

A Prediction Model for Postoperative Pulmonary Complication in Pulmonary Function-Impaired Patients Following Lung Resection

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Purpose: Most patients with lung cancer have impaired pulmonary function. Single pulmonary function parameters have been suggested as good indices for predicting postoperative pulmonary complications (PPC). The purpose of this retrospective study was to construct a prediction model, including more than one pulmonary function parameter, for better prediction of PPC in patients with lung cancer and impaired pulmonary function.

Patients and Methods: Our database of patients who underwent lung resection for non-small cell lung cancer was reviewed and those with impaired pulmonary function were enrolled. Clinical data, including PPC, were recorded. Univariate and logistic regression analyses were applied to explore potential predictors and a prediction model constructed based on the results of logistic regression.

Results: Patients with impaired pulmonary function (n = 124) were enrolled. Most patients were male, current smokers, >60 years old, and had adenocarcinoma and mild ventilatory dysfunction or diffusion dysfunction. In univariate analysis, we identified six pulmonary function parameters that differed significantly between the PPC and non-PPC groups. Receiver operating characteristic curves were used to determine the best cutoff values. In logistic regression, only forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC%), peak expiratory flow (PEF%), and post predictive operation (ppo)-FEV1% remained significant. Based on these results, we constructed a prediction model for PPC including FEV1/FVC%, PEF%, and ppo-FEV1%, which had an good diagnostic performance of, with 76.7% sensitivity and 67.6% specificity.

Conclusion: Our prediction model, including the pulmonary function parameters, FEV1/FVC%, PEF%, and ppo-FEV1%, shows excellent performance for predicting PPC in patients with lung cancer and impaired pulmonary function following resection, and has potential for wide application in clinical practice.

Keywords: non-small-cell lung, retrospective studies, forced expiratory volume, logistic models, respiratory function tests

Introduction

Lung cancer is the leading cause of cancer-related deaths in China and elsewhere in the world.^{1,2} Surgery is the optimal treatment for early-stage lung cancer, particularly non-small cell lung cancer.⁴ The death rate in the 30 days after lung resection is approximately 4.4%, and the rate of postoperative pulmonary complications (PPC) is around 20%–40%.^{4,5}

Good pulmonary and heart function is necessary for lung cancer surgery. The American College of Chest Physicians (ACCP) also suggests that careful preoperative

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physiological assessment is useful for identifying patients for whom surgery is appropriate.⁶ Several tests are usually conducted before pulmonary resection, including pulmonary function test, cardiopulmonary exercise test, pulmonary ventilation and perfusion scan, and impulse oscillation, among others; overall, pulmonary function is key. However, patients with lung cancer may have impaired pulmonary function. First, most patients with lung cancer are elderly, have a history of smoking, and have chronic respiratory comorbidities.^{7,8,10} Second, the tumor may block the bronchus and the tumor cell embolus can also block blood vessels, leading to unbalanced ventilation and blood flow.¹⁰ Third, respiratory movement depends on thoracic integrity, which is destroyed by the surgery itself.¹¹ Fourth, nerve damage, pain caused by surgical incision, and the central inhibition generated by anesthesia impair respiratory movement and cause PPC.¹²

The rate of PPC is established as related to impaired pulmonary function.^{13–17} Alam et al reported significant differences in the percentages of predicted forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) in patients who developed atelectasis and respiratory tract infection following cardiac surgery.¹⁴ Shin et al found that diffusing capacity of the lung for carbon monoxide (DLco) value before neoadjuvant concurrent chemoradiotherapy was significantly associated with risk of PPC.¹⁵ Further, peak expiratory flow (PEF) and maximal ventilatory volume (MVV) may be valuable for predicting PPC following lung surgery.^{16,17}

Previous studies to identify factors influencing PPC were clearly limited by the inclusion of only single potentially-associated indices. Prediction models are currently widely-applied in clinical practice because they are concise and clear, and always involve more than one index for risk calculation.^{18,19} Here, we conducted a retrospective study to construct a prediction model based on pulmonary function parameters for better prediction of PPC in patients who underwent lung cancer resection with impaired pulmonary function.

Methods

Patient Selection

We reviewed our database, which includes basic clinical data and PPC data from patients who underwent lung resection in Shanghai Chest Hospital, Shanghai Jiao Tong University in 2012 and 2013. The inclusion criteria were: (1) age 18–80 years; (2) underwent lung resection in Shanghai Chest Hospital, Shanghai Jiao Tong University; (3) pulmonary function test performed within

1 week before surgery; (4) impaired pulmonary function, according to the guidelines edited by Chinese Thoracic Society: FEV1 < 80% or DLco < 80%.^{20,21} The exclusion criteria were: (1) incomplete clinical data for analysis; (2) final pathologic diagnosis not non-small cell lung cancer; (3) contraindications for pulmonary function examination, (4) severe cardiac insufficiency determined by electrocardiogram or echocardiography; (5) had previously undergone lung resection; (6) other severe cerebrovascular diseases, or other conditions, that exclude lung resection. Clinical data were extracted, including: age, sex, smoking history, main comorbidities, surgery type, pathologic diagnosis, and details of PPC.

Ethics Statement

The Ethics Committee of Shanghai Chest Hospital approved this study (KS1924). All the patients provided signed informed consent. All authors followed the Declaration of Helsinki.

Pulmonary Function Test

Pulmonary function tests were conducted using a Jaeger MasterScreen Body Plethysmograph. All patients underwent routine pulmonary function examination within one week before surgery. Before testing, the instrument was calibrated to meet the appropriate use standard. Pulmonary function curves were repeated at least three times (maximum five times) for each patient. Primary observation indices were: FVC%, MVV, FEV1%, FEV1/FVC%, and PEF. To control for the influence of age, height, and weight on lung function, detection indices are expressed as the percentage of the measured value relative to that of the predicted value.²² Normal reference values were those for the Shanghai area.²³ Post predictive operation (ppo) FEV1% and carbon monoxide diffusing capacity (DLCO%) were also calculated, according to the formula developed by Juhl and Frost.²⁴

According to the pulmonary function guidelines formulated by the Chinese Medical Association, patients were classified as follows: normal function, ventilation dysfunction (including restrictive ventilation dysfunction, obstructive ventilation dysfunction, mixed ventilation dysfunction), or diffuse dysfunction.^{20–22,25}

Postoperative Pulmonary Complications

PPC were defined as occurring within 1 month after lung resection, as follows: (1) Pneumonia characterized by new lung infiltration on imaging examination, and any of the

following: A. fever (body temperature $\geq 38^{\circ}\text{C}$) lasting for more than 5 days, B. white blood cell count $> 10.5 \times 10^9/\text{L}$, C. antibiotic upgrade treatment or antibiotic application for > 7 days; (2) Atelectasis; (3) Long term mechanical ventilation, due to postoperative respiratory failure (mechanical ventilation time > 48 h); (4) Secondary tracheal intubation; (5) Long-term (> 7 days) drainage because of air leakage or persistent pleural effusion; (6) Bronchopleural fistula; (7) Pulmonary embolism; (8) Other pulmonary complications.^{26,27}

Statistics

SPSS 20.0 software (IBM co. ltd) was used to perform statistical analyses. Measurement data were expressed as mean \pm SD. Comparisons between groups were conducted by one-way ANOVA and *t*-test. Categorical data were analyzed by Pearson χ^2 test and Fisher exact probability test. Receiver operating characteristic (ROC) curves were applied to assess the diagnostic value of each parameter, and the Youden index was used to determine the best cutoff value. Correlation between postoperative complications and pulmonary function indices was analyzed by logistic regression. Values of $p < 0.05$ were considered significant. Prediction model construction followed previous publications.^{28,29}

Results

Patient Characteristics

A total of 124 patients met the inclusion criteria and were enrolled in this study. Among all patients, most were male (77%), > 60 years old (61%), current smokers (47%), and suffered adenocarcinoma (53%). Of all patients, 91 had ventilatory dysfunction and 84 patients had diffusion dysfunction or both. Patient characteristics are presented in Table 1. In total, 34 patients with 42 PPC were included in our study, representing a PPC incidence of 27%. The most frequent PPC were long-term drainage tube and pneumonia. Six patients had more than one PPC. PPC details are provided in Table 2.

Univariate Analysis of Patient Characteristics Associated with Postoperative Pulmonary Complications

Univariate analysis of the relationships between patient characteristics and PPC demonstrated that sex, FEV1%, FEV1/FVC%, PEF%, MVV%, and ppo-FEV1% differed significantly between the PPC and non-PPC groups. Analysis by sex showed that males were more likely to

Table 1 Patient Characteristics

Factor	Variable	No. (%)
Total patients		124
Sex	Male	95 (76.61%)
	Female	29 (23.39%)
Age (years)	> 60	75 (60.48%)
	≤ 60	49 (39.52%)
Smoking history	Never	52 (41.93%)
	Current	58 (46.77%)
	Former	14 (11.30%)
Surgery type	WR/SR/ST	13 (10.48%)
	LB /SR+WVR/WVR+WVR	102 (82.26%)
	LB + WR/LB + SR /LB+ ST/PN	9 (7.26%)
Pathological diagnosis	Adenocarcinoma	66 (53.23%)
	Squamous cell carcinoma	48 (38.71%)
	Large cell lung cancer	5 (4.03%)
	Other type	5 (4.03%)
Ventilatory dysfunction Type	Obstructive	35 (28.23%)
	Restrictive	40 (32.26%)
	Mixed	16 (12.90%)
Ventilatory dysfunction Level	Mild	54 (43.55%)
	Moderate	19 (15.32%)
	Moderate-severe	13 (10.48%)
	Severe	5 (4.03%)
Diffusion dysfunction level	Mild	68 (54.84%)
	Moderate	14 (11.29%)
	Severe	2 (1.61%)

Abbreviations: WR, wedge resection; SR, sleeve resection; ST, segmentectomy; LB, lobectomy; PN, pneumonectomy.

have PPC than females. Further, pulmonary function was worse in the PPC than the non-PPC group (Table 3). Next, we constructed ROC curves to determine the optimal cutoff values and found that area under the curve (AUC) values for FEV1/FVC%, FEV1%, PEF%, MVV%, and ppo-FEV1% were all > 0.5 , with $p < 0.05$ (Figure 1). The Youden index was used to determine optimal cutoff values. Detailed cutoff, sensitivity, specificity, and diagnostic yield values for each parameter are presented in Supplementary Table 1.

Table 2 Postoperative Pulmonary Complications

PPC	No. (%)
Pneumonia	13 (30.95%)
Atelectasis	2 (4.76%)
Mechanical ventilation > 48 h	2 (4.76%)
Re-intubation	1 (2.38%)
Long-term drainage tube	23 (54.77%)
Pneumorrhagia	1 (2.38%)
Total events	42 (100%)
1 event	28 (82.35%)
> 1 event	6 (17.65%)
Total patients	34 (100%)

Abbreviation: PPC, postoperative pulmonary complications.

Logistic Regression Model of Factors Associated with Postoperative Pulmonary Complications

Subsequently, we constructed a logistic regression model including the five pulmonary function parameters and sex. Only FEV1/FVC%, PEF%, and ppo-FEV1 remained significant and were included in the model (Table 4).

Based on those findings, we constructed a points system including the three parameters, FEV1/FVC%, PEF, and ppo-FEV1%. Each parameter had two options, low and high, based on ROC curve analysis (Supplementary Table 1), and each option of pulmonary parameter was corrected by a defined point. Score sheets for prediction of PPC using the FEV1/FVC%, PEF, and ppo-FEV1% categorical variables were developed based on the coefficients calculated using the logistic regression model.²⁹ Hence, we established a prediction model for risk of PPC after lung resection in patients with impaired pulmonary function using the three clinically significant risk factors identified by multivariate analysis. The finally prediction model is as follows:

$$PPCrate = \frac{1}{1 + \exp(0.3 \times totalpoints - 1.108)} \quad (1)$$

(Table 5) Using this system, we could calculate a patient's score and use it to determine their corresponding PPC risk. Further, we drew a heat map of the three parameters, which facilitated easy determination of patient PPC risk levels according to color (Figure 2).

Table 3 Univariate Analysis of Differences Between the PPC and Non-PPC Groups

Factor	Variable	PPC	Non-PPC	P-value
Sex	Male	31	64	0.018
	Female	3	26	
Age (years)	≤ 60	12	37	0.681
	> 60	22	53	
Smoking history	Never	13	39	0.875
	Current	17	41	
	Former	4	10	
Surgery type	WR/SR/ST	3	10	0.465
	LB/SR + WR/WR + WR	30	72	
	LB + WR/LB + SR/LB + ST/PN	1	8	
FEV1%		68.11	77.64	< 0.001
FVC%		78.94	81.96	0.236
FEV1/FVC%		66.42	74.31	< 0.001
DLCO%		71.43	75.60	0.160
PEF%		67.032	78.289	0.001
MVV%		91.03	99.95	0.021
ppo-FEV1%		51.58	60.58	< 0.001
ppo-DLCO%		54.06	58.83	0.073
Number of segments removed		4.62	4.21	0.237

Abbreviations: PPC, post pulmonary complications; WR, wedge resection; SR, sleeve resection; ST, segmentectomy; LB, lobectomy; PN, pneumonectomy; FEV1, Forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, carbon monoxide diffusing capacity; PEF, peak expiratory flow; MVV, maximal ventilatory volume; ppo, post-pulmonary operation.

Table 4 Logistic Regression Analysis

Risk Factor	P value	OR	95% CI
FEV1/FVC%	0.018	0.319	0.124, 0.819
PEF	0.032	0.293	0.096, 0.897
ppo-FEV1	0.022	0.213	0.057, 0.802

Abbreviations: FEV1, Forced Expiratory Volume in the first second; FVC, forced vital capacity; PEF, peak expiratory flow; ppo, post-pulmonary operation; OR, odds ratio; CI, confidence interval.

The predictive performance of our model was assessed by ROC analysis, which demonstrated that the AUC value of the model was 0.793 (95% confidence interval, 0.701–0.885; $P < 0.001$); hence the model had good predictive performance and sensitivity and specificity values of 76.7% and 67.6%, respectively (Figure 3).

Discussion

Lung cancer causes the most cancer-related deaths in China and worldwide,^{1,2} and approximately 80% of cases are non-small cell lung cancer (NSCLC).³⁰ Radical operation is a valuable strategy for multidisciplinary teams to treat patients with early-stage NSCLC.⁴ Patients with lung cancer are usually elderly, have a history of smoking, and have cardiovascular or respiratory comorbidities, and those factors increase the risk of PPC incidence.^{10,31} Although surgery and nursing techniques have advanced over the last decade, PPC still occur in 20–30% patients.³² As mentioned above, pulmonary function also influences the occurrence of PPC, and

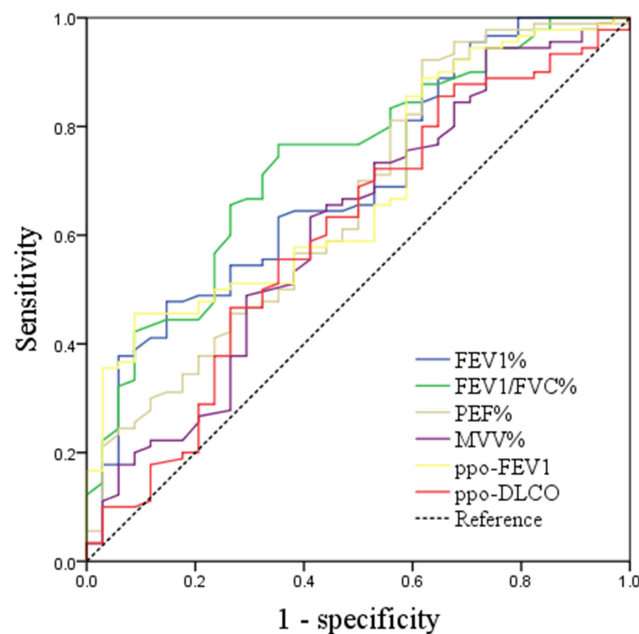


Figure 1 ROC curves of pulmonary function parameters.

Table 5 Postoperative Pulmonary Complications Score System

Item	Classification	Cutoff (%)	Points
FEV1/FVC%	High	> 68.25	4
	Low	< 68.25	0
PEF%	High	> 56.8	4
	Low	< 56.8	0
ppo-FEV1%	High	> 61.65	5
	Low	< 61.65	0

Abbreviations: FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; PEF, peak expiratory flow; ppo, post-pulmonary operation.

most patients with NSCLC have impaired pulmonary function. In this study, we focused on the predictors of impaired pulmonary function in patients with NSCLC.

In our cohort of enrolled patients with impaired pulmonary function, the incidence of PPC was approximately 27%, which is higher than that in previous reports. Overall, pneumonia and long-term air leakage were the most common PPC. In univariate analysis, sex, FEV1%, FEV1/FVC%, PEF%, MVV%, and ppo-FEV1% were identified as predictors of PPC. In clinical practice, we classify abnormal pulmonary function according to indications including FEV1%, FVC%, FEV1/FVC%, and DLCO %, among others. Several studies have demonstrated that the incidence of PPC increases with severe impaired pulmonary function.^{13–17,33,34} FEV1/FVC% reflects airway obstruction and airway resistance, hence significant decreases in this parameter indicate that patients have pulmonary ventilation dysfunction and the possibility of pulmonary complications after lung resection is increased. Fernandes et al reported that $FEV1/FVC\% < 60\%$ is a predictor of postoperative mortality and PPC.³⁵ Further, FEV1% can be a predictor of PPC. Kroenke et al found that patients with poor FEV1% experience higher rates of

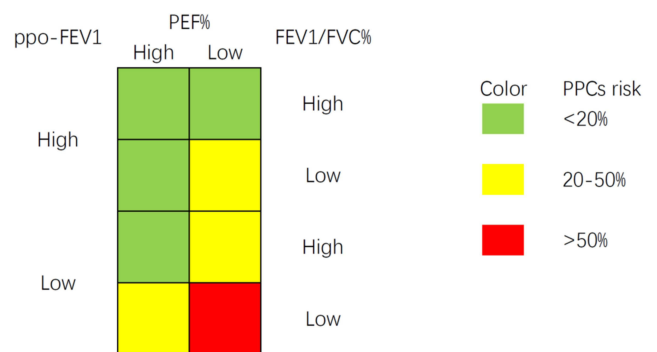


Figure 2 Heat map of association of different pulmonary functions and postoperative pulmonary complications.

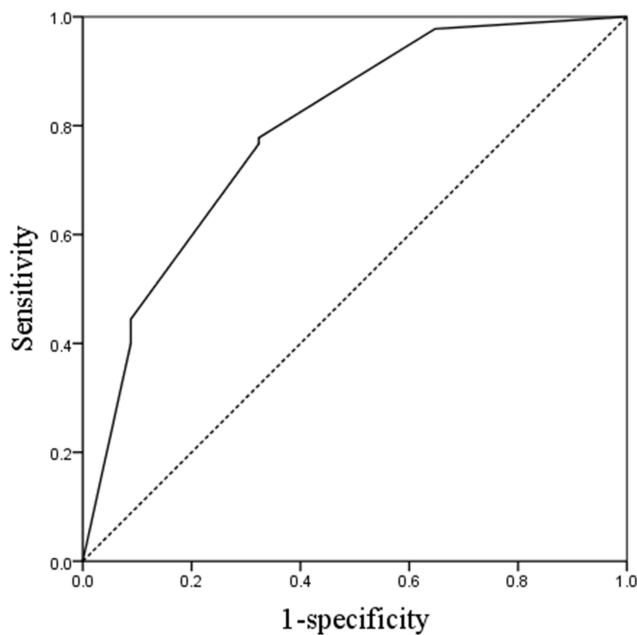


Figure 3 ROC curve of the postoperative pulmonary complications prediction model.

serious pulmonary complications and death.³⁶ PEF is a useful parameter that reflects the strength of respiratory muscles and whether the airway is blocked,²⁰ while MVV % reflects the elasticity of thoracic lung tissue, airway resistance, and respiratory muscle strength,²⁰ these two parameters are related to respiratory muscle strength, which affects cough following surgery. DLCO% is an index that reflects lung diffusion function, and Sandri et al found that patients with DLCO% < 50% have a higher incidence of cardiopulmonary complications and longer postoperative stay.³⁷ Further, Stamenovic concluded that better lung function (FEV1 > 72%, DLCO > 57%) is associated with improved patient outcomes.³⁸

In this study, we did not find that the number of lung segments removed influenced PPC rates. Values of ppo-FEV1% and ppo-DLCO% are calculated based on the number of segments removed and preoperative pulmonary function; these two parameters reflect the pulmonary reserve following lung resection, and we identified ppo-FEV1% as a good predictor of PPC.³⁹ Some reports have suggested that ppo-FEV1% is more clinically meaningful.^{40,41} Clinicians will likely decide to remove fewer segments from a patient with severely abnormal pulmonary function attending for lung resection.^{42,43}

Previous studies have only explored the predictive value of single pulmonary function parameters, while methods used to determine diagnostic value are more

modern. Inclusion of several risk factors in a model can produce synergistic effects; thus, combining two or more parameters can improve diagnostic performance. Based on previous findings, we conducted logistic regression analysis and found that only FEV1/FVC%, PEF%, and ppo-FEV1% remained clinically significant. Using those three parameters, we constructed a prediction model to evaluate the PPC rate of patients with NSCLC and abnormal pulmonary function. This model includes several pulmonary function parameters, both preoperative and postoperative, that can be used to directly evaluate the risk of PPC before operation. The performance of this model is excellent, as demonstrated by the results of ROC analysis in this study. With the help of this model, it is easy to predict the probability of PPC after lung resection in patients with impaired pulmonary function. The model indicates that the PPC rate of patients with all low values for all indices was 24 times higher than that of patients with all high index values. For each patient, we could determine the PPC rate from Table 6 after calculating their total score. Further, the heat map generated in this study also provides a simple method to evaluate the likelihood of PPC after surgery. Red blocks indicate that the patient has a high risk of developing PPC, whereas green blocks indicate low risk. This model is simple and easy to apply in daily clinical practice. If the predictive probability is high, or the corresponding heatmap is yellow or red, then the patient has a high risk of developing PPC and should be closely monitored during the whole postoperative period. Hence, it is possible to identify patients at high risk of postoperative PPC. If the predictive probability is low, or the corresponding heatmap is green, then the patient has a low risk of developing PPC, thus routine medical care is sufficient, which could save valuable medical resources.

Our study also has some limitations. First, this is a retrospective study; therefore, although we screened patients without bias and excluded those with incomplete data, selection bias could not be avoided. Second, we judged the PPC categories according to medical and examination records. Some PPC records were missing due to mistakes in the records. Third, conventional spirometry is insensitive for detecting early damage to the small airways

Table 6 Postoperative Pulmonary Complications Risk Rate

Total Points	0	4	5	8	9	13
PPC risk	0.73	0.42	0.34	0.15	0.11	0.03

and assessing the distribution of ventilation. The new technique, multiple-breath washout, is valuable for evaluating peripheral airway function and ventilation homogeneity, and is sensitive in detecting lung complications;⁴⁴ however, due to equipment limitations, we did not conduct this type of analysis.

Conclusion

In summary, our prediction model, including the parameters, FEV1/FVC%, PEF%, and ppo-FEV1%, can be widely applied in clinical practice. More prospective studies are required to further verify the effectiveness of this model.

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Disclosure

The authors declare that they have no conflicts of interest related to this work.

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