in patients with NSCLC who had undergone pulmonary resection [9–11]. However, the present study revealed that these indices were not predictors of the prognosis in patients with ILD and concomitant lung cancer who had undergone surgery. These findings

suggest that the severity of ILD, expressed as the ILD-GAP index, has more prognostic impact than the nutritional and immunological status in the population.

Surgery may be the best treatment for patients with early-stage NSCLC, if they meet the criteria for surgery. However, in patients with ILD and concomitant lung cancer, we have to carefully consider whether it is safe to perform surgery because some patients will experience ILD-AE as a complication of surgery, which may result in a poor prognosis. In the present study, 11 patients (11.0%) had ILD-AE and 4 of them died (mortality rate: 36%). Our findings suggest that the ILD-GAP index and prognostic indices that are indicative of the nutritional and immunological status were not associated with the incidence of ILD-AE. In contrast, the serum CRP levels and systemic inflammatory response indices, which are calculated based on serum CRP levels, were associated with the incidence of ILD-AE. The previous study revealed that serum CRP levels were identified as possible risk factors for ILD-AE in patients with usual intersitital puneumonia (UIP) appearance on chest CT and concomitant lung cancer who had undergone surgery [6]. The CRP induced by a cytokine consortium, in which interleukin-6 is the dominant partner, was shown to be an important adverse survival determinant in advanced cancer, including NSCLC [15]. Thus, it is possible that the preoperative systemic inflammation due to high activity of ILD and/or lung cancer is associated with the postoperative ILD-AE.

The previous study reported that 11% of patients with ILD and lung cancer required LTOT after surgery and that respiratory failure was an important factor that was associated with poor long-term survival [31]. Thus, respiratory failure is an important postoperative complication, and it is caused by not only ILD-AE. In the present study, 17 patients (16.7%) required LTOT after surgery, but only 2 of them experienced ILD-AE. Our findings suggest that the BMI, severity of ILD on chest HRCT, serum KL-6 levels, and ILD-GAP index were associated with the use of LTOT after surgery. The severity of ILD on chest HRCT and the ILD-GAP index reflect the radiological severity and physiological severity of ILD, respectively, while serum KL-6 levels

reflect the disease activity of ILD serologically [8, 32, 33]. Thus, these variables are assumed to be associated with chronic respiratory failure, which result in the use of LTOT after surgery.

To the best of our knowledge, no previous studies have described an association between the BMI and the incidence of ILD-AE or between the BMI and the use of LTOT in patients with ILD and concomitant lung cancer after surgery. Our findings suggest that the BMI was associated with the incidence of ILD-AE and the use of LTOT after surgery but not with the risk of death in these patients. Regarding the association of the BMI with the prognosis in patients with IPF, previous studies reported that a higher BMI was associated with a better survival in patients with IPF [34, 35]. Regarding the association of the BMI with the prognosis in patients with lung cancer, a lower BMI and significant body weight loss before surgery had a negative effect on the surgical outcomes for patients with NSCLC [36]. In contrast, a higher BMI was a significant independent risk factor for acute exacerbations of IPF in patients with IPF, and acute exacerbation was an independent prognostic factor in IPF [37]. However, it is difficult to compare our findings with the results of previous studies [34–37], as the patient populations were different. Thus, further studies are needed to clarify the association of the BMI with the risk of death and the incidence of ILD-AE in patients with ILD and concomitant lung cancer after surgery.

The present study is associated with several limitations. First, this was a retrospective single-center study, and the sample size of patients with CTD-ILD and unclassifiable ILD was particularly small. Additional prospective studies should be performed with large study populations including more patients with these ILD subtypes in order to confirm our results. Second, the assessment of emphysema and ILD on chest HRCT was performed using a visual scoring method, as previously described [19–24], rather than a software-based method. However, the reproducibility of the visual scoring system was demonstrated in our previous report [24]. Third, as described in the Materials and Methods, 23 of the 125 lung cancer patients with ILD who had undergone surgery were excluded from the study because their DLCO values

were not measured. There is a possibility that fewer patients with normal spirometry underwent a DLCO measurement in comparison to patients with abnormal spirometry. Thus, the proportion of patients with abnormal spirometry might have been higher in the present study, which might have resulted in a selection bias. Fourth, our findings suggest that the ILD of the IPF group might be more severe in histological, serological, radiological, and physiological findings than that of the non-IPF group. Thus, patients with NSIP and other ILD subtypes may undergo pulmonary resection for primary lung cancer more frequently than patients with IPF, which might have resulted in a selection bias. Fifth, the differences in pharmacotherapy, such as chemotherapy and antifibrotic agents, among patients might affect the results.

In conclusion, the cross-sectional preoperative ILD-GAP index can predict the prognosis in surgically resected patients with ILD and concomitant lung cancer. In particular, patients with ILD-GAP index scores of more than 4 have a significantly higher mortality risk. In contrast, the BMI and serum CRP levels were independent determinants that predicted the incidence of ILD-AE after surgery. The severity of ILD on chest HRCT was an independent determinant that predicted the use of LTOT after surgery. These indices and parameters may provide additional information to guide therapeutic decision-making when considering whether it is safe to perform surgery.

Statement of Ethics

The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Dr. Yoshiaki Kitaguchi is the guarantor of the article. Dr. Fumika Ueno: contributed to the data generation and producing the initial draft of the manuscript; participated in the data analysis, interpretation of the analysis, final preparation of the manuscript; and read and approved the final manuscript. Dr. Yoshiaki Kitaguchi: contributed to conceiving the study design, the data generation, producing the initial draft of the manuscript; participated in the data analysis, interpretation of the analysis, final preparation of the manuscript; and read and approved the final manuscript. Drs. Takayuki Shiina, Shiho Asaka, and Akihiko Yoshizawa: contributed to the data generation and analysis and to the final preparation of the manuscript, and read and approved the final manuscript. Drs. Masanori Yasuo, Yosuke Wada, Takumi Kinjo, and Masayuki Hanaoka: contributed to interpretation of the analysis and to the final preparation of the manuscript, and read and approved the final manuscript.

References

1 Saito Y, Kawai Y, Takahashi N, Ikeya T, Murai K, Kawabata Y, et al. Survival after surgery for pathologic stage IA non-small cell lung cancer associated with idiopathic pulmonary fibrosis. Ann Thorac Surg. 2011 Nov;92(5):1812–7.

2 Watanabe A, Higami T, Ohori S, Koyanagi T, Nakashima S, Mawatari T. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? J Thorac Cardiovasc Surg. 2008 Nov;136(5):1357–63.

3 Lee T, Park JY, Lee HY, Cho YJ, Yoon HI, Lee JH, et al. Lung cancer in patients with idiopathic pulmonary fibrosis: clinical characteristics and impact on survival. Respir Med. 2014 Oct;108(10):1549–55.

4 Omori T, Tajiri M, Baba T, Ogura T, Iwasawa T, Okudela K, et al. Pulmonary Resection for Lung Cancer in Patients With Idiopathic Interstitial Pneumonia. Ann Thorac Surg. 2015 Sep;100(3):954–60.

5 Goto T, Maeshima A, Oyamada Y, Kato R. Idiopathic pulmonary fibrosis as a prognostic factor in non-small cell lung cancer. Int J Clin Oncol. 2014 Apr;19(2):266–73.

6 Sato T, Teramukai S, Kondo H, Watanabe A, Ebina M, Kishi K, et al.; Japanese Association for Chest Surgery. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg. 2014 May;147(5):1604–1611.e3.

7 Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012 May;156(10):684–91.

8 Ryerson CJ, Vittinghoff E, Ley B, Lee JS, Mooney JJ, Jones KD, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest. 2014 Apr;145(4):723–8.

9 Shoji F, Morodomi Y, Akamine T, Takamori S, Katsura M, Takada K, et al. Predictive impact for postoperative recurrence using the preoperative prognostic nutritional index in pathological stage I non-small cell lung cancer. Lung Cancer. 2016 Aug;98:15–21.

10 Shimizu K, Okita R, Saisho S, Yukawa T, Maeda A, Nojima Y, et al. Prognostic nutritional index before adjuvant chemotherapy predicts chemotherapy compliance and survival among patients with non-small-cell lung cancer. Ther Clin Risk Manag. 2015 Oct;11:1555–61.

11 Shimizu K, Okita R, Saisho S, Maeda A, Nojima Y, Nakata M. Preoperative neutrophil/lymphocyte ratio and prognostic nutritional index predict survival in patients with non-small cell lung cancer. World J Surg Oncol. 2015 Sep;13(1):291.

12 Bar-Ad V, Palmer J, Li L, Lai Y, Lu B, Myers RE, et al. Neutrophil to lymphocyte ratio associated with prognosis of lung cancer. Clin Transl Oncol. 2017 Jun;19(6):711–7.

13 Ding N, Pang Z, Shen H, Ni Y, Du J, Liu Q. The Prognostic Value of PLR in Lung Cancer, a Meta-analysis Based on Results from a Large Consecutive Cohort. Sci Rep. 2016 Oct;6(1):34823.

14 Kurishima K, Watanabe H, Ishikawa H, Satoh H, Hizawa N. Modified glasgow prognostic score in patients with small-cell lung cancer. Mol Clin Oncol. 2017 Jul;7(1):121–4.

15 Kasymjanova G, MacDonald N, Agulnik JS, Cohen V, Pepe C, Kreisman H, et al. The predictive value of pre-treatment inflammatory markers in advanced non-small-cell lung cancer. Curr Oncol. 2010 Aug;17(4):52–8.

16 Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al.; International Association for the Study of Lung Cancer International Staging Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol. 2007 Aug;2(8):706–14.

17 Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al.; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013 Sep;188(6):733–48.

18 Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 2016 Aug;194(3):265–75.

19 Kitaguchi Y, Fujimoto K, Hanaoka M, Honda T, Hotta J, Hirayama J. Pulmonary function impairment in patients with combined pulmonary fibrosis and emphysema with and without airflow obstruction. Int J Chron Obstruct Pulmon Dis. 2014 Jul;9:805–11.

20 Ueno F, Kitaguchi Y, Shiina T, Asaka S, Miura K, Yasuo M, et al. The Preoperative Composite Physiologic Index May Predict Mortality in Lung Cancer Patients with Combined Pulmonary Fibrosis and Emphysema. Respiration. 2017;94(2):198–206.

21 Kitaguchi Y, Fujimoto K, Hayashi R, Hanaoka M, Honda T, Kubo K. Annual changes in pulmonary function in combined pulmonary fibrosis and emphysema: over a 5-year follow-up. Respir Med. 2013 Dec;107(12):1986–92.

22 Kitaguchi Y, Fujimoto K, Hanaoka M, Kawakami S, Honda T, Kubo K. Clinical characteristics of combined pulmonary fibrosis and emphysema. Respirology. 2010 Feb;15(2):265–71.

23 Kitaguchi Y, Fujimoto K, Kubo K, Honda T. Characteristics of COPD phenotypes classified according to the findings of HRCT. Respir Med. 2006 Oct;100(10):1742–52.

24 Fujimoto K, Kitaguchi Y, Kubo K, Honda T. Clinical analysis of chronic obstructive pulmonary disease phenotypes classified using high-resolution computed tomography. Respirology. 2006 Nov;11(6):731–40.

25 Kurashima K, Takayanagi N, Tsuchiya N, Kanauchi T, Ueda M, Hoshi T, et al. The effect of emphysema on lung function and survival in patients with idiopathic pulmonary fibrosis. Respirology. 2010 Jul;15(5):843–8.

26 Goddard PR, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. Clin Radiol. 1982 Jul;33(4):379–87.

27 Todd NW, Lavania S, Park MH, Iacono AT, Franks TJ, Galvin JR, et al. Variable prevalence of pulmonary hypertension in patients with advanced interstitial pneumonia. J Heart Lung Transplant. 2010 Feb;29(2):188–94.

28 Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, et al.; Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires (GERM O P). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005 Oct;26(4):586–93.

29 Kobayashi H, Omori S, Nakashima K, Wakuda K, Ono A, Kenmotsu H, et al. Modified GAP index for prediction of acute exacerbation of idiopathic pulmonary fibrosis in non-small cell lung cancer. Respirology. 2017 Oct;22(7):1379–85.

30 Kobayashi H, Naito T, Omae K, Omori S, Nakashima K, Wakuda K, et al. ILD-NSCLC-GAP index scoring and staging system for patients with non-small cell lung cancer and interstitial lung disease. Lung Cancer. 2018 Jul;121:48–53.

31 Chiyo M, Sekine Y, Iwata T, Tatsumi K, Yasufuku K, Iyoda A, et al. Impact of interstitial lung disease on surgical morbidity and mortality for lung cancer: analyses of short-term and long-term outcomes. J Thorac Cardiovasc Surg. 2003 Oct;126(4):1141–6.

32 Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M. New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. Chest. 1989 Jul;96(1):68–73.

33 Kohno N, Awaya Y, Oyama T, Yamakido M, Akiyama M, Inoue Y, et al. KL-6, a mucin-like glycoprotein, in bronchoalveolar lavage fluid from patients with interstitial lung disease. Am Rev Respir Dis. 1993 Sep;148(3):637–42.

34 Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. Chest. 2007 May;131(5):1448–53.

35 Kim JH, Lee JH, Ryu YJ, Chang JH. Clinical predictors of survival in idiopathic pulmonary fibrosis. Tuberc Respir Dis (Seoul). 2012 Sep;73(3):162–8.

36 Nakagawa T, Toyazaki T, Chiba N, Ueda Y, Gotoh M. Prognostic value of body mass index and change in body weight in postoperative outcomes of lung cancer surgery. Interact Cardiovasc Thorac Surg. 2016 Oct;23(4):560–6.

37 Kondoh Y, Taniguchi H, Katsuta T, Kataoka K, Kimura T, Nishiyama O, et al. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010 Jul;27(2):103–10.

Appendix after References (Editorial Comments)

Legend(s)

Fig. 1. Kaplan-Meier curve of the overall survival of the 102 patients with ILD and concomitant lung cancer who had undergone surgery. MST, median survival time.

Fig. 2. Kaplan-Meier curves of analyses among ILD-GAP index: 0–1 (*n* = 46, MST: 5.68 years), ILD-GAP index: 2–3 (*n* = 32, MST: 3.32 years), and ILD-GAP: ≥4 (*n* = 24, MST: 1.91 years) groups. Differences in survival were assessed using the log-rank test. ILD, interstitial lung disease; GAP, gender-age-physiology.

Table(s)

Footnote(s)

Table 1. Clinical characteristics of patients with ILD and concomitant lung cancer who had undergone surgery (*n* = 102)

	All subjects (*n* = 102)
Age, years, mean ± SD	72.3±0.6
Gender, female/male	7/95
BMI, kg/m^2, mean ± SD	23.39±0.33
Brinkman index, pack-years, mean ± SD	54.3±3.2
Histologic diagnoses of lung cancer, *n* (%)	
Small-cell carcinoma	1 (1.0)
Squamous cell carcinoma	48 (47.1)
Adenocarcinoma	43 (41.2)
Large-cell carcinoma	3 (2.9)
Other non-small-cell carcinoma	7 (6.9)
Pathological stage of lung cancer, *n* (%)	
Stage I A,B	61 (60.0)
Stage II A,B	20 (19.6)
Stage III A,B	17 (16.7)
Stage IV	4 (3.9)
Advanced stage(III B, IV)	7 (6.9)
Primary site of lung cancer, *n* (%)	
Right upper lobe	28 (27.5)
Right middle lobe	4 (3.9)
Right lower lobe	33 (32.4)
Left upper lobe	24 (23.5)
Left lower lobe	13 (12.7)
Laboratory data, mean ± SD	
Serum Alb, g/dL	4.01±0.04
Serum CRP, mg/dL	0.29±0.04
Serum LDH, IU/L	207.29±3.75
Serum CEA, ng/mL	7.81±1.12
Serum KL-6, U/mL	601.97±37.35
Chest HRCT findings, mean ± SD	
Severity of emphysema (LAA score)	8.37±0.61
Severity of ILD, 1: minimum/2: moderate/ 3: severe	1.40±0.06
Prognostic indices, mean ± SD	
ILD-GAP index	2.17±0.14
PNI	49.61±0.55
NLR	2.18±0.10
PLR	122.36±5.17
mGPS	0.06±0.02
PI	0.07±0.03
Pulmonary function tests, mean ± SD	
VC, L	3.29±0.08
%VC, %	99.01±1.57
FVC, L	3.21±0.08
%FVC, %	98.75±1.79
FEV_1, L	2.28±0.06
%FEV_1, %	89.47±1.91
FEV_1/FVC, %	71.38±0.90
%TLC, %	104.46±1.91
%$D_L$co, %	58.30±1.80
%$D_L$co/VA, %	80.05±2.63
Postoperative respiratory complications, *n* (%)	
Acute exacerbation of ILD	11 (10.8)
Bacterial pneumonia	3 (2.9)
Pyothorax	6 (5.9)
Hypoxemia (respiratory failure)	17 (16.7)
Prolonged air leak	12 (11.8)
Paroxysmal atrial fibrillation	9 (8.8)
Others	2 (2.0)
Surgery-related death	4 (3.9)
Chemotherapy, *n* (%)	
Adjuvant chemotherapy	22 (21.6)
Postoperative recurrence of lung cancer	47 (46.1)

Chemotherapy after developing recurrence	23 (22.5)
Chemotherapy-related acute exacerbation	6 (5.9)
Chemotherapy-related death	2 (2.0)

BMI, body mass index; HRCT, high-resolution computed tomography; LAA, low attenuation areas; CRP, C-reactive protein; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; KL-6, Krebs von den Lungen-6; ILD, interstitial lung disease; GAP, gender-age-physiology; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; DLco, diffusing capacity for carbon monoxide; DLco/VA, diffusing capacity for carbon monoxide corrected for alveolar volume; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; mGPS, modified Glasgow prognostic score; PI, prognostic index.

Table 2. Univariate cox proportional hazards regression analysis of the risk of death in patients with ILD and concomitant lung cancer who had undergone surgery (*n* = 102)

Variable	HR	95% CI	*p* value
Age, years	1.00265	0.96448–1.04232	0.8937
BMI, kg/m^2	0.98313	0.90218–1.07134	0.6979
Brinkman index, pack-years	1.01105	1.00343–1.01872	0.0044
Chest HRCT findings			
Severity of emphysema (LAA score)	1.02200	0.98483–1.06057	0.2497
Severity of ILD, 1: minimum/2: moderate/3: severe	1.66800	1.17401–2.36983	0.0043
Primary site of lung cancer: upper lobe	0.84821	0.51390–1.40001	0.5196
Pathological stage of lung cancer	1.40387	1.05530–1.86756	0.0198
Laboratory data			
Serum Alb, g/dL	0.37824	0.18949–0.75501	0.0058
Serum CRP, mg/dL	1.05638	0.50091–2.22785	0.8854
Serum LDH, IU/L	1.00221	0.99588–1.00859	0.4939
Serum CEA, ng/mL	1.01021	0.99558–1.02505	0.1722
Serum KL-6, U/mL	1.00057	0.99981–1.00134	0.1405
Prognostic indices			
ILD-GAP index	1.44034	1.22234–1.69722	<0.0001
PNI	0.96616	0.92052–1.01406	0.1632
NLR	1.08417	0.85568–1.37368	0.5033
PLR	0.99927	0.99400–1.00456	0.7852
mGPS	0.31480	0.04357–2.27431	0.2520
PI	0.62127	0.15150–2.54772	0.5086

BMI, body mass index; HRCT, high-resolution computed tomography; LAA, low attenuation areas; CRP, C-reactive protein; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; KL-6, Krebs von den Lungen-6; ILD, interstitial lung disease; GAP, gender-age-physiology; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; mGPS, modified Glasgow prognostic score; PI, prognostic index.

Table 3. Multivariate cox proportional hazards regression analysis of the risk of death in patients with ILD and concomitant lung cancer who had undergone surgery (*n* = 102)

Variable	HR	95% CI	*p* value
Brinkman index, pack-years	1.00666	0.99854–1.01485	0.1083
Pathological stage of lung cancer	1.54113	1.14207–2.07961	0.0047
Chest HRCT finding			
Severity of ILD, 1: minimum/2: moderate/3: severe	1.34753	0.92430–1.96457	0.1210
ILD-GAP index	1.32030	1.08329–1.60917	0.0059
Serum Alb, g/dL	0.48403	0.22093–1.06044	0.0698

HRCT, high-resolution computed tomography; ILD, interstitial lung disease; GAP, gender-age-physiology; HR, hazard ratio.

Table 4. Univariate logistic regression analysis of the incidence of acute exacerbations of ILD after surgery in patients with ILD and concomitant lung cancer who had undergone surgery (*n* = 102)

Variable	HR	95% CI	*p* value
Age, years	1.03302	0.93091–1.14634	0.5407
BMI, kg/m^2	1.25117	1.04243–1.50172	0.0161
Brinkman index, pack-years	1.00643	0.98823–1.02496	0.4914
Chest HRCT findings			
Severity of emphysema (LAA score)	0.92724	0.82470–1.04294	0.2084
Severity of ILD, 1: minimum/2: moderate/3: severe	1.16111	0.43765–3.08049	0.7641
Primary site of lung cancer: upper lobe	0.55901	0.15305–2.04171	0.3789
Pathological stage of lung cancer	0.98499	0.48675–1.99323	0.9664
Laboratory data			
Serum Alb, g/dL	1.71540	0.27123–10.8490	0.5663
Serum CRP, mg/dL	11.6523	2.63392–51.5491	0.0012
Serum LDH, IU/L	1.01046	0.99456–1.02662	0.1986
Serum CEA, ng/mL	0.93629	0.80520–1.08873	0.3924
Serum KL-6, U/mL	1.00069	0.99918–1.00220	0.3712
Prognostic indices			
ILD-GAP index	0.86080	0.54674–1.35526	0.5175
PNI	0.98954	0.88477–1.10671	0.8538
NLR	1.04346	0.57901–1.88047	0.8874
PLR	1.00045	0.98860–1.01245	0.9408
mGPS	11.0000	1.89939–63.7046	0.0075
PI	8.15625	1.54635–43.0202	0.0134

BMI, body mass index; HRCT, high-resolution computed tomography; LAA, low attenuation areas; CRP, C-reactive protein; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; KL-6, Krebs von den Lungen-6; ILD, interstitial lung disease; GAP, gender-age-physiology; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; mGPS, modified Glasgow prognostic score; PI, prognostic index.

Table 5. Multivariate logistic regression analysis of the incidence of acute exacerbations of ILD after surgery in patients with ILD and concomitant lung cancer who had undergone surgery (n = 102)

Variable	HR	95% CI	p value
BMI, kg/m^2	1.28336	1.03908–1.58507	0.0206
Serum CRP, mg/dL	26.3943	1.81631–383.556	0.0165
mGPS	0.33921	0.01199–9.59776	0.5261

The PI was excluded as a candidate to avoid multicollinearity because the variable was highly correlated with the mGPS score (Pearson's r = 0.9210).

ILD, interstitial lung disease; BMI, body mass index; CRP, C-reactive protein; mGPS, modified Glasgow prognostic score; PI, prognostic index.

Table 6. Univariate logistic regression analysis of the use of long-term oxygen therapy after surgery in patients with ILD and concomitant lung cancer who had undergone surgery (*n* = 102)

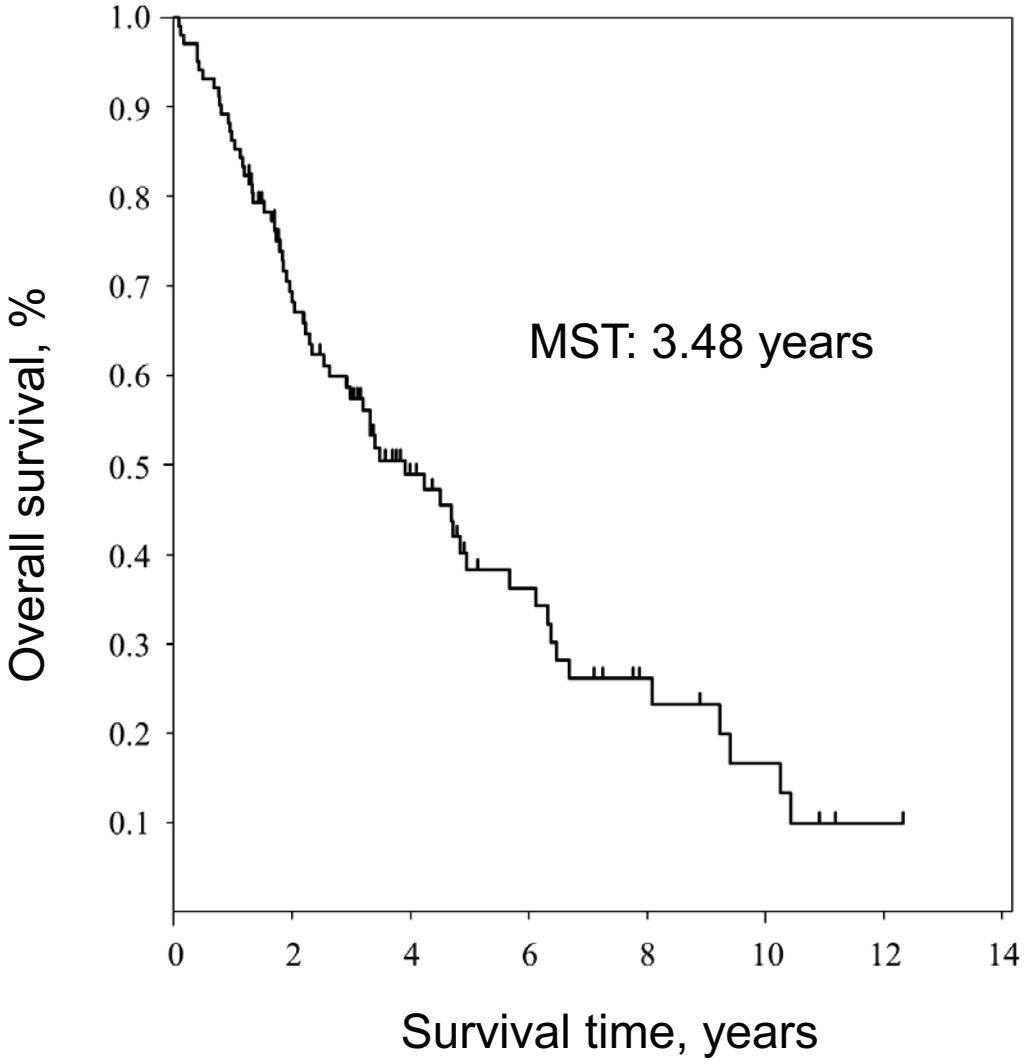
Variable	HR	95% CI	*p* value
Age, years	1.03744	0.94898–1.13414	0.4189
BMI, kg/m^2	1.18178	1.00923–1.38382	0.0381
Brinkman index, pack-years	1.01223	0.99663–1.02808	0.1251
Chest HRCT findings			
Severity of emphysema (LAA score)	1.07429	0.98709–1.16918	0.0971
Severity of ILD, 1: minimum/2: moderate/3: severe	2.97738	1.35475–6.54346	0.0066
Primary site of lung cancer: upper lobe	1.04762	0.36031–3.04598	0.9319
Pathological stage of lung cancer	0.96735	0.52849–1.77063	0.9143
Laboratory data			
Serum Alb, g/dL	2.36275	0.46405–12.0301	0.3005
Serum CRP, mg/dL	1.12899	0.27711–4.59966	0.8656
Serum LDH, IU/L	1.00325	0.98940–1.01729	0.6478
Serum CEA, ng/mL	1.03172	0.99376–1.07112	0.1025
Serum KL-6, U/mL	1.00172	1.00015–1.00329	0.0316
Prognostic indices			
ILD-GAP index	1.58858	1.08501–2.32587	0.0173
PNI	1.07768	0.97178–1.19513	0.1563
NLR	0.88495	0.50981–1.53614	0.6640
PLR	0.99049	0.97774–1.00341	0.1485
mGPS	1.08000	0.11770–9.91007	0.9457
PI	0.88889	0.09972–7.92378	0.9160

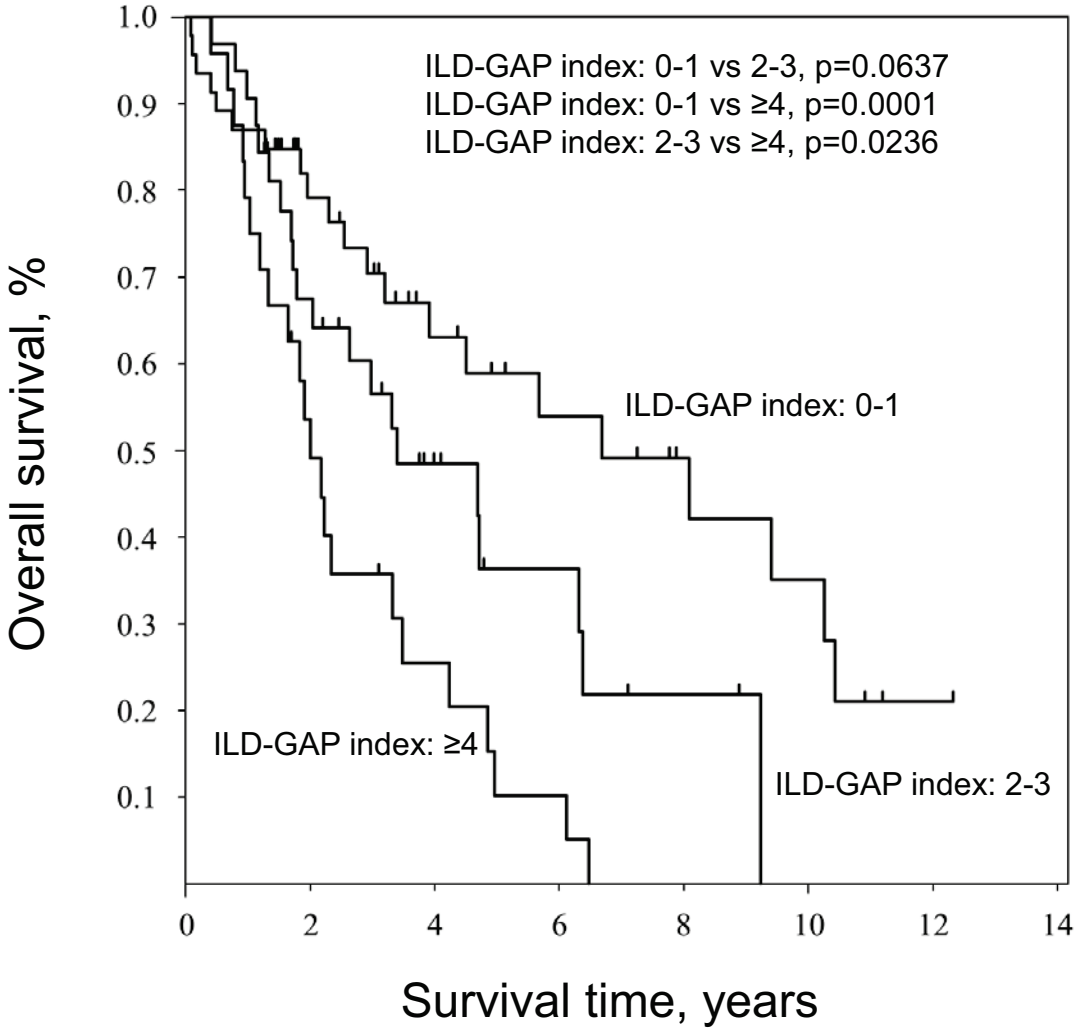
BMI, body mass index; HRCT, high-resolution computed tomography; LAA, low attenuation areas; CRP, C-reactive protein; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; KL-6, Krebs von den Lungen-6; ILD, interstitial lung disease; GAP, gender-age-physiology; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; mGPS, modified Glasgow prognostic score; PI, prognostic index.

Table 7. Multivariate logistic regression analysis of the use of long-term oxygen therapy after surgery in patients with ILD and concomitant lung cancer who had undergone surgery (*n* = 102)

Variable	HR	95% CI	*p* value
BMI, kg/m^2	1.14709	0.93135–1.41281	0.1967
Chest HRCT finding severity of ILD, 1: minimum/2: moderate/3: severe	2.78670	1.09624–7.08390	0.0313
Serum KL-6, U/mL	1.00125	0.99962–1.00288	0.1329
ILD-GAP index	1.08323	0.09057–12.9559	0.9497

BMI, body mass index; HRCT, high-resolution computed tomography; KL-6, Krebs von den Lungen-6; ILD, interstitial lung disease; GAP, gender-age-physiology.


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Overall survival, %
MST: 3.48 years
0
2
4
6
8
10
12
14
Survival time, years


ILD-GAP index: 0-1 vs 2-3, p=0.0637
ILD-GAP index: 0-1 vs ≥4, p=0.0001
ILD-GAP index: 2-3 vs ≥4, p=0.0236
ILD-GAP index: 0-1
ILD-GAP index: ≥4
ILD-GAP index: 2-3
Overall survival, %
Survival time, years
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2
4
6
8
10
12
14

Supplementary Table 1. Clinical characteristics of the IPF group (n=44) and the non-IPF group (n=58).

	All subjects (n=102)	IPF (n=44)	Non-IPF (n=58)
Age, years	72.3±0.6	71.8±1.0	72.55±0.8
Gender, female / male	7 / 95	2 / 42	5 / 53
Body mass index, kg/m^2	23.39±0.33	23.69±0.55	23.17±0.42
Brinkman index, pack-years	54.3±3.2	57.61±4.5	51.7±4.5
Histologic diagnoses of lung cancer, n(%)			
Small-cell carcinoma	1 (1.0%)	1 (2.3%)	0 (0.0%)
Squamous cell carcinoma	48 (47.1%)	20 (45.5%)	28 (48.3%)
Adenocarcinoma	43 (41.2%)	17 (38.6%)	26 (44.8%)
Large-cell carcinoma	3 (2.9%)	1 (2.3%)	2 (3.4%)
Other non-small-cell carcinoma	7 (6.9%)	5 (11.4%)	2 (3.4%)
Pathological stage of lung cancer, n(%)			
Stage Ⅰ A,B	61 (60.0%)	26 (59.1%)	35 (60.3%)
Stage Ⅱ A,B	20 (19.6%)	6 (13.6%)	14 (24.1%)
Stage Ⅲ A,B	17 (16.7%)	9 (20.5%)	8 (13.8%)
Stage Ⅳ	4 (3.9%)	3 (6.8%)	1 (1.7%)
Advanced stage(Ⅲ B, Ⅳ)	7 (6.9%)	6 (13.6%)	1 (1.7%) *
Primary site of lung cancer, n(%)			
Right upper lobe	28 (27.5%)	11 (25.0%)	17 (29.3%)
Right middle lobe	4 (3.9%)	1 (2.3%)	3 (5.2%)
Right lower lobe	33 (32.4%)	16 (36.4 %)	17 (29.3%)
Left upper lobe	24 (23.5%)	12 (27.3%)	12 (20.7%)
Left lower lobe	13 (12.7%)	4 (9.1%)	9 (15.5%)
Laboratory data			
Serum Alb, g/dL	4.01±0.04	3.95±0.05	4.06±0.05
Serum CRP, mg/dL	0.29±0.04	0.31±0.07	0.28±0.04
Serum LDH, IU/L	207.29±3.75	210.05±5.95	205.21±4.83
Serum CEA, ng/mL	7.81±1.12	8.34±1.57	7.41±1.58
Serum KL-6, U/mL	601.97±37.35	720.56±71.09	501.18±29.97 *
Chest HRCT findings			
Severity of emphysema (LAA score)	8.37±0.61	9.95±0.93	7.14±0.78 *

Severity of ILD, 1: Minimum / 2: Moderate / 3: Severe	1.40±0.06	1.64±0.11	1.21±0.06 **
Prognostic indices			
ILD-GAP index	2.17±0.14	3.50±0.15	1.17±0.10 **
Prognostic nutritional index (PNI)	49.61±0.55	49.26±0.84	49.88±0.74
Neutrophil-to-Lymphocyte ratio (NLR)	2.18±0.10	2.17±0.14	2.19±0.15
Platelet-to-lymphocyte ratio (PLR)	122.36±5.17	112.42±6.65	129.90±7.47
Modified Glasgow prognostic score (mGPS)	0.06±0.02	0.05±0.03	0.07±0.03
Prognostic index (PI)	0.07±0.03	0.05±0.03	0.09±0.04
Pulmonary function tests			
VC, L	3.29±0.08	3.23±0.11	3.34±0.11
%VC, %	99.01±1.57	99.37±2.35	98.74±2.13
FVC, L	3.21±0.08	3.18±0.12	3.24±0.11
%FVC, %	98.75±1.79	99.92±2.72	97.87±2.39
FEV_1, L	2.28±0.06	2.29±0.09	2.27±0.08
%FEV_1, %	89.47±1.91	93.00±2.82	86.79±2.55
FEV_1/FVC, %	71.38±0.90	72.43±1.24	70.59±1.27
%TLC, %	104.46±1.91	102.69±3.53	105.80±2.05
%$D_L$co, %	58.30±1.80	49.38±2.52	65.76±2.14 **
%$D_L$co/VA, %	80.05±2.63	70.51±4.21	87.29±3.06 **
Postoperative respiratory complications, n(%)			
Acute exacerbation of ILD	11 (10.8%)	3 (6.8%)	8 (13.8%)
Bacterial pneumonia	3 (2.9%)	1 (2.3%)	2 (3.4%)
Pyothorax	6 (5.9%)	1 (2.3%)	5 (8.6%)
Hypoxemia (respiratory failure)	17 (16.7%)	11 (25.0%)	6 (10.3%) *
Prolonged air leak	12 (11.8%)	5 (11.4%)	7 (12.1%)
Paroxysmal atrial fibrillation	9 (8.8%)	3 (6.8%)	6 (10.3%)
Others	2 (2.0%)	0 (0.0%)	2 (3.4%)
Surgery-related death	4 (3.9%)	1 (2.3%)	3 (5.2%)
Chemotherapy, n(%)			
Adjuvant chemotherapy	22 (21.6%)	10 (22.7%)	12 (20.7%)
Postoperative recurrence of lung cancer	47 (46.1%)	24 (54.5%)	23 (39.7%)
Chemotherapy after developing recurrence	23 (22.5%)	13 (29.5%)	10 (17.2%)
Chemotherapy-related acute exacerbation	6 (5.9%)	5 (11.4%)	1 (1.7%) *
Chemotherapy-related death	2 (2.0%)	2 (4.5%)	0 (0.0%)

Values are presented as means ± SE unless indicated otherwise. ** $p<0.01$, * $p<0.05$ versus the IPF group

HRCT, high-resolution computed tomography; LAA, low attenuation areas CRP, C-reactive protein; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; KL-6, Krebs von den Lungen-6; ILD, interstitial lung disease; GAP, Gender-Age-Physiology; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; D_{LCO}, diffusing capacity for carbon monoxide; D_{LCO}/VA, diffusing capacity of lung for carbon monoxide corrected for alveolar volume