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Clinical Research

Different DL_{CO} Parameters as Predictors of Postoperative Pulmonary Complications in Mild Chronic Obstructive Pulmonary Disease Patients with Lung Cancer

Mil Hoo Kim, M.D.[1], Joonseok Lee, M.D.[1], Joung Woo Son, M.D.[1], Beatrice Chia-Hui Shih, M.D.[1], Woohyun Jeong, M.D.[1], Jae Hyun Jeon, M.D.[1], Kwhanmien Kim, M.D., Ph.D.[1,2], Sanghoon Jheon, M.D., Ph.D.[1,2], Sukki Cho, M.D., Ph.D.[1,2]

[1]Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seongnam; [2]Department of Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine, Seoul, Korea

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Corresponding author
Sukki Cho
Tel 82-32-787-7132
Fax 82-32-787-4050
E-mail tubincho@snu.ac.kr
ORCID
https://orcid.org/0000-0002-9309-8865

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Background: Numerous studies have investigated methods of predicting postoperative pulmonary complications (PPCs) in lung cancer surgery, with chronic obstructive pulmonary disease (COPD) and low forced expiratory volume in 1 second (FEV_1) being recognized as risk factors. However, predicting complications in COPD patients with preserved FEV_1 poses challenges. This study considered various diffusing capacity of the lung for carbon monoxide (DL_{CO}) parameters as predictors of pulmonary complication risks in mild COPD patients undergoing lung resection.
Methods: From January 2011 to December 2019, 2,798 patients undergoing segmentectomy or lobectomy for non-small cell lung cancer (NSCLC) were evaluated. Focusing on 709 mild COPD patients, excluding no COPD and moderate/severe cases, 3 models incorporating DL_{CO}, predicted postoperative DL_{CO} ($ppoDL_{CO}$), and DL_{CO} divided by the alveolar volume (DL_{CO}/VA) were created for logistic regression. The Akaike information criterion and Bayes information criterion were analyzed to assess model fit, with lower values considered more consistent with actual data.
Results: Significantly higher proportions of men, current smokers, and patients who underwent an open approach were observed in the PPC group. In multivariable regression, male sex, an open approach, DL_{CO} <80%, $ppoDL_{CO}$ <60%, and DL_{CO}/VA <80% significantly influenced PPC occurrence. The model using DL_{CO}/VA had the best fit.
Conclusion: Different DL_{CO} parameters can predict PPCs in mild COPD patients after lung resection for NSCLC. The assessment of these factors using a multivariable logistic regression model suggested DL_{CO}/VA as the most valuable predictor.

Keywords: Pulmonary diffusing capacity, Postoperative complications, Chronic obstructive pulmonary disease, Lung resection, Non-small cell lung carcinoma

Introduction

Lung cancer remains leading cancer in terms of both incidence and mortality worldwide [1]. However, the increasing detection of early-stage lung cancer has led to improved survival rates, and surgical treatment has been established as the primary curative approach for these early-stage cases [2]. Patients with lung cancer often have comorbidities, including advanced age, chronic obstructive pulmonary disease (COPD), diffuse interstitial lung disease, or inflammatory lung disease [3]. These comorbidities can result in a high incidence of postoperative complications, which complicates surgical treatment even for early-stage lung cancer. Therefore, it is crucial to assess the potential for postoperative pulmonary complications (PPCs) following lung resection.

COPD is a common pulmonary condition, occurring in approximately 5% of lung cancer patients [4]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend diagnosing COPD based on the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC). According to the most recent GOLD guidelines, COPD is diagnosed in patients with FEV_1/FVC <0.7, and severity is classified based on predicted FEV_1% [5]. Numerous studies have shown that poor FEV_1 is associated with an increased frequency of PPCs. Consequently, risk stratification for PPCs is well-established in patients with moderate or severe COPD [6,7]. However, it remains unclear which mild COPD patients are at elevated risk for PPCs.

Numerous studies have shown the clinical efficacy of diffusing capacity of the lung for carbon monoxide (DL_{CO}) and the predicted postoperative DL_{CO} (ppoDL_{CO}) in predicting postoperative morbidity and mortality in patients with lung cancer [8,9]. There are 3 DL_{CO} parameters in pulmonary function testing (PFT). First, DL_{CO} represents the ability of the lung to diffuse carbon monoxide across its membranes. Second, ppoDL_{CO} represents the predicted DL_{CO} value after surgery. Third, DL_{CO}/VA represents the DL_{CO} divided by the alveolar volume (VA). Therefore, this study aimed to determine which DL_{CO} value could best predict PPCs after lung resection for lung cancer.

Methods

Study population

This study initially evaluated 2,798 patients who underwent segmentectomy or lobectomy at Seoul National University Bundang Hospital (SNUBH) due to non-small cell lung cancer (NSCLC) from January 2011 to December 2019. Institutional Review Board (IRB) of SNUBH approval was received (IRB approval no., B-2402-880-101). The requirement for informed consent was waived because of the retrospective study design. The choice of surgical approach, such as video-assisted thoracic surgery (VATS) or open thoracotomy, and the extent of lung resection were determined by the operating surgeon based on the patient's clinical stage and condition. Patients who underwent PFT with DL_{CO} within 1 month of surgery were selected for the study. All PFTs, including DL_{CO}, were conducted at our institution, and all instruments were calibrated before each test. The COPD diagnosis followed the GOLD guidelines, with FEV_1/FVC less than 0.7 diagnosed as having COPD. Severity was categorized based on FEV_1, with FEV_1 ≥80% classified as mild, 50%≤ FEV_1 <80% as moderate, 30%≤ FEV_1 <50% as severe COPD, and FEV_1 <30% as very severe COPD [5]. For this study, patients with FEV_1/FVC above 0.7 were excluded, resulting in the exclusion of 1,844 patients. Additionally, 246 patients with FEV_1 <80%, including those with moderate and severe COPD, were excluded. Finally, 709 patients were included (Fig. 1).

Various DL_{co} measurement definitions

DL_{CO} is a test that, in simple terms, measures the lung's ability to transfer air. This value is influenced by factors such as lung cell surface area, blood flow, and others, making it subject to variation based on factors like height and sex. To account for these factors, the concept of VA has been introduced, and DL_{CO} corrected for VA is measured as DL_{CO}/VA. Additionally, ppoDL_{CO} represents the predicted DL_{CO} value after surgery, and its formula is as follows.

$$ppoDL_{CO} = \frac{preop.\ DL_{CO}}{100} \times \frac{19 - no.of\ segments\ resected}{19}$$

Preoperative DL_{CO} measurement allows the prediction of ppoDL_{CO} by excluding the segment removed from the 19 segments and dividing by 19.

The VA is a measure of lung size that is most often determined during the measurement of DL_{CO} via the single-breath helium dilution technique. The patient breathes

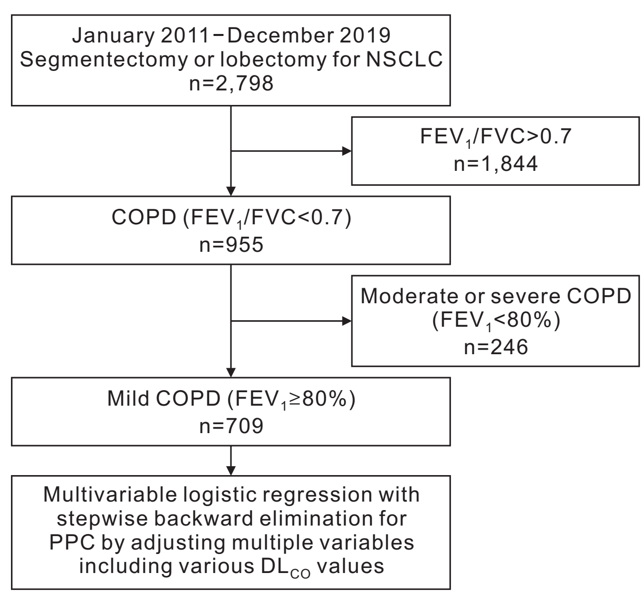

Fig. 1. Flow chart showing the patient selection method. A multivariable logistic regression model was constructed for a total of 709 patients. NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PPC, postoperative pulmonary complication; DL_{CO}, diffusing capacity of the lungs for carbon monoxide.

normally and then exhales to the residual volume. At the residual volume, a gas mixture (carbon monoxide and helium) is inhaled forcefully to the total lung capacity (TLC), which is held for 10 seconds, after which the patient exhales. The exhaled helium concentration is used to calculate a single-breath estimate of TLC and the initial alveolar concentration of carbon monoxide. The VA is the TLC minus the physiologic dead space. In healthy individuals, the VA equals the TLC. However, in subjects with ventilatory impairment, the VA often is much lower than the TLC [10].

Postoperative pulmonary complications

This study analyzed PPCs occurring within 30 days, including prolonged air leak lasting more than 5 days; pneumonia, which was defined as meeting 3 of 5 characteristics (fever, leukocytosis, new infiltration on chest X-ray, positive sputum culture, or treatment with antibiotics); atelectasis requiring bronchoscopic toileting, bronchopleural fistula, which was defined as a major bronchial air leak confirmed by bronchoscopy; and acute respiratory distress syndrome.

Statistical analysis

Data are presented as means with standard deviations for normally distributed variables, and categorical data are presented as counts and percentages. The independent t-test was used for numerical value comparisons. All p-values were derived from 2-sided tests, and values less than 0.05 were considered statistically significant. Multivariable logistic regression analysis was conducted, including variables such as age, sex, smoking (never versus ever), Eastern Cooperative Oncology Group (ECOG) scale (<2 versus ≥2), neoadjuvant treatment, tumor size on chest computed tomography, clinical N stage (N0 versus N+), approach (VATS versus open), extent of surgery, and 3 DL_{CO} parameters (DL_{CO} versus $ppoDL_{CO}$ versus DL_{CO}/VA). Stepwise backward elimination was employed for statistical analysis. The Akaike information criterion (AIC) and Bayes information criterion (BIC), which indicate how closely the model's distribution matches the actual data distribution, were analyzed to assess model fit. Lower values of AIC and BIC are considered more consistent with actual data [11]. All statistical analyses were performed using R software ver. 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among a total of 709 patients, PPCs developed in 106 patients (15%). Prolonged air leak, which was the most common PPC, occurred in 58 patients (55%), followed by pneumonia in 37 (35%), atelectasis in 14 (13%), empyema in 8 (7%), bronchopleural fistula in 4, and acute respiratory distress syndrome in 2 patients.

The preoperative and intraoperative characteristics of

Table 1. Preoperative and intraoperative characteristics between non-PPC and PPC groups

Characteristic	No PPC (N=603)	PPC (N=106)	p-value
Age (yr)	69.1±7.6	70.4±9.2	0.164
Sex (male)	457 (75.8)	95 (89.6)	0.002
Smoking (yes)	448 (74.3)	90 (84.9)	0.032
ECOG scale ≥2	91 (15.1)	15 (14.2)	0.918
Neoadjuvant treatment (yes)	25 (4.1)	9 (8.5)	0.092
DL_{CO} (predicted %)	103.6±19.3	100.8±24.2	0.250
DL_{CO} (predicted %: <80%)	55 (9.1)	20 (18.9)	0.005
$ppoDL_{CO}$ (predicted %)	82.9±16.6	80.3±19.9	0.198
$ppoDL_{CO}$ (predicted %: <60%)	39 (6.5)	17 (16.0)	0.002
DL_{CO}/VA (predicted %)	99.1±18.6	91.5±19.9	<0.001
DL_{CO}/VA (predicted %: <80%)	91 (15.1)	35 (33.0)	<0.001
Tumor size on chest CT (cm)	2.7±1.7	3.0±1.9	0.127
Clinical N positive (yes)	70 (11.6)	12 (11.3)	0.619
Approach (open)	49 (8.0)	20 (18.9)	<0.001
Extent of surgery (lobectomy)	559 (92.7)	97 (91.5)	0.818

Values are presented as mean±standard deviation or number (%).
PPCs, postoperative pulmonary complications; ECOG scale, Eastern Cooperative Oncology Group scale; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; $ppoDL_{CO}$, predicted postoperative diffusing capacity of the lungs for carbon monoxide; DL_{CO}/VA, diffusing capacity of the lung for carbon monoxide divided by alveolar volume; CT, computed tomography.

the non-PPC and PPC groups are presented in Table 1. There were no significant differences in age, ECOG performance status, neoadjuvant therapy, tumor size, clinical N stage, or extent of surgery between the 2 groups. However, the PPC group had a significantly higher proportion of men, current smokers, and patients who underwent an open surgical approach. The preoperative DL_{CO} values were similar between the non-PPC group (103.6±19.3) and the PPC group (100.8±24.2), with no significant difference (p=0.250). However, a significantly greater percentage of patients in the PPC group had DL_{CO} values below 80% (non-PPC versus PPC, 9.1% versus 18.9%; p=0.005). Although the mean $ppoDL_{CO}$ values did not differ significantly between the non-PPC group (82.9±16.6) and the PPC group (80.3±19.9, p=0.198), the PPC group had a significantly higher proportion of cases with $ppoDL_{CO}$ values below 60% (non-PPC versus PPC, 6.5% versus 16.0%; p=0.002). Additionally, the DL_{CO}/VA values were significantly lower in the PPC group (non-PPC versus PPC, 99.1±18.6 versus 91.5±19.9; p<0.001), and a significantly higher percentage of patients in the PPC group had DL_{CO}/VA values below 80% (non-PPC versus PPC, 15.1% versus 33.0%; p<0.001).

The multivariable analysis incorporated all variables used in the initial univariable analysis, with the inclusion of DL_{CO}, $ppoDL_{CO}$, and DL_{CO}/VA. The outcomes of the multivariable regression models, which designated a DL_{CO} below 80% as a predictor, identified significant determinants of PPCs: male sex (p=0.001), open surgical approach (p<0.001), and a DL_{CO} below 80% (odds ratio [OR], 2.12; 95% confidence interval [CI], 1.16–3.88; p=0.015) (Table 2). Similarly, when $ppoDL_{CO}$ below 60% was used as a predictor, the multivariable regression model demonstrated significant predictors of PPCs: male sex (p<0.001), open surgical approach (p<0.001), and $ppoDL_{CO}$ below 60% (OR, 2.83; 95% CI, 1.46–5.48; p=0.002) (Table 3). When DL_{CO}/VA below 80% was considered as a predictor, the model revealed significant associations with PPCs for the following variables: male sex (p=0.013), open surgical approach (p=0.001), and DL_{CO}/VA below 80% (OR, 2.14; 95% CI, 1.31–3.48; p=0.002) (Table 4). Finally, when analyzing the 3 DL_{CO} parameters, the multivariable regression model indicated that $ppoDL_{CO}$ and DL_{CO}/VA remained significant factors (Table 5).

To determine which DL_{CO} value was the best predictor, the AIC and BIC for each model were investigated. As shown in Table 6, DL_{CO}/VA had the lowest AIC and BIC, indicating that it was the model with the best fit. It was found that 1.8% of patients with DL_{CO} <80% but DL_{CO}/VA >80% had PPCs (n=2), whereas PPCs occurred in 16.0% of

Table 2. Multivariable logistic regression model for postoperative pulmonary complications, adjusting for multiple variables, including DL_{CO} (model 1)

	OR (95% CI)	p-value
Sex (male)	3.04 (1.56–5.92)	0.001
Neoadjuvant treatment (yes)	2.67 (0.94–7.60)	0.065
DL_{CO} (<80%)	2.12 (1.16–3.88)	0.015
Approach (open)	3.02 (1.61–5.67)	<0.001

DL_{CO}, diffusing capacity of the lungs for carbon monoxide; OR, odds ratio; CI, confidence interval.

Table 3. Multivariable logistic regression model for postoperative pulmonary complication, adjusting for multiple variables including $ppoDL_{CO}$ (model 2)

	OR (95% CI)	p-value
Sex (male)	3.14 (1.61–6.16)	<0.001
Neoadjuvant treatment (yes)	2.58 (0.90–7.40)	0.078
$ppoDL_{CO}$ (<60%)	2.83 (1.46–5.48)	0.002
Approach (open)	3.20 (1.70–6.01)	<0.001

$ppoDL_{CO}$, predicted postoperative diffusing capacity of the lungs for carbon monoxide; OR, odds ratio; CI, confidence interval.

Table 4. Multivariable logistic regression model for postoperative pulmonary complications, adjusting for multiple variables, including DL_{CO}/VA (model 3)

	OR (95% CI)	p-value
Sex (male)	2.35 (1.20–4.61)	0.013
Neoadjuvant treatment (yes)	2.68 (0.94–7.67)	0.066
DL_{CO}/VA (<80%)	2.14 (1.31–3.48)	0.002
Approach (open)	2.66 (1.46–4.85)	0.001

DL_{CO}/VA, diffusing capacity of the lung for carbon monoxide divided by alveolar volume; OR, odds ratio; CI, confidence interval.

Table 5. Multivariable logistic regression model for postoperative pulmonary complication by adjusting multiple variables, including DL_{CO}, $ppoDL_{CO}$, and DL_{CO}/VA (model 3)

	OR (95% CI)	p-value
Sex (male)	2.63 (1.32–5.24)	0.006
Neoadjuvant treatment (yes)	2.442 (0.84–7.00)	0.103
$ppoDL_{CO}$ (<60%)	2.12 (1.03–4.34)	0.041
DL_{CO}/VA (<80%)	1.76 (1.03–3.00)	0.038
Approach (open)	3.03 (1.60–5.72)	0.001

DL_{CO}, diffusing capacity of the lungs for carbon monoxide; $ppoDL_{CO}$, predicted postoperative diffusing capacity of the lungs for carbon monoxide; DL_{CO}/VA, diffusing capacity of the lung for carbon monoxide divided by alveolar volume; OR, odds ratio; CI, confidence interval.

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Table 6. The AIC and BIC for each model

	AIC	BIC
Model 1: variables with DL_{CO}	576.93	608.88
Model 2: variables with $ppoL_{CO}$	573.79	605.74
Model 3: variables with DL_{CO}/VA	573.55	600.94

AIC, Akaike information criterion; BIC, Bayesian information criterion; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; $ppoDL_{CO}$, predicted postoperative diffusing capacity of the lungs for carbon monoxide; DL_{CO}/VA, diffusing capacity of the lung for carbon monoxide divided by alveolar volume.

patients with DL_{CO} >80% but DL_{CO}/VA <80% (n=17).

Discussion

The reason for conducting this study was that if a patient has a DL_{CO} of less than 60%, there are concerns about PPCs and dyspnea after surgery; however, in reality, many of these patients did not develop PPCs or dyspnea, making this criterion difficult to apply. In patients without symptoms of dyspnea after surgery, the DL_{CO}/VA value was found to be greater than the DL_{CO} value. Conversely, in patients who had severe dyspnea or developed PPCs, the DL_{CO}/VA value was lower than the DL_{CO} value. Therefore, we investigated which of the 3 values—DL_{CO}, $ppoDL_{CO}$, and DL_{CO}/VA—was the best predictor of PPCs in COPD patients with preserved FEV_1. It was found that DL_{CO} <80%, $ppoDL_{CO}$ <60%, and DL_{CO}/VA <80% were significant risk factors for the development of PPCs. Among them, DL_{CO}/VA was the best predictor of PPCs based on the values of the AIC and BIC as indicators of model fit.

DL_{CO} measures the lung's ability to absorb oxygen and eliminate carbon monoxide, and it has shown clinical efficacy in predicting patients' symptoms or pulmonary complications after surgery [12,13]. The study by Ferguson et al. [14], analyzing 854 lung cancer surgery patients, found that in univariate analysis, hazard ratios (HRs) increased for patients with DL_{CO} <80% (70%–79%, 1.12; 60%–69%, 1.29; <60%, 1.35). In multivariable analysis, DL_{CO} emerged as an independent predictor of overall survival for all patients (HR, 1.04; 95% CI, 1.00–1.08; p=0.05). At our institution, the results of PFTs included FVC (measurement, % reference), FEV_1 (measurement, % reference), FEV_1/FVC (%), DL_{CO} (measurement, % reference), VA, and DL_{CO}/VA (measurement, % reference). Among them, the DL_{CO}/VA measures the DL_{CO} divided by the effective VA, which is the TLC minus the dead space. Because VA represents a more accurate assessment of functioning alveoli, theoretically, DL_{CO}/VA is the most effective predictor of remaining lung function after surgical resection. Cerfolio et al. [15] conducted a similar study that attempted to elucidate the clinical significance of DL_{CO}/VA. They found that patients with a normal DL_{CO} but a low DL_{CO}/VA had a slightly higher complication rate than patients who had a low DL_{CO} but a normal DL_{CO}/VA. In our study, 1.8% of patients with DL_{CO} <80% but DL_{CO}/VA >80% had PPCs, whereas PPCs occurred in 16.0% of patients with DL_{CO} >80% but DL_{CO}/VA <80%.

This study was designed to explore predictors of PPCs in COPD patients with preserved FEV_1 instead of moderate or severe COPD because patients and caregivers should be adequately informed and medical staff should be prepared for the risk of pulmonary complications in COPD patients with relatively good FEV_1. An exemplary study by Sekine et al. [16] compared the frequency of postoperative respiratory failure between COPD patients and those without COPD. Most pulmonary complications had a higher incidence in COPD patients than in non-COPD patients (p<0.01). In this study, the average FEV_1 for COPD patients was 48.79%±10.9%, and the majority had moderate or severe COPD (p<0.001). Thus, we did not think it was necessary to study the associations with DL_{CO} in patients with moderate to severe COPD because low FEV_1 alone could adequately predict the risk of PPCs in these patients and their caregivers when deciding to operate.

The similarity between the multivariable logistic regression model and the actual data was assessed using the AIC and the BIC. These are statistical metrics that evaluate the fit of a model to the data and its complexity. Generally, smaller values for both AIC and BIC are indicative of a better-fitting model. It is common practice to consider both metrics together when selecting a model [17]. In this study, AIC and BIC were used to evaluate the model's fit. Since there are no absolute criteria for these values and they are considered relative measures, the relative values of AIC and BIC were taken into account. DL_{CO}/VA, which had the smallest AIC and BIC values among the 3 DL_{CO}-related variables, was determined to be the best variable in predicting PPCs. In summary, the study identified several significant risk factors for PPCs, and the assessment of these factors using a multivariable logistic regression model indicated that DL_{CO}/VA was the most valuable predictor.

In our institution, we commonly use the 6-minute walk test in conjunction with PFT and DL_{CO} to predict PPCs. This test is not administered to all patients; rather, it is performed based on an individual's overall health status and physical fitness. It serves as a tool to evaluate a patient's capacity to avoid PPCs, such as pneumonia, following lung surgery. The relationship between the 6-minute walk test and PPCs has been the subject of investigation both at our institution and in external studies. For instance, Lee et al. [18] found that patients in the moderate-risk category who covered shorter distances during the test were at a higher risk for postoperative cardiopulmonary complications than those who walked longer distances. In the future, we aim to explore the correlation between the 6-minute walk distance and DL_{CO}/VA in order to develop more accurate predictors of PPCs.

Limitations

This study has several limitations that need to be taken into consideration. First, DL_{CO} is a test that is highly influenced by the patient's condition, and it may have limitations in accurately representing the patient's true lung function. In other words, variations in the patient's condition on the day of the test could affect DL_{CO} values, introducing variability in the prediction of outcomes. Second, the significant difference in the number of patients between the PPC group and non-PPC group and the single-center study design could potentially introduce bias. Third, there was a lack of consideration for operation time, presence of diffuse interstitial lung disease, pack-years of smoking, and other factors that could be expected to affect PPCs.

Conclusions

Different DL_{CO} parameters can predict PPCs in mild COPD patients after pulmonary resection for NSCLC. Although DL_{CO} and ppoDL_{CO} are well-known predictors of PPCs, DL_{CO}/VA was identified as an even stronger predictor and should be considered for predicting PPCs in mild COPD patients.

Article information

ORCID

Mil Hoo Kim: https://orcid.org/0000-0001-5093-1629
Joonseok Lee: https://orcid.org/0000-0002-9999-0782
Joung Woo Son: https://orcid.org/0000-0003-0704-6987
Beatrice Chia-Hui Shih: https://orcid.org/0000-0001-9211-0853
Woohyun Jeong: https://orcid.org/0000-0002-4980-3264
Jae Hyun Jeon: https://orcid.org/0000-0003-3582-3165
Kwhanmien Kim: https://orcid.org/0000-0002-6581-2750
Sanghoon Jheon: https://orcid.org/0000-0001-9366-5981
Sukki Cho: https://orcid.org/0000-0002-9309-8865

Author contributions

Conceptualization: MHK, SC, JL. Data curation: SJ, KK, SC, JHJ, WHJ, BCHS. Formal analysis: MHK, JL, JWS. Methodology: MHK, JL, JHJ. Visualization: MHK, JL, SC. Writing–original draft: MHK, SC. Writing–review & editing: all authors. Final approval of the manuscript: all authors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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