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【 ORIGINAL ARTICLE 】

# The Evaluation of Interstitial Abnormalities in Group B of the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Classification of Chronic Obstructive Pulmonary Disease (COPD)

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**Abstract:**

**Objective** In 2011, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification categorized chronic obstructive pulmonary disease (COPD) patients into 4 groups. A report demonstrated that the mortality in Group B was higher than that in Group C. Ischemic heart disease and cancer were suggested to be the cause. The aim of the present study was to test the hypothesis that interstitial lung abnormalities (ILAs) are more prevalent in Group B than Group C and that they may be responsible for the higher mortality in Group B.

**Methods** Patients were selected based on their pulmonary function test results. The inclusion criterion was a forced expiratory volume in 1 second ($FEV_1$)/forced vital capacity (FVC) of <70% after the inhalation of a bronchodilator. Patients without a smoking history or computed tomography (CT) scan were excluded. The medical records of the patients were retrospectively reviewed, and the selected patients were categorized into Groups A to D. High-resolution CT scans were used to investigate the presence of ILAs and determine the low attenuation area (LAA).

**Results** Among the 349 COPD patients, ILAs were detected in 10.3% of the patients in Group A, 22.5% of the patients in Group B, 5.6% of the patients in Group C, and 23.1% of the patients in Group D. In Group B, the frequency of ILAs was significantly higher and the area affected by the ILAs was significantly greater in comparison to Group C. Among the patterns of interstitial abnormalities, the area of honeycombing in Group B was significantly greater than that in Group C. Furthermore, among the patients in Group B, the LAA in the ILA-positive patients was significantly greater than that in the ILA-negative patients.

**Conclusion** In Group B, the area occupied by ILAs-especially honeycombing-was greater than that in Group C. This contributed to the preserved %$FEV_1$ and possibly to the poorer prognosis of the patients in Group B.

**Key words:** COPD, CPFE, interstitial lung abnormalities

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## Introduction

In 2011, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), in collaboration with the National Heart, Lung, and Blood Institute, National Institutes of Health, and the World Health Organization, proposed a new system for the classification of chronic obstructive pulmonary disease (COPD), which was included in the national guidelines. COPD was classified into four categories, A-D, based on the level of risk as defined by the degree of airflow limitation and the frequency of acute exacerbations, and the severity of the symptoms, as defined by the dyspnea scale of the modified British medical research council

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dyspnea scale (mMRC) and a COPD assessment test (CAT) (1, 2).

In 2012, Lange et al. determined the prognosis of COPD patients in each category of the 2011 GOLD classification and also in Stage 1 to 4 of the 2007 GOLD classification (3). The authors concluded that the mortality of Group B patients with more symptoms and a better percent predicted forced expiratory volume in 1 second (%$FEV_1$) value was higher in comparison to Group C patients who showed fewer symptoms and worse %$FEV_1$ values because a Group B classification was more frequently associated with ischemic heart disease and malignancy (4, 5).

On the other hand, comorbid interstitial pneumonia, which was not evaluated closely in the above studies, might affect the %$FEV_1$ and a patient's symptoms (6-8). Interstitial abnormalities, if present in emphysematous lungs, could increase the %$FEV_1$ value, the dyspnea score, and the mortality of the COPD patients (9). We, therefore, evaluated the interstitial lung abnormalities (ILAs) in each category of COPD to test the hypothesis that the frequency and severity of ILAs might be higher in comparison to Group C.

## Materials and Methods

### *Patient selection and classification* (Fig. 1)

The study population included patients whose $FEV_1$/forced vital capacity (FVC) value was <70% after bronchodilator inhalation and who were treated from January 2011 to July 2014. Patients without a history of smoking, patients with bronchial asthma and patients for whom computed tomography (CT) scans had not been performed were excluded from the study (10). When more than one pulmonary function test was performed, the one performed closest (in time) to the CT scan was selected. Patient confidentiality was maintained.

GOLD 2011 classified COPD patients into 4 groups based on risk, as determined by the %$FEV_1$ value and/or the frequency of acute exacerbations, and the severity of symptoms as assessed by the mMRC and/or the CAT score. In this study, the risk was estimated based on the %$FEV_1$ alone and not by the incidence of acute exacerbations. The present study was retrospective in nature; thus, we could not check all of the events related to a patient's acute exacerbations in their medical records. Symptoms were determined by the mMRC alone because the CAT score was not available for most of the patients.

### *The assessment of emphysema and interstitial abnormalities*

Emphysematous changes were evaluated on a high resolution CT (HRCT) scan according to Goddard's method (11) with modifications; the percentage of the low attenuation area (LAA) was estimated by two independent pulmonologists and scored as 0 (0-10% LAA) to 9 (90-100% LAA) on 3 planes (at the level of aortic arch, the carina, and 2 cm above the right diaphragm) on each side of the lung. ILAs were estimated on HRCT images on 4 planes; these included the three above-mentioned planes and a plane under the top of the right diaphragm, which was incorporated for the estimation of the area of the ILA, similar to a previous report (12). The percent area of the ILA on the 4 planes on both sides was estimated by two independent pulmonologists and scored from 0 (0-10% ILA) to 9 (90-100% ILA). The severity of the ILAs was classified into 4 groups: very mild (average score of 4 planes ≤ 1), mild ( ≤ 2), moderate (≤ 4), and intense (>4) (Table).

The patterns of ILA, i.e. honeycombing, reticular abnormalities and ground glass opacities, and their percent area were also evaluated on the same planes (Fig. 1b). When the two pulmonologists did not agree, their scores were averaged. In addition, interstitial lung abnormalities were also assessed according to the serum levels of Krebs von den Lungen (KL)-6.

### *Statistical analysis*

The Prism (Ver.5) software program (GraphPad Software CA, USA) was used for the statistical analysis. The Mann-Whitney test, $\chi^2$ test, and an analysis of variance (ANOVA) were performed as appropriate.

### *Compliance*

Our study is performed in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of our hospital.

## Results

### *The patient profiles*

Among the 645 patients with airflow limitation ($FEV_1$/FVC<70%), 349 patients were finally evaluated in the present study (Fig. 1a). These patients were categorized into Group A (n=181), Group B, (n=75), Group C (n=49), and Group D (n=44). The mMRC scores and %$FEV_1$ values of each category are shown in Fig. 2. The mMRC dyspnea scale was highest in Group D and lowest in Group C. The %$FEV_1$ value decreased according to the patient's classification from Group A to D, while the LAA increased. Although the frequency of acute exacerbations was not evaluated for the COPD classification in this study, to the best of our knowledge, none of the patients in this study experienced more than one acute exacerbation. None of the COPD patients with ILAs received antifibrotic drugs or glucocorticosteroids for the treatment of interstitial pneumonia. Our review of the medical records in Group B revealed that 8 patients (10.7%) had acute coronary syndrome and 10 patients (13.3%) had lung carcinoma.

### *The evaluation of the ILAs in each of the COPD groups* (Fig. 3)

ILAs were detected in 10.3% of the patients in Group A,

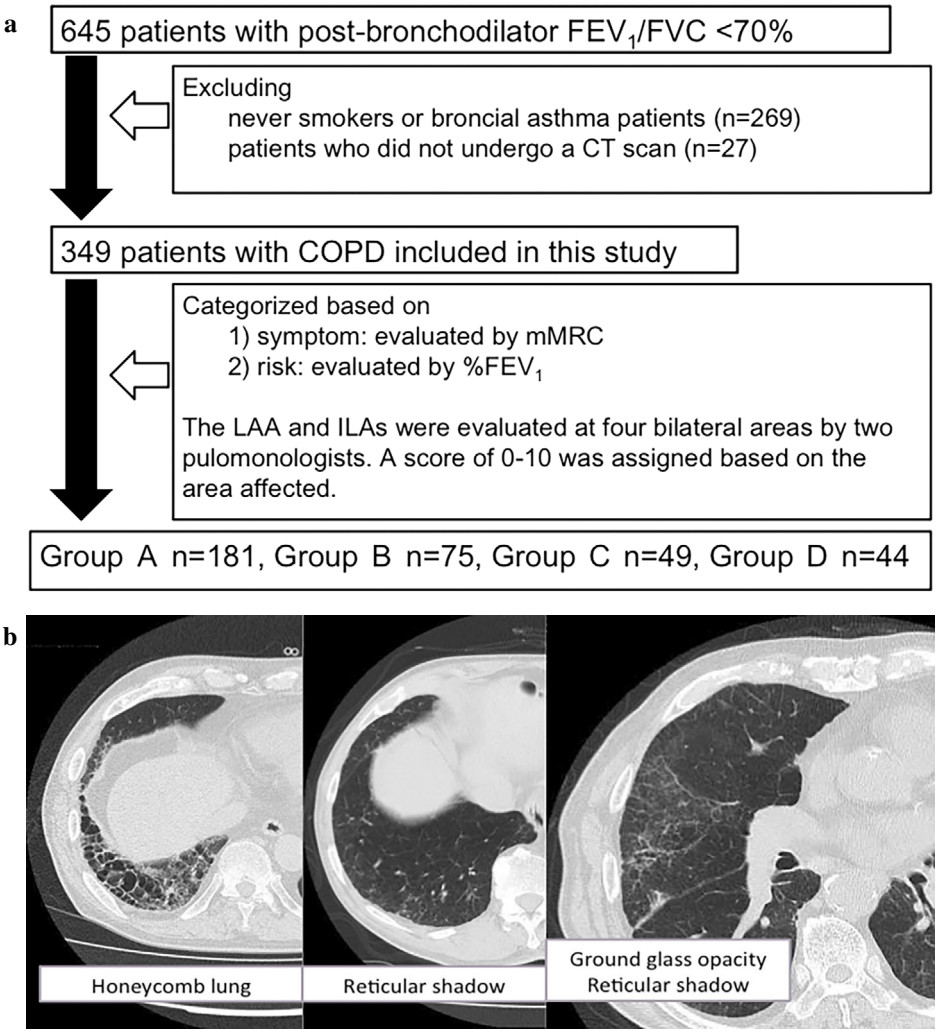


**Figure 1.** **The method of patient selection and categorization. (a) After selecting the patients with a post-bronchodilator $FEV_1/FVC$ value of <70%, patients without a history of smoking, patients with bronchial asthma and patients who did not undergo a CT scan were excluded. The areas of low attenuation and interstitial lung abnormalities were evaluated. A total of 349 patients were included and were subsequently categorized into 4 groups based on their degree of risk and the severity of their symptoms. CT: computed tomography, mMRC: the Modified British Medical Research Council dyspnea scale, $\%FEV_1$: percent predicted forced expiratory volume in 1s, FVC: forced vital capacity. (b) Representative pictures of the patterns of ILA (honeycombing, reticular abnormalities and ground glass opacities).**

**Table.** **The Profiles of the Patients in Each Group.**

| | A | B | C | D |
|---|---|---|---|---|
| Number of patients | 181 | 75 | 49 | 44 |
| Age (years old) | 68.9±10.8 | 75.2±9.9 | 69.0±10.9 | 74.0±7.4 |
| BMI | 22.5±3.4 | 23.1±3.7 | 21.9±3.7 | 20.3±3.0 |
| ILA degree of severity | | | | |
| Very mild | 9 | 8 | 3 | 10 |
| Mild | 10 | 5 | 0 | 0 |
| Moderate | 1 | 2 | 0 | 0 |
| Intence | 0 | 2 | 0 | 0 |

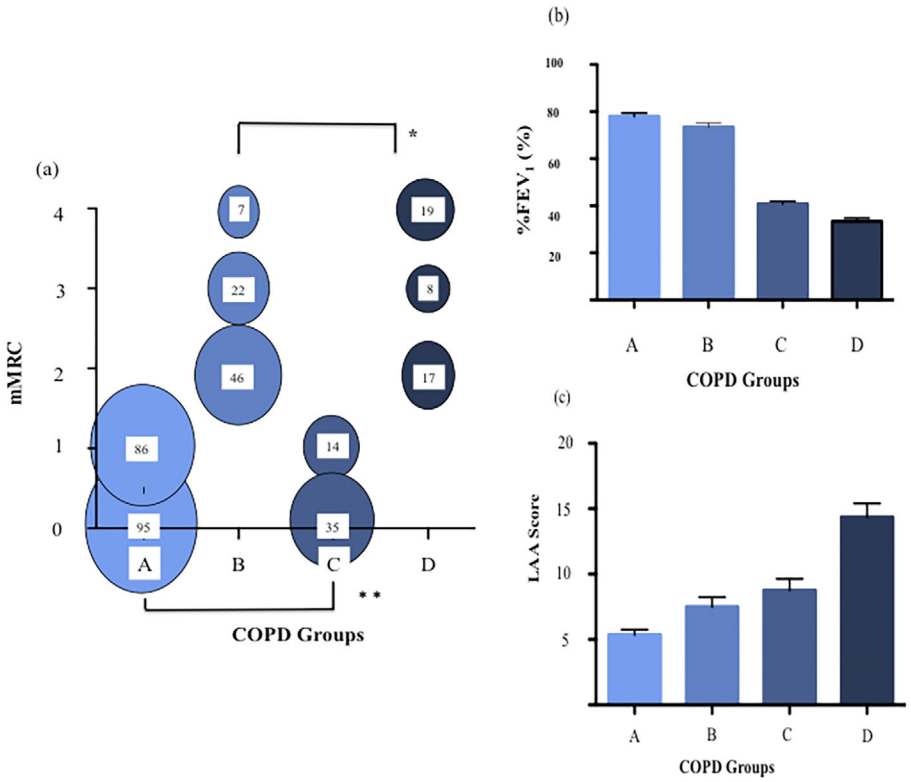


**Figure 2.** **The symptom severity, airflow limitation, and emphysematous changes among the four groups. (a) The severity of the symptoms was classified according to the mMRC score (0-4) four groups. (b) The %FEV$_1$ values of the four groups. (c) The magnitude of the low attenuation area (according to the LAA score) in the four groups. The Kruskal-Wallis test was used to test the statistical significance of the differences. *p<0.05, **p<0.01. mMRC: the Modified British Medical Research Council dyspnea scale, %FEV$_1$: percent predicted forced expiratory volume in 1 s, LAA: low attenuation area**

22.5% of the patients in Group B, 5.6% of the patients in Group C, and 23.1% of the patients in Group D. Among the COPD patients with ILAs, the serum level of KL-6 was 353.2±148.5 (U/mL) in the very mild group (n=21), 631.7±513.6 (U/mL) in the mild group (n=10), 408.8±208.4 (U/mL) in the moderate group (n=4), and 963.0±956.0 (U/mL) in the intense group (n=2). The severity of the ILAs was highest in Group B and lowest in Group C. The frequency and severity of the ILAs were significantly higher in Group B than in Group C. The patterns of ILA were classified as honeycombing, reticular abnormalities or ground glass opacities. The prevalence of each ILA pattern and the corresponding degree of severity are shown in Fig. 3. In the Group B patients, honeycombing and reticular abnormalities were detected more frequently and in a wider area in comparison to the Group C patients. In contrast, the rates at which ground glass opacities and their degree of severity were similar in all 4 groups.

### *The effects of ILAs among the patients in Group B* (Fig. 4)

In the Group B patients, patients with ILAs demonstrated greater %FEV$_1$ values and higher LAA scores than patients without ILAs; however, this result did not reach statistical without significance. A significant difference was observed in the LAA scores of patients with and without honeycombing, suggesting that the airflow limitation associated with large LAAs might be neutralized by honeycombing, but not by reticular abnormalities or ground glass opacities.

## Discussion

Combined pulmonary fibrosis and emphysema (CPFE) was first proposed as idiopathic pulmonary fibrosis with emphysematous change (13) and was then expanded to encompass the pulmonary diseases of smokers with airflow obstruction, emphysematous changes, and pulmonary fibrosis (9, 14). In this study, we first selected patients with COPD and then examined their HRCT scans to investigate their ILAs. Since even the slightest ILAs were included in this study, many of the COPD patients with ILAs only exhibited "very mild" to "mild", subclinical interstitial changes that were often not visible on chest X-rays. Although CPFE is not defined strictly, these patients were considered to have COPD with ILAs in the present study. The differences in the clinical course and the pathophysiology between CPFE and COPD with ILAs were beyond the scope of this study.

Among the 349 COPD patients, 47 patients (13.5%) ex-

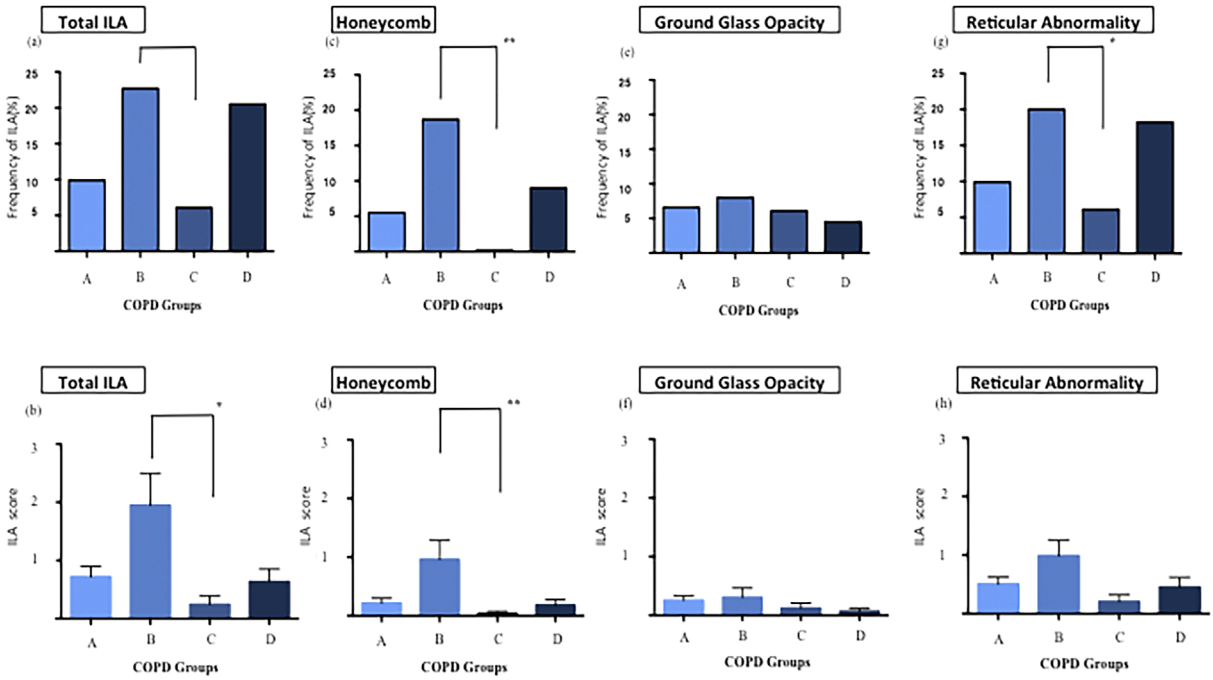


**Figure 3.** **The frequency, area and patterns of interstitial lung abnormalities in Groups A-D. (a) The prevalence of interstitial lung abnormalities was investigated in each group of COPD patients. (b) The area of interstitial lung abnormalities was evaluated as the ILA score in each group of COPD patients. (c) The prevalence of honeycombing in each group of COPD patients. (d) The area of honeycombing (evaluated as the ILA score) in each group of COPD patients. (e) The prevalence of ground glass opacities in each group of COPD patients. (f) The area of ground glass opacity (evaluated as the ILA score) in each group of COPD patients. (g) The prevalence of reticular shadow in each group of COPD patients. (h) The area of reticular shadow, evaluated as the ILA score in each group of COPD patients. Error bars indicated standard errors of the mean. *p<0.05, **p<0.01. mMRC: the Modified British Medical Research Council dyspnea scale, %FEV$_1$: percent predicted forced expiratory volume in 1 s, ILA: interstitial lung abnormalities, COPD: chronic obstructive pulmonary disease**

hibited ILA, similar to a previous report (3). As hypothesized, the prevalence of ILAs and the percent area affected were highest in Group B (Fig. 3). The patients in Group B were supposed to have lower risks according to the GOLD 2011 classification, in which patients were classified as being at greater risk based on either a low %FEV$_1$ value or the frequency of acute exacerbations. However, the %FEV$_1$ values of COPD patients seem to improve as their associated ILAs progress (6-8). As a result, COPD patients with ILAs tended to fall from other groups into the Group B; thus Group B consisted of patients with better %FEV$_1$ values but worse symptoms.

We further evaluated the patterns of ILA by investigating the prevalence and percent area of honeycombing, reticular abnormalities and ground glass opacities. The greatest differences were observed between Group B and Group C in both the frequency and the percent area of honeycombing (Fig. 3). The tension caused by the contraction of the lung interstitium in the presence of ILAs may compensate for the airflow limitation due to the collapse or narrowing of the airways in COPD patients. Since the contraction of the lung parenchyma was most frequently induced by honeycombing (8), honeycombing would most frequently induce the improvement of the %FEV$_1$. As a result, COPD patients with ILAs, especially those with honeycombing, tended to show better %FEV$_1$ values and were more frequently classified into Groups A and B.

The frequency and degree of ILAs in Group B were greater than those in Group A because COPD patients with ILAs tended to show higher mMRC scores. This is probably explained by lower diffusing capacity of the lung for carbon monoxide (DLco) and pulmonary hypertension; however, these factors were not measured in most of the patients in this study. The composite physiologic index, which requires the measurement of DLco, has been shown to be associated with the prognosis of COPD (15, 16).

There were two possible reasons for the increase in the LAA in the presence of ILAs among the Group B patients (Fig. 4). The contraction of the lung interstitium due to the ILA might lead to the stretching of the LAA, leading to an increase in the LAA. Another possible reason is that even with the increased LAA, contraction by the ILA might compensate for the airflow limitation, resulting in the preservation of the %FEV$_1$ value.

The poorer prognosis of the patients in Group B compared to those in Group C was explained by the presence of

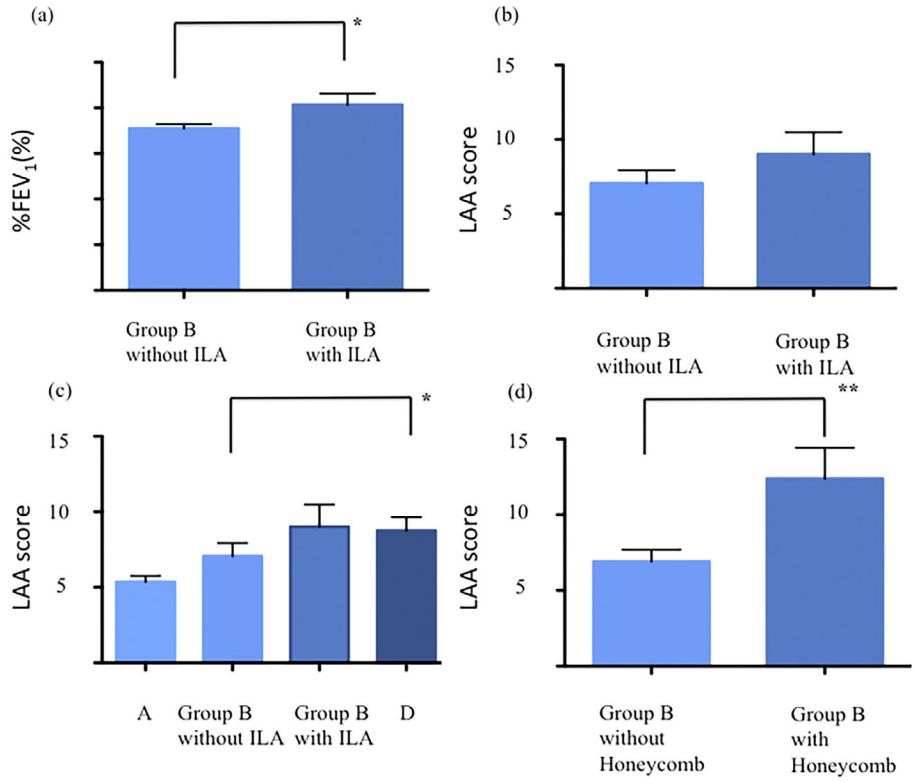


**Figure 4.** **The airflow limitation and emphysematous changes in Group B patients with interstitial lung abnormalities (ILAs) and those without ILAs. (a) The %FEV$_1$ values in Group B patients with and without ILA. (b) The magnitude of the low attenuation area was expressed as the LAA score was compared in Group B patients with and without ILA. (c) (b) was included with the data of other groups to indicate the differences. (d) The magnitude of the low attenuation area was expressed as the LAA score and was compared in Group B patients with and without honeycombing. The Mann-Whitney test was used for a, b, d. The Kruskal-Wallis test used for c. The error bars indicate the standard error of the mean. *p<0.10, **p<0.05. %FEV$_1$: percent predicted forced expiratory volume in 1 s, LAA: low attenuation area, ILAs: interstitial lung abnormalities**

comorbid ischemic heart disease, malignant tumors (3), as well as mental disorders (i.e. anxiety or depression) and osteoporosis) (17). We would add the presence of ILAs as another reason for the shorter life of the Group B patients. In a previous study, 35% of patients with idiopathic pulmonary fibrosis (IPF) exhibited emphysematous change, leading to a poorer prognosis, partly due to pulmonary hypertension (9, 14, 17, 18). There is also a report suggesting that the coexistence of fibrosis and emphysema was an independent factor that predicted a poor prognosis (14, 19). In addition, patients with IPF are expected to survive for 2-3 years after their diagnosis; thus, their prognosis is worse than COPD alone (20, 21). COPD patients with honeycombing, who are prone to be categorized into Group B because of their better %FEV$_1$ values and higher mMRC scores, might have contributed to the poorer prognosis of the Group B patients.

This study is associated with three limitations. First, since patients were selected from a list of patients who underwent pulmonary function tests, some of the most severe patients without recent pulmonary function tests were not included in this study. Second, some important data were missing from this cross-sectional retrospective study (e.g. DLco, CAT, the frequency of acute exacerbations). Although we checked the medical records for comments about acute exacerbations of COPD and found no patients with two or more exacerbations in one year, we were of the opinion that the data would have underestimated their frequency. Finally, we could not determine the prognosis of the patients with and without ILAs. A longitudinal or prospective study might be needed to clarify this point.

In conclusion, since the presence of ILAs helped to preserve the %FEV$_1$ value in COPD patients, ILAs, especially honeycombing, were most prevalent in Group B of the 2011 GOLD classification. We suspect that this would explain why the prognosis of Group B was poorer in comparison to Group C.

**The authors state that they have no Conflict of Interest (COI).**

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