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Prediction formula for predicted diffusion capacity of lung for carbon monoxide in pulmonary surgery

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Abstract

[Objectives] Diffusion capacity of the lung for carbon monoxide (D_{LCO}) is a useful value for perioperative risk assessment of non-small cell lung cancer (NSCLC). The percentage of the predicted D_{LCO} (%D_{LCO}: D_{LCO}/predicted D_{LCO} ×100) is often evaluated by setting cutoff values as in the clinical field, but several formulae are available for calculating the predicted D_{LCO}, and the %D_{LCO} thus varies depending on the formula used to predict D_{LCO}. We examined differences in %D_{LCO} calculated using several commonly used prediction formulae.

[Methods] A total of 490 eligible patients who underwent completed video-assisted thoracoscopic surgery (c-VATS), especially radical pulmonary lobectomy, for NSCLC were analyzed retrospectively. Predicted D_{LCO} was calculated using the prediction formulae described by Burrows, Nishida, Cotes, and Kanagami, then the relationships with postoperative complications were evaluated.

[Results] The %D_{LCO} from Nishida's formula was two-thirds the value of that from Burrows' (p<0.05). On logistic regression analysis, predicted postoperative %D_{LCO} (ppo-D_{LCO}) based on the formulae of Burrows, Cotes and Kanagami were independent factors related to postoperative pulmonary complications after c-VATS lobectomy for NSCLC (odds ratios 2.46, 1.79 and 2.33, p=0.005, 0.043 and 0.009, respectively).

[Conclusions] The %D_{LCO} is a useful index for surgical risk assessment of c-VATS lobectomy for NSCLC, while the results differ markedly between individual prediction formulae. Specification of the formula used is necessary in cases considering risk evaluations.

Introduction

Although various advances have been made in the management of non-small cell lung cancer (NSCLC), complete anatomical resection remains the most effective treatment in patients with early-stage NSCLC. Surgical indications for resection of NSCLC are evaluated by: 1) oncological assessment based on the clinical stage considering the postoperative prognosis; and 2) physiological assessment of the tolerability and risks of pulmonary resection. Because radical surgery for NSCLC results in a loss of respiratory function according to resected lung volume, preoperative pulmonary functional evaluations offer useful indices for perioperative risk assessment, and the diffusion capacity of the lung for carbon monoxide (D_{LCO}) is regarded as only secondary to forced expiratory volume in 1 s (FEV_1) in importance [1, 2].

The percentage of the predicted D_{LCO} ($\%D_{LCO}$: measured D_{LCO}/predicted D_{LCO} ×100) is automatically calculated from the respiratory function test equipment. The predicted postoperative $\%D_{LCO}$ (ppo-$\%D_{LCO}$) was calculated based on the number of segments remaining after surgery [3]. This ppo-$\%D_{LCO}$ is often applied to one of the postoperative pulmonary function assessments, and evaluated by setting cutoff values as it is in the clinical field. Various cutoffs have been reported to date and reviewed by the American College of Clinical Pharmacy (ACCP) guideline, and cases in which both ppo-$\%FEV_1$ and ppo-$\%D_{LCO}$ exceed 60% of the cutoff are categorized as a low-risk group for complications. For cases with values less than this, further preoperative evaluations such as exercise testing is recommended. This has led to widespread recognition of 60% of ppo-$\%D_{LCO}$ as a standard cutoff value. This indicator has been effectively applied in clinical practice, since no constant indicators have been shown so far.

However, several formulae have been reported for calculating the predicted D_{LCO} [4-7], and the $\%D_{LCO}$ varies depending on the prediction formula applied, as $\%D_{LCO}$ is determined as the measured D_{LCO} divided by the predicted D_{LCO} ($\%D_{LCO}$ = measured D_{LCO}/predicted D_{LCO} ×100). However, this is not well known in actual clinical settings, and previous reports have often not described which formula has been applied to determine % D_{LCO}.

The aim of this study was to examine whether $\%D_{LCO}$ differs among the four commonly used formula described by Burrows, Nishida, Cotes, and Kanagami [4-7] using actual clinical data, and to evaluate associations between ppo-$\%D_{LCO}$ as determined using each formula and postoperative pulmonary complications (PPC).

Methods

Patients

Data for this retrospective cohort study were obtained from the medical records of all patients who underwent radical pulmonary resection for NSCLC between January 2013 and December 2018 in the Department of Thoracic Surgery at Iwate Medical University. This retrospective study was approved by the institutional review board at our institute (permit number: MH2018-540). The need to obtain informed consent was waived for this retrospective review of medical records. All patients underwent complete preoperative pulmonary evaluation. Any patients who smoked were instructed to refrain from smoking for at least 8 weeks before the surgery. Surgical indications for video-assisted thoracic surgery (VATS), particularly complete VATS lobectomy, comprise the concept of a thoracoscopically resectable lesion, covering 88.7% (500/564) of surgical patients with NSCLC in our institute. Patients who had received preoperative chemotherapy or radiation, who underwent sublobar resection, segmentectomy, bilobectomy, pneumonectomy, or posterolateral thoracotomy or who could not receive preoperative pulmonary evaluation due to any clinical reason (e.g., cases of tracheostomy or in which D_{LCO} difficult to measure due to low vital capacity (VC), etc.) were excluded. A final total of 490 patients met all inclusion criteria and no exclusion criteria.

Pulmonary function testing

Pulmonary function was tested at our institute using a spirometer (SpiroSift SP-770 COPD; Fukuda Denshi, Tokyo, Japan) according to American Thoracic Society standards [8]. VC and FEV_1 were measured in patients within 1 month before surgery. Measurements were documented in the form of the actual volume and the ratio of the actual volume to the standard volume predicted according to the age, sex, and height of the patient. The percentage of the predicted FEV_1 (%FEV_1) is defined as the FEV_1 of the patient divided by the average FEV_1 in the population for an individual of the same age, sex and body composition. Body surface area (BSA) was calculated using the method described by Du Bois and Du Bois [9].

D_{LCO} was measured using the single-breath method. Briefly, the patient was seated upright in a chair with the nose pinched closed using a clip. The patient was then asked to breathe normally and exhale to residual volume. At residual volume, a gas mixture (a combination of 0.3% carbon monoxide (CO) and 10% helium) was inhaled forcefully within 4 s to total lung capacity, held for 10 s, then exhaled within 4 s. An initial exhaled washout volume of 0.75 L was discarded as an estimate of mechanical and anatomical dead space, then the following 1.0 L was collected as an alveolar sample, and D_{LCO} was calculated from the total volume of the lung,

breath-hold time, and initial and final alveolar concentrations of CO. Alveolar volume (VA) was obtained by the helium dilution technique prior to D_{LCO} measurement. The larger value from two attempts within 10% of each other was recorded as the D_{LCO}. In this study, all values of D_{LCO} were corrected for the hemoglobin concentration of the patient using the method described by Cotes et al. [10], and the predicted D_{LCO} was calculated using each of the following formulae:

1) Burrows [4] Male: $15.5 \times BSA - 0.238 \times age + 6.8$

Female: $15.5 \times BSA - 0.117 \times age + 0.5$

2) Nishida [5] Male: $(20.6 - 0.086 \times age) \times height$

Female: $(15.9 - 0.038 \times age) \times height$

3) Cotes [6] Male: $(10.9 \times height - 0.067 \times age - 5.89) \times 2.986$

Female: $(7.1 \times height - 0.054 \times age - 0.89) \times 2.986$

4) Kanagami [7] Male and female: $(24.85 - 0.225 \times age) \times BSA$

The $\%D_{LCO}$ was calculated as the measured D_{LCO} divided by the predicted D_{LCO} which is the value resulting from each prediction formula ($\%D_{LCO}$ = measured-D_{LCO} / predicted-D_{LCO}). After that, predicted postoperative pulmonary functions such as ppo-D_{LCO} were calculated according to the formula described in a previous report [3]. The calculation was based on the number of segments that remained after surgery.

Surgical procedures

Pulmonary lobectomy was performed under general anesthesia with a double-lumen endotracheal tube for single-lung ventilation. The affected lung was deflated as soon as the pleural space was opened, and deflation was maintained throughout most of the operative period. The fraction of inspired oxygen (FiO_2) during surgery ranged from 0.3 to 1.0, based on intraoperative blood gas analysis. Complete VATS lobectomy was performed via 3 ports under monitor vision only. Complete and systematic hilar and mediastinal lymph node dissection was performed in all cases. After procedure completion, sealing test was performed before wound closure and confirmed during reinflation of the affected lung. A chest tube (Blake®, 19 Fr; Ethicon, Somerville, NJ) was placed from the 5th intercostal trocar to the apex.

Postoperative management

In general, patients were extubated at the end of the operation and transferred to the ward after a brief stay in the recovery area. Suction (-5 cmH_2O) was provided through the chest tube on the morning of

postoperative day 1 when without air leakage. If postoperative air leakage was present, a water seal was applied. Chest X-rays were obtained daily. Criteria for chest tube withdrawal were: absence of air leakage through the chest tube at the time of evaluation; pleural fluid drainage <200 mL/24 h; and postoperative chest X-ray showing no pneumothorax. The morning after chest tube withdrawal, a chest X-ray was obtained to rule out pneumothorax. Routine postoperative pain management was performed in all patients. Briefly, oral analgesia was started 6 h after surgery; this typically included loxoprofen at 60 mg, 3 times per day, sometimes with 25-mg diclofenac suppository, 1-2 times per day as needed. Patients were discharged when convenient if no complications occurred during this perioperative period. Our institutional standard protocol is to perform follow-up of all patients every 3-6 months after surgery for 5 years.

Postoperative complications

Postoperative complications within 30 days after surgery were defined as those complications of Clavien-Dindo classification grade II or higher [11]. PPC [12] included pneumonia, prolonged air leakage, interstitial pneumonitis, atelectasis, bronchopleural fistula, bronchial asthma, hypoxemia and acute respiratory distress syndrome. Cases showing multiple complications were categorized according to the complication that most affected the postoperative outcome. Prolonged air leakage was defined as air leakage lasting 7 days or more [13]. Late complications, such as delayed pneumothorax, were not included in this study.

Statistical analysis

JMP version 14.1.0 statistical software (SAS Institute, Cary, NC) was used for all statistical analyses. Groups were compared using Pearson's chi-square test or the Wilcoxon rank-sum test. Differences in the results of each formula were assessed using the Tukey-Kramer honest significant difference (HSD) test. Multivariate predictors were evaluated using logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. On logistic regression analysis, the conventional receiver operating characteristic (ROC) curve was used to determine the cut-off for each variable that yielded maximal sensitivity and specificity for PPC in this study population. Differences between groups were considered significant for values of $p < 0.05$. Continuous data are expressed as mean ± standard deviation, and categorical data are expressed as count and proportion.

Results

All 731 patients who underwent radical pulmonary resection for NSCLC during the study period were retrospectively reviewed (Fig 1), of whom 490 patients (410 patients from the non-PPC group, 80 patients from the PPC group) were enrolled for analysis in this study. The most common reasons for loss to measurement of D_{LCO} were insufficient VC (n=4) or presence of permanent tracheostomy after total laryngectomy (n=2). PPC occurred in 2 cases (20%) from the D_{LCO}-unmeasurable group, representing a significantly higher number than in the D_{LCO}-measurable group (80 cases, 16.3%).

Clinical characteristics of eligible patients in this study are summarized in Table 1. PPC were observed 80 cases (16.3%). Age, height, body weight, Brinkman index, prevalence rates for chronic obstructive pulmonary disease (COPD), prevalence rates for Interstitial lung disease (ILD) and operation time were significantly higher in the PPC group than in the non-PPC group. Furthermore, preoperative pulmonary function, especially %VC, FEV_1%, and D_{LCO}, were significantly worse in the PPC group. Table 2 provides details of PPC showing Clavien-Dindo classification grade II or higher. Among PPC, 39 cases involved pneumonia (48.8%) and 27 cases involved prolonged air leakage (33.8%).

Individual clinical data (such as age, sex, height, BSA, etc.) were applied to each D_{LCO} prediction formula, and differences in $\%D_{LCO}$ from each prediction formula were estimated (Fig 2). The $\%D_{LCO}$ was 117.6 ± 29.5% with Burrows' formula, 81.8 ± 19.2% with Nishida's, 90.8 ± 21.6% with Cotes', and 129.3 ± 35.2% with Kanagami's, Significant differences were observed between all combinations (each, $p<0.0001$). Notably, the value from Burrows' formula was 1.5-times that from Nishida's ($p<0.0001$).

The ROC curve was used to analyze cutoff values for ppo-$\%D_{LCO}$ to distinguish PPC from non-PPC. The threshold providing maximal sensitivity and specificity for ppo-$\%D_{LCO}$ was 70.4% for Burrows' formula, 57.8% for Nishida's, 64.3% for Cotes' and 75.5% for Kanagami's. Results of logistic regression analysis for predictors of PPC after surgery are shown in Table 3. The threshold was determined based on ROC analysis, as mentioned in the Methods section. Use of this cutoff value is not generalizable beyond this study cohort, because the threshold was determined based on ROC analysis of the study population. On logistic regression analysis, ppo-$\%D_{LCO}$ based on the formulae of Burrows, Cotes and Kanagami were independent factors related to PPC after radical pulmonary resection for NSCLC (ORs 2.46, 1.79 and 2.33, $p=0.005$, 0.043 and 0.009, respectively).

Discussion

The $\%D_{LCO}$ is one a well-known and useful index for assessment of surgical risk with pulmonary resection and surgical indications for NSCLC. The present study examined differences in $\%D_{LCO}$ calculated using several commonly used predictive formulae. The calculated values of $\%D_{LCO}$ differed markedly between predictive formulae. In particular, the $\%D_{CLO}$ from Nishida's formula was two-thirds of that from Burrows' formula ($p<0.05$). With logistic regression analysis, ppo-D_{LCO} based on the formulae of Burrows, Cotes and Kanagami were independent factors related to PPC after c-VATS lobectomy for NSCLC. This study indicated that $\%D_{LCO}$ offers a useful index for assessing surgical risk of c-VATS lobectomy for NSCLC, while the results differ substantially depending on the predictive formula applied. Specification of which predictive formula was used thus seems necessary in cases involving risk evaluation.

With recent advances in medical equipment, respiratory function test equipment has changed to a complex and difficult to understand mechanism. Since results of pulmonary function test are usually output by automatic calculations based on the set predictive formula, the influence on indications for surgery or postoperative risk in clinical settings is commonly evaluated without knowing which specific formula has been applied. In particular, several predictive formulae are available for predicted D_{LCO}, and risk assessments may be erroneous if judged solely from $\%D_{LCO}$ without considering differences in predictive formulae. The problem that many prediction formulas exist has long been pointed out [14], but it has not been improved at all, and moreover it is not always widely known. The D_{LCO} is also a variable index influenced by lung volume, nonuniform disturbance of ventilation and perfusion throughout the lungs, pulmonary blood flow disturbance, hemoglobin concentration, and so on. Many assumptions are implicit in the theoretical formula for D_{LCO}, and diffusion capacity in clinical pulmonary function and physical diffusion might well be essentially different. However, in practice, D_{LCO} is a clinically established test for the diffusion ability of lung, and its utility as a clinical pulmonary function test is considered sufficient. To calculate predicted D_{LCO}, information such as sex, age, and height are needed, as described in the Materials and Methods. Many predictive formulae subtract the age value multiplied by the coefficient from the BSA or height multiplied by the coefficient. Therefore, the larger the age coefficient, the smaller the predicted D_{LCO} tends to be, which would be the reason the formulae of Burrows and Kanagami result in smaller values. As a result, $\%D_{LCO}$ (measured D_{LCO}/predicted D_{LCO}) should be a larger value. In this study, the $\%D_{LCO}$ calculated based on Burrows' predictive formula was about 1.5-times that from Nishida's formula.

In general, Burrows' predictive formula is adopted as the initial setting for respiratory function testing

equipment, so many hospitals can be considered to use Burrows' prediction formula. It is also true that several hospitals use predictive formulae other than Burrows', as models that have long been used in those individual facilities. In most case reports and research reports, the $\%D_{LCO}$ values are provided without specifying the predictive formula applied. As clearly shown in this study, predicted-D_{LCO} obtained by each predictive formula differ markedly from each other, and in the absence of information on the predictive formula, the results of studies using $\%D_{LCO}$ cannot be directly compared between facilities. This seems to represent a serious problem in clinical settings where evaluations are likely to use $\%D_{LCO}$ rather than the measured D_{LCO} value. Conversely, the present study demonstrated that even if predictive formulae differ, an appropriately set cutoff allows ppo-$\%D_{LCO}$ to be used as an index for estimating risk of PPC. Therefore, there is no actual problem with $\%D_{LCO}$ risk assessment, but understanding which predictive formula is used is very important, especially in risk assessments among multiple facilities. In addition, $\%D_{LCO}$/VA is also a useful indicator [15], but again various predictive formulae have been descried [4, 5, 14, 16-19]. Although it is easy to understand notations in percentage, clinicians need to recognize that these are not absolute values.

The D_{LCO} is known to decrease with aging, smoking, history of COPD or interstitial pneumonia [20], and D_{LCO} may be lower in patients with NSCLC than in healthy individuals before surgery. When pulmonary resection was performed, FEV_1 decreased according to the resected lung volume, and D_{LCO} also decreased due to the reduced membrane area. Prediction of postoperative pulmonary function is thus extremely important, especially in patients with low pulmonary function. This is because standard surgery is useful for improving overall survival over the long term, but is associated with risks of postoperative complications or death in the short term among high-risk cases. Conversely, limited surgeries such as sublobar resection risk cancer recurrence, but allow preservation of residual lung function associated with a decrease in resected lung volume and thus reduce the risk of perioperative complications and mortality. To improve the outcomes of lung cancer treatment, decisions on surgical procedure based on such trade-offs should be carefully examined in each case, and perioperative risk assessment for PPC is extremely important. These assessments are aimed at improving treatment outcomes, but may offer further contributions, such as making informed consent meaningful and responding with appropriate treatment in clinical practice according to risk assessment, resulting in improved quality of life. Moreover, if these functions are achieved, more appropriate use of medical resources may also result. The purpose of this study is to evaluate the difference of the calculated value depending on the formula in the retrospective single institute study, but the critical points in the clinical setting must be to show the cutoff value of PPC onset using any predicted formula. Although we are currently conducting a prospective study, a

multicenter prospective study is necessary to prove this, and we would like to expand this in the future.

This study involved several limitations, including the retrospective nature of the study and the small number of patients from a single institute. In addition, some patients with early-stage lung cancer and patients with severely low pulmonary function were not included in the study population because they had undergone sublobar resection. For these reasons, the ppo-$\%D_{LCO}$ cutoff for predicting PPC can be set statistically, but the process might contain several biases. To reach stronger conclusions, a randomized study is essential. Nevertheless, the present findings should contribute to recognition of the significance of D_{LCO} measurement and to risk assessment for patients with NSCLC. A multicenter, prospective study is required to validate our results. Until then, it is a defensive measure to follow the cutoff at each institution and to confirm which formula is used when in risk assessments among multiple facilities.

In summary, the present findings suggest that $\%D_{LCO}$ represents a useful index for surgical risk assessment of c-VATS lobectomy for NSCLC, while the results differ markedly depending on the predictive formula applied. In the absence of any consideration of the predictive formula, risk evaluations and judgment of surgical indications may be flawed, since specification of which predictive formula was used seems necessary. This information should be included to help guide the selection of patients for pulmonary resection and to determine preoperative risk stratification.

Conclusions

The $\%D_{LCO}$ is a useful index for surgical risk assessment of c-VATS lobectomy for NSCLC, while the results differ markedly between individual prediction formulae. Specification of the formula used is necessary in cases considering risk evaluations.

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Conflict of interest

None of the authors have any conflicts of interest to declare.

References

1) Sawabata N, Nagayasu T, Kadota Y, Goto T, Horio H, Mori T, et al. Risk assessment of lung resection for lung cancer according to pulmonary function: republication of systematic review and proposals by guideline committee of the Japanese association for chest surgery 2014. *Gen Thorac Cardiovasc Surg*. 2015; 63:14-21.

2) Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013; 143(Suppl): e166S-e190S.

3) Zeiher BG, Gross TJ, Kern JA, Lanza LA, Peterson MW. Predicting postoperative pulmonary function in patients undergoing lung resection. *Chest*. 1995; 108:68-72.

4) Burrows B, Kasik JE, Niden AH, Barclay WR. Clinical usefulness of the single-breath pulmonary diffusing capacity test. *Am Rev Respir Dis*. 1961; 84:789-806.

5) Nishida S, Kambe M, Sewake N, Takano M, Kawane H. Pulmonary function in healthy subjects and its prediction. 5. Pulmonary diffusing capacity in adults. *Clinical Pathology*. 1976; 24:941-7.

6) Cotes J. Lung function. In: Assessment and application in medicine, 1st edition, Blackwell Scientific Publications. London, 1965.

7) Kanagami H, Katsura T, Shiroishi K, Baba K, Ebina T. Studies on the pulmonary diffusing capacity by the carbon monoxide breath holding technique. I. Normal subjects. *Acta Med Scand*. 1961; 169:583-94.

8) American Thoracic Society (1987) Standardization of spirometry--1987 update. Statement of the American Thoracic Society. *Am Rev Respir Dis*. 1987; 136:1285-98.

9) Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*. 1989; 5:303-11.

10) Cotes JE, Dabbs JM, Elwood PC, Hall AM, McDonald A, Saunders MJ. Iron-deficiency anaemia: its effect on transfer factor for the lung (diffusiong capacity) and ventilation and cardiac frequency during sub-maximal exercise. *Clin Sci*. 1972; 42:325-35.

11) Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004; 240:205-13.

12) Miskovic A, Lumb AB. Postoperative pulmonary complications. *Br J Anaesth*. 2017; 118:317-34.

13) Rivera C, Bernard A, Falcoz PE, Thomas P, Schmidt A, Bénard S, et al. Characterization and prediction of prolonged air leak after pulmonary resection: a nationwide study setting up the index of prolonged air leak. *Ann Thorac Surg*. 2011, 92:1062-8.

14) Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, Selikoff IJ. Single breath diffusing capacity in a representative sample of the population of Michigan, a large industrial state. Predicted values, lower limits of normal, and frequencies of abnormality by smoking history. *Am Rev Respir Dis.* 1983; 127:270-7.

15) Cerfolio RJ, Bryant AS. Different diffusing capacity of the lung for carbon monoxide as predictors of respiratory morbidity. *Ann Thorac Surg*. 2009; 88:405-10.

16) Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis*. 1981; 123:185-9.

17) Paoletti P, Viegi G, Pistelli G, Di Pede F, Fazzi P, Polato R, et al. Reference equations for the single-breath diffusing capacity. A cross-sectional analysis and effect of body size and age. *Am Rev Respir Dis*. 1985; 132:806-13.

18) Knudson RJ, Kaltenborn WT, Knudson DE, Burrows B. The single-breath carbon monoxide diffusing capacity. Reference equations derived from a healthy nonsmoking population and effects of hematocrit. *Am Rev Respir Dis*. 1987; 135:805-11.

19) Roca J, Rodriguez-Roisin R, Cobo E, Burgos F, Perez J, Clausen JL. Single-breath carbon monoxide diffusing capacity prediction equations from a Mediterranean population. *Am Rev Respir Dis*. 1990; 141:1026-32.

20) Cotes JE, Chinn DJ, Miller MR. Lung function: Physiology measurement and application in medicine, 6th edition. Blackwell Publishing, London, 2006.

Table 1. Clinical details of NSCLC patients who underwent pulmonary lobectomy. *p<0.05 vs. PPC group.

Category	Total patients	PPC (n = 80)	Non-PPC (n = 410)	*P*-value
Gender Male	295	72	223	< 0.001*
Female	195	8	187	
Age (years)	70.0 ± 8.8	73.0 ± 5.5	69.5 ± 9.2	0.003*
Height (cm)	158.9 ± 8.8	162.1 ± 7.3	158.3 ± 8.9	< 0.001*
Weight (kg)	59.1 ± 10.5	61.9 ± 11.5	58.6 ± 10.2	0.033*
Hb (g/dL)	13.4 ± 1.4	13.5 ± 1.6	13.4 ± 1.4	0.212
Brinkman index	520.4 ± 586.1	892.6 ± 627.2	447.8 ± 549.9	< 0.001*
History of COPD	75 (15.3)	29 (36.3)	46 (11.2)	< 0.001*
History of ILD	49 (10.0)	18 (22.5)	31 (7.56)	< 0.001*
Pulmonary function test				
VC (mL)	3217.2 ± 756.9	3370.8 ± 669.9	3187.2 ± 769.9	0.024*
%VC (%)	107.1 ± 15.3	103.0 ± 15.7	107.9 ± 15.1	0.018*
FEV1 (mL)	2326.5 ± 550.0	2262.0 ± 468.9	2339.0 ± 564.1	0.540
FEV1% (%)	73.8 ± 9.0	68.5 ± 9.2	74.9 ± 8.6	< 0.001*
D_{LCO} (mL/min/mmHg)	18.3 ± 4.7	16.3 ± 4.7	18.6 ± 4.5	< 0.001*
Operation				
Right-upper lobectomy	157 (32.0)	25	132	-
Right-middle lobectomy	35 (7.1)	5	30	-
Right-lower lobectomy	128 (26.1)	26	102	-
Left-upper lobectomy	94 (19.2)	18	76	-
Left-lower lobectomy	76 (15.5)	6	70	-
Operation time (min)	255.8 ± 67.0	279.0 ± 77.3	251.2 ± 63.9	0.003*
Blood loss (g)	43.2 ± 39.2	52.0 ± 45.5	41.4 ± 37.6	0.061
Tumor size (mm)	24.8 ± 14.0	26.4 ± 12.9	24.5 ± 14.2	0.139
Lymph node metastasis (presence)	114 (23.3)	24 (30.0)	90 (22.0)	0.147

Table 2. Details of complications in NSCLC patients after pulmonary lobectomy.

Category	Number of case	(percentage)
Pneumonia	39	(48.8)
Prolonged air leakage	27	(33.8)
Acute exacerbation of interstitial pneumonia	7	(8.8)
Bronchial asthma attack	4	(5.0)
Acute respiratory distress syndrome	2	(2.5)
Bronchopleural fistula	1	(1.3)
Total	80	(100)

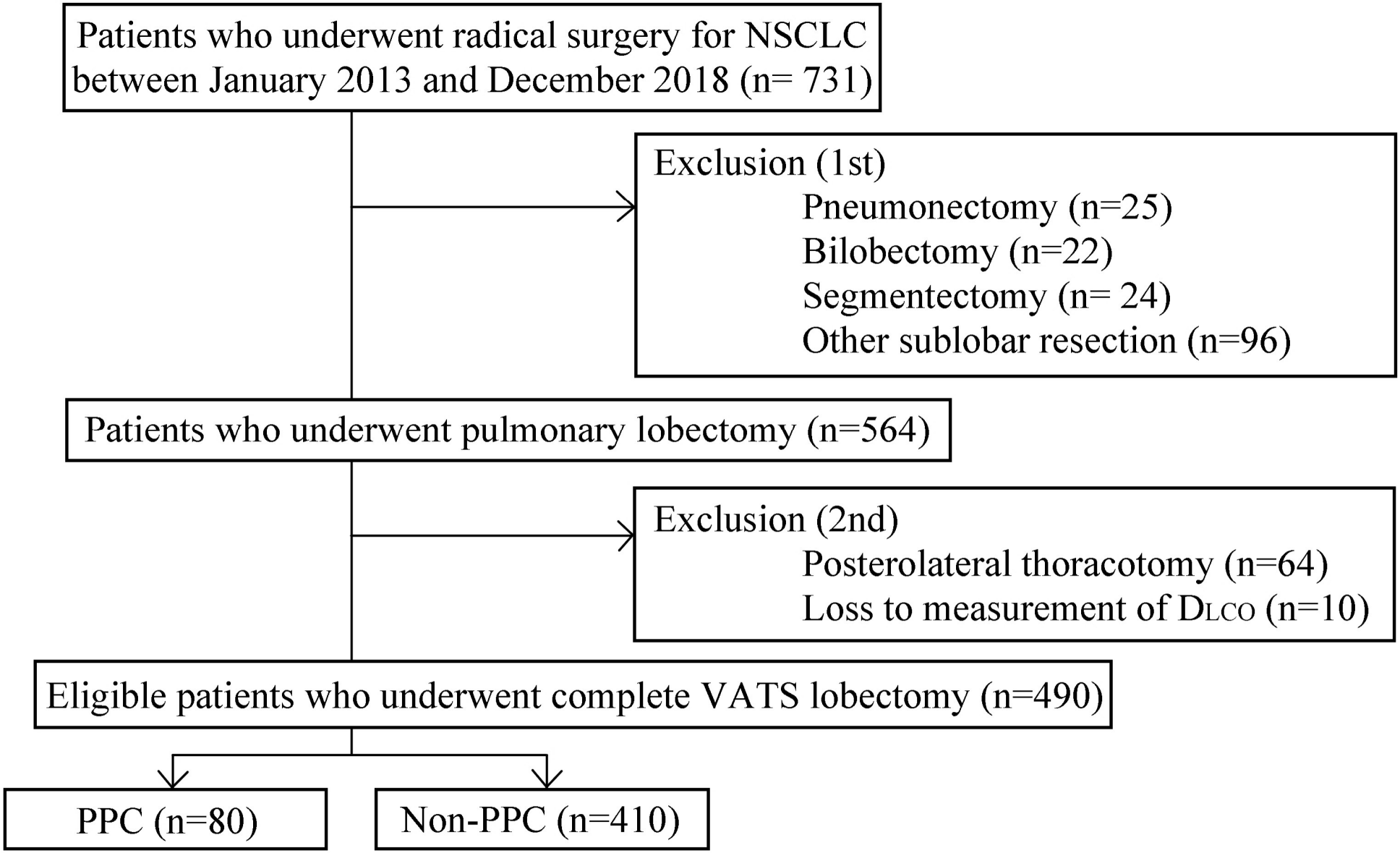
Table 3. Logistic regression analysis for predictors of the incidence of postoperative pulmonary complications in NSCLC patients after lobectomy. *p<0.05 vs. PPC group.

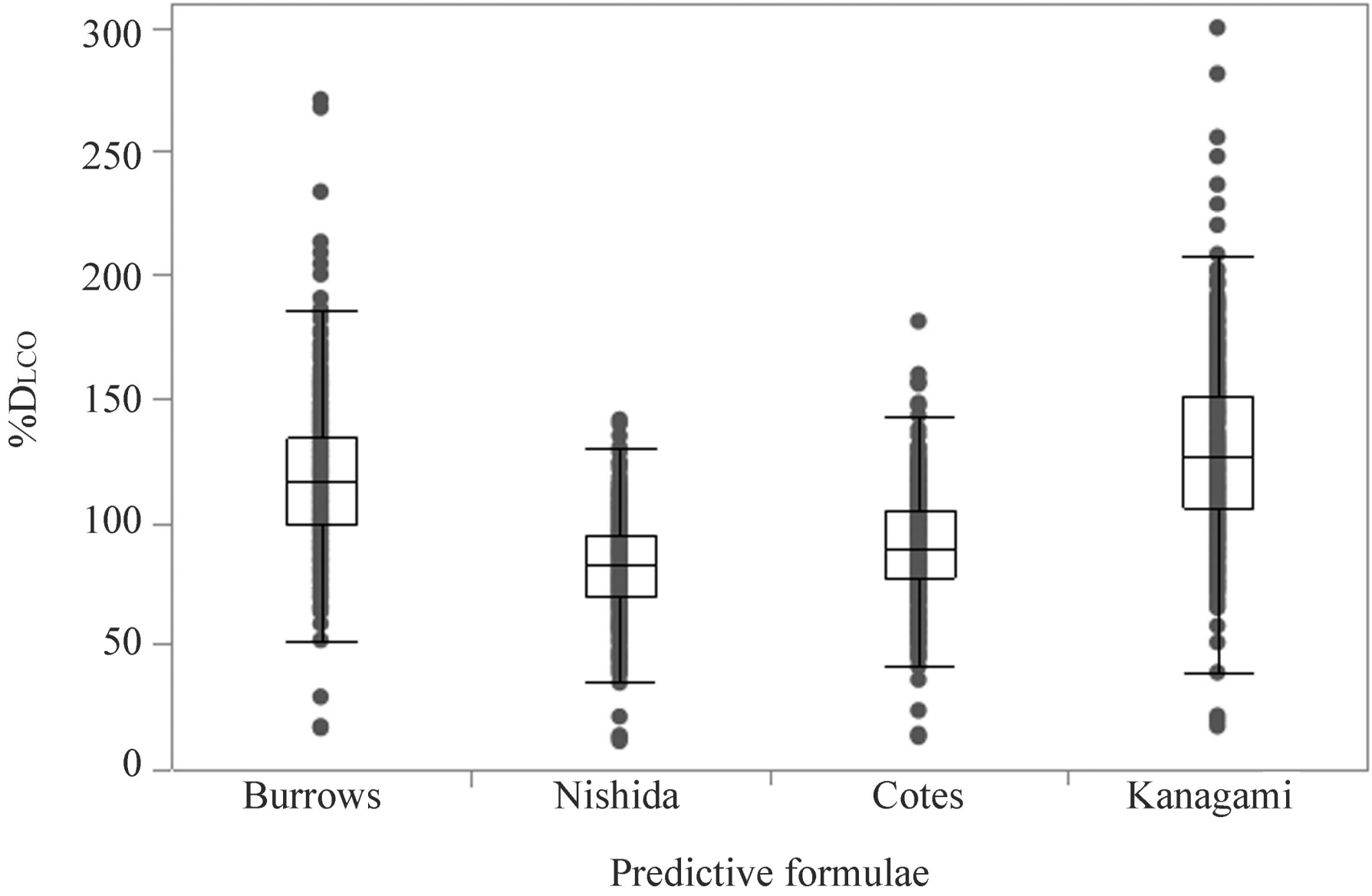
	Burrows		Nishida		Cotes		Kanagami	
Category	OR	*P*-value	OR	*P*-value	OR	*P*-value	OR	*P*-value
Age (> 65)	13.34	< .001*	11.34	0.001*	12.53	< .001*	15.76	< .001*
Gender (male)	5.81	< .001*	5.26	< .001*	5.20	< .001*	5.15	< .001*
Operation time (> 280 min)	1.49	0.171	1.48	0.176	1.47	0.183	1.47	0.185
Blood loss (> 65 g)	1.33	0.371	1.35	0.351	1.35	0.347	1.37	0.321
Tumur size (> 30 mm)	0.87	0.653	0.98	0.943	0.96	0.896	0.88	0.682
Lymph node metastasis (presence)	1.39	0.282	1.39	0.274	1.39	0.275	1.37	0.306
ppo-%FEV_1 (< 75%)	1.40	0.249	1.41	0.245	1.38	0.278	1.43	0.222
ppo-%D_{LCO} (< cutoff value)	2.46	0.005*	1.71	0.058	1.79	0.043*	2.33	0.009*
ppo-%D_{LCO} cutoff value:	70%		58%		64%		76%	

FIGURE LEGENDS

Fig 1: Diagram of patient flow in this study.

Fig 2: Comparison of % D_{LCO} calculated using each predictive formula. Significant differences were observed in all combinations (p<0.0001). The value from Burrows' formula was 1.5 times that from Nishida's (p<0.0001).


Patients who underwent radical surgery for NSCLC between January 2013 and December 2018 (n= 731)
Exclusion (1st)
Pneumonectomy (n=25)
Bilobectomy (n=22)
Segmentectomy (n= 24)
Other sublobar resection (n=96)
Patients who underwent pulmonary lobectomy (n=564)
Exclusion (2nd)
Posterolateral thoracotomy (n=64)
Loss to measurement of DLCO (n=10)
Eligible patients who underwent complete VATS lobectomy (n=490)
PPC (n=80)
Non-PPC (n=410)


300
250
200
150
100
50
0
%DLCO
Burrows
Nishida
Cotes
Kanagami
Predictive formulae