Original Article

Preoperative peak expiratory flow (PEF) for predicting postoperative pulmonary complications after lung cancer lobectomy: a prospective study with 725 cases

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Background: The study aimed to investigate the correlation between peak expiratory flow (PEF) and postoperative pulmonary complications (PPCs) for lung cancer patients undergoing lobectomy.

Methods: Patients who were diagnosed with resected non-small cell lung cancer (NSCLC) (n=725) were prospectively analyzed and the relationship between the preoperative PEF and PPCs was evaluated based on patients' basic characteristics and clinical data in hospital

Results: Among the 725 included patients, 144 of them were presented PPCs in 30 days after lobectomy, which were divided into PPCs group. PEF value (294.2±85.1 *vs.* 344.7±89.6 L/min; P<0.001) were found lower in PPCs group, compared with non-PPCs group; PEF (OR, 0.984, 95% CI: 0.980–0.987, P<0.001) was a significant independent predictor for the occurrence of PPCs; based on an receiver operating characteristic (ROC) curve , with the consideration of balancing the sensitivity and specificity, a cutoff value of 300 (L/min) (Youden index: 0.484, sensitivity: 69.4%, specificity: 79.0%) was selected and a PEF ≤300 L/min indicated a 8-fold increase in odds of having PPCs after lung surgery (OR, 8.551, 95% CI: 5.692–12.845, P<0.001). With regard to PPCs rate, patients with PEF value ≤300 L/min had high PPCs rate than those with PEF >300 L/min (45.0%, 100/222 *vs.* 8.7%, 44/503, P<0.001); Meanwhile, pneumonia (24.8%, 55/222 *vs.* 6.4%, 32/503, P<0.001), atelectasis (9.5%, 21/222 *vs.* 4.0%, 20/503, P=0.003) and mechanical ventilation >48 h (5.4%, 12/222 *vs.* 2.4%, 12/503, P=0.036) were higher in the group with PEF value ≤300 L/min.

Conclusions: The presented study revealed a significant correlation between a low PEF value and PPCs in surgical lung cancer patients receiving lobectomy, indicating the potential of a low PEF as an independent risk factor for the occurrence of PPCs and a PPC-guided (PEF value ≤300 L/min) risk assessment could be meaningful for the perioperative management of lung cancer candidates waiting for surgery.

Keywords: Lung cancer; lobectomy; peak expiratory flow (PEF); postoperative pulmonary complications (PPCs)

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Introduction

Lung cancer, as a leading cause of cancer-related deaths worldwide, has been one of the most health-threatening and death-causing diseases to humans with the morbidity and mortality rate ranking first in China (1-5). Among various therapeutic methods aiming at curing the disease, surgery is still the primary or optimal strategy, especially for intermediate-stage patients with pre-malignant or early lesions which are amenably resectable (6). Postoperative pulmonary complications (PPCs) are deemed to be strongly correlated to short- and long-term survival after lung cancer surgery (5,7,8). Hence, the preoperative state of candidates waiting for lung cancer surgery and predictive risks for PPCs with up-to-date data is urgently needed to be investigated, helping to set realistic expectations for perioperative interventions, therapies and care.

Resent years, some predictive factors of PPCs after lung resection, for example, forced expiratory volume in 1 s (FEV1) or 6-min walk distance (6-MWD), have been deeply investigated, aiming at better assessing the risk of PPCs preoperatively (8-15). peptide level peak expiratory flow (PEF), which is defined as the maximum flow achieved during expiration delivered with maximal force starting from maximal lung inflation , has been investigated as a risk assessment tool aiming at old populations. Recent years several researches have been performed to investigate associations of PEF with long-term cause-specific mortality, for it has cross-sectionally associations with health status as well as physical and cognitive function (16-20). However, few researches were conducted to validate the effectiveness of PEF to predict the occurrence of PPCs after lung cancer lobectomy.

Based on this, we set this prospective study to examine the correlation between PEF and clinical variables in lung cancer patients undergoing lung lobectomy.

Methods

Ethical review

This protocol has been approved by the university's clinical trials and biomedical ethics committee (No. 2016-121). The WHO registering number is ChiCTR-COC-17010720. We declared that the research was adhered the tenets of the Declaration of Helsinki, with written informed consent obtained from the patients.

Patients

Records of consecutive patients who diagnosed with non-small cell lung cancer (NSCLC) undergoing lung cancer lobectomy at West China Hospital of Sichuan University, between March 1st, 2017 and December 31th, 2017 were involved. Inclusive criteria were listed as follow: (I) diagnosed as NSCLC; (II) undergoing lung cancer lobectomy; (III) age between 40–85 years; (IV) with agreement of informed consent. Finally, data of 725 patients were finally included and analyzed. All patients were received similar routine perioperative preparation or care, including early mobilization, ambulation and breathing exercise by the specialized nurses. The pathological stage was determined based on the eighth edition of the TNM staging system for lung cancer (21,22). Preoperative pulmonary functions, including forced vital capacity (FVC), FEV1 and PEF, were routinely measured at the lung function laboratory of the hospital before the operation.

PPCs

Based on the STS/ESTS complication definition (23), categories and criteria of the PPCs experienced by the patients were as follows: (I) atelectasis documented clinically or radiographically; (II) pneumonia defined according to the criteria including: new or progressive and persistent infiltrate, consolidation or cavitation found by chest radiographs and at least one of the following must be met: fever (>38 ℃) without other recognized reasons; leukopenia (<4,000 WBC/mm^3) or leukocytosis (<12,000 WBC/mm^3); for patients >70 years old, change in mental status with: purulent sputum or change in character, respiratory secretions increasing or needing suction; onset or worsening symptoms (dyspnea, tachypnea, e.g.,) or clinical signs (rales, bronchial breath sounds, e.g.,); (III) adult respiratory distress syndrome (ARDS); (IV) mechanical ventilation >48 h; (V) air leak >7 days; (VI) reintubation; (VII) back to ICU or needing tracheotomy; (VIII) empyema; (IX) chylothorax/bronchopleural fistula.

Statistics analysis

Continuous variables were presented as the means ± standard deviations (SD) and binary variables as proportions (n, %). Fisher's exact test, Chi square test, and Student's *t*-test were used for comparing variables as appropriate. Univariate and multivariate logistic regression analyses were performed, aiming to investigate potential predictive factors of PPCs and evaluate the predictive significance of PEF value for PPCs. Variables with a $P<0.20$ in the univariate analysis were involved into the multivariate analysis along with the PEF. A receiver operating characteristic (ROC) curve was performed to evaluate the sensitivity and specificity of PEF value for predicting the occurrence of PPCs in lung cancer patients after lung cancer lobectomy. All results were determined significant at a value of $P<0.05$. Statistical analyses were conducted via SPSS software v.22.0.

Results

Baseline of the patients' characteristics

Among the 725 included patients, 144 of them were presented PPCs in 30 days after lobectomy, which were divided into PPCs group. The rates of pneumonia (12.0%, 87/725), atelectasis (5.7%, 41/725) and air leak (5.1%, 37/725) ranked at the top of the categories of PPCs. Details were listed in *Table 1*.

The characteristics of PPCs group and non-PPCs group were summarized in *Table 1*. FEV1 (1.83±0.57 *vs.* 2.00±0.69 L; P=0.007) and PEF value (294.2±85.1 *vs.* 344.7±89.6 L/min; P<0.001) were found lower in PPCs group, compared with non-PPCs group. Regarding comorbidities, proportions of COPD (22.2%, 32/144 *vs.* 14.1%, 82/581; P=0.018) was higher in PPCs group than in non-PPCs group. Additionally, patients in PPCs group had longer length of stay (LOS) including postoperative (7.82±4.83 *vs.* 4.16±2.50 days; P<0.001), total LOS (13.77±5.29 *vs.* 9.71±4.41 days; P<0.001) and more total in-hospital expense (51,143.1±12,293.2 *vs.* 48,603.6±12,636.0 ¥; P=0.030) as well as drug cost (9,959.6±3,966.1 *vs.* 8,086.7±4,484.8 ¥; P<0.001).

Logistics regression for PPCs

Variables with a P<0.20 in the univariate analysis were into the multivariate analysis, including age (OR: 1.019, P=0.078); diabetes mellitus (OR: 1.476, P=0.053), COPD (OR: 1.739, P=0.018), coronary heart disease (CHD) (OR: 1.512, P=0.138), FEV1 (OR: 0.673, P=0.007), PEF (OR: 0.993; P<0.001), blood loss (OR: 1.001, P=0.057) and operation time (OR: 1.003, P=0.121). By using Multivariate logistic regression analysis, PEF (OR: 0.984, 95% CI: 0.980–0.987, P<0.001) was a significant independent predictors for the occurrence of PPCs. Details were listed in *Table 2*. Next, factors affecting PEF were examined. Spearman or Pearson's correlations between PEF and clinical variables of all patients were showed in *Table 3*. Gender (P<0.001), age (P<0.001), FEV1 value (P<0.001) and operation time (P=0.044) were significantly correlated with PEF.

Optimal cutoff of the PEF for predicting PPCs

The distribution of PEF in patients with and without PPCs was shown in *Figure 1*. We selected the optimal cutoff value of the PEF for predicting PPCs based on a ROC curve (*Figure 2*), with the consideration of balancing the sensitivity and specificity. Hence, we chose a cutoff value of 300 (L/min) (Youden index: 0.484, sensitivity: 69.4%, specificity: 79.0%). Moreover, A PEF ≤300 L/min indicated an 8-fold increase in odds of having PPCs after lung surgery (OR, 8.551, 95% CI: 5.692–12.845, P<0.001).

The patients were divided into two groups based on whether the PEF value ≤300 L/min (*Table 4*). Older age (62.5±9.0 *vs.* 61.0±8.7 years, P=0.029), lower average FEV1 (1.86±0.62 *vs.* 2.02±0.69 L, P=0.002), longer operation time (113.8±50.3 *vs.* 105.2±51.6 min, P=0.039) and postoperative LOS (5.74±4.26 *vs.* 4.51±2.91 days, P<0.001) as well as total LOS (11.68±5.35 *vs.* 10.01±4.56 days, P<0.001) were found in the group with PEF value ≤300 L/min. With regard to PPCs rate, patients with PEF value ≤300 L/min had high PPCs rate than those with PEF >300 L/min (45.0%, 100/222 *vs.* 8.7%, 44/503, P<0.001); meanwhile, pneumonia (24.8%, 55/222 *vs.* 6.4%, 32/503, P<0.001), atelectasis (9.5%, 21/222 *vs.* 4.0%, 20/503, P=0.003) and mechanical ventilation >48 h (5.4%, 12/222 *vs.* 2.4%, 12/503, P=0.036) were higher in the group with PEF value ≤300 L/min (*Table 5*).

Discussion

The significant finding of this prospective study was that for lung cancer patients undergoing lobectomy, preoperative PEF value was significantly lower in patients with PPCs after lobectomy than those who without, and PEF ≤300 L/min was a good predictive parameter in discriminating PPCs and PEF.

Numerous studies related to cause-specific mortality have validated that impaired or poor lung function predicts mortality from other specific conditions including lung cancer, rather than from non-neoplastic respiratory disease. Some variables of lung function, for example, FEV1, traditionally has been considered as the critical component of the functional workup of lung cancer candidates waiting for surgery (13-15), as a reduced FEV1 value is considered to be associated with increased respiratory morbidity and mortality rates for surgical lung cancer patients. In the ACCP guidelines [2013] of Physiologic Evaluation of the Patient with Lung Cancer Being Considered for Resectional Surgery, it is also recommended to evaluate preliminary cardiac-pulmonary function (24). Recent years, several studies has been performed to state PEF as a useful measure of physical functioning and health status in elderly population, which is considered to be an independent predictor of increased health-care utilization. Meanwhile, several other studies concerning the relationships between

Table 1 Baseline and clinical characteristics between the PPCs groups and non-PPCs group

Variables	PPCs group (N=144)	Non-PPCs group (N=581)	P value
Age, mean ± SD	62.6±8.3	61.2±8.9	0.078
Gender (n, %)			0.502
Male	86 (59.7)	329 (56.6)	
Female	58 (40.3)	252 (43.4)	
Smoking status (n, %)			0.362
Current smoking	48 (33.3)	171 (29.4)	
Ex- or non-smokers	96 (66.7)	410 (70.6)	
Cardio-pulmonary function, mean ± SD			
FEV1 (L)	1.83±0.57	2.00±0.69	0.007
FVC (L)	2.88±0.60	2.89±0.66	0.884
PEF (L/min)	294.2±85.1	344.7±89.6	<0.001
Comorbidities (n, %)			
COPD	32 (22.2)	82 (14.1)	0.018
Diabetes mellitus	48 (33.3)	147 (25.3)	0.053
Hypertension	16 (11.1)	56 (9.6)	0.597
Coronary heart disease	20 (13.9)	56 (9.6)	0.138
Pathological stage (n, %)			0.066
Stage I	74 (51.4)	332 (57.1)	
> Stage I	70 (48.6)	249 (42.9)	
Surgical approach (n, %)			0.306
VATS	99 (68.7)	373 (64.2)	
Open	45 (31.3)	208 (35.8)	
Amount of blood loss (mL)	106.3±225.6	80.7±98.5	0.057
Operation time (min)	113.8±63.4	106.4±47.8	0.121
Length of stay, mean ± SD			
Total	13.77±5.29	9.71±4.41	<0.001
Preoperative	5.59±1.84	5.55±3.52	0.0509
Postoperative	7.82±4.83	4.16±2.50	<0.001
In-hospital expense (¥), mean ± SD			
Total	51,143.1±12,293.2	48,603.6±12,636.0	0.030
Material cost	22,470.0±7,614.8	23,501.5±7,088.8	0.124
Drug cost	9,959.6±3,966.1	8,086.7±4,484.8	<0.001

Data are presented as mean ± SD, median (range) or n (%). PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity.

Table 2 Relationships between postoperative pulmonary complications and clinical characteristics

Variables	Description	Univariate analysis			Multivariate analysis		
		OR	P value	95% CI	OR	P value	95% CI
Age	Per 1 year increase	1.019	0.078	0.998–1.042	0.990	0.427	0.965–1.015
Gender (M)	Yes	1.136	0.502	0.784–1.646	–	–	–
Smoking status	Yes	1.199	0.362	0.812–1.770	–	–	–
Hypertension	Yes	1.172	0.597	0.651–2.110	–	–	–
Diabetes mellitus	Yes	1.476	0.053	0.996–2.188	1.525	0.082	0.948–2.455
COPD	Yes	1.739	0.018	1.101–2.746	1.584	0.099	0.917–2.737
CHD	Yes	1.512	0.138	0.875–2.612	0.970	0.928	0.498–1.888
FVC	Per unit decrease	0.979	0.884	0.739–1.298	–	–	–
FEV1	Per unit decrease	0.673	0.007	0.506–0.896	0.978	0.904	0.687–1.393
PEF	Per unit decrease	0.993	<0.001	0.991–0.995	0.984	<0.001	0.980–0.987
Blood loss	Per unit increase	1.001	0.057	1.000–1.002	1.001	0.175	1.000–1.002
Operation time	Per unit increase	1.003	0.121	0.999–1.006	1.000	0.942	0.996–1.005
VATS procedure	Yes	0.815	0.306	0.551–1.205	–	–	–

PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; CHD, coronary heart disease.

Table 3 Spearman or Pearson's correlations between PEF and other variables

Variables	Rho/rs	P value
Variables age	–0.132	<0.001
Gender (M)	0.150	<0.001
Smoking status	0.019	0.614
Hypertension	–0.065	0.082
Diabetes mellitus	–0.013	0.727
COPD	–0.019	0.607
CHD	–0.086	0.120
FVC	0.045	0.228
FEV1	0.245	<0.001
Blood loss	–0.014	0.715
Operation time	–0.075	0.044
VATS procedure	0.009	0.817

Rho, Spearman's correlation coefficient; rs, Pearson's correlation coefficient; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s.

PEF and subsequent cause–specific mortality also reveal associations with cardiovascular events as well as lung-cancer mortality (16-20,25). PEF, as it can be rapidly and easily measured by an in-expensive and hand-held device, may be potentially useful as an indicator of health status for populations with limited access to healthcare, though it has not be validated (18-20). Meanwhile, the PEF reflects airway patency and resistance, respiratory muscle strength and other aspects of lung function, and reduced PEF was evident in a variety of chronic illnesses, and its validity as a health status measure was confirmed by some studies. Hence, we hypothesized that a low PEF suggested poor respiratory muscle strength and lung function, and may be correlated with the occurrence of PPCs after lung cancer lobectomy.

In our study, among the 725 included patients, 19.8% of them were presented PPCs in 30 days after lobectomy with pneumonia, atelectasis and air leak ranking at the top of the categories of PPCs. The occurrence of PPCs inevitably prolonged hospitalization, slowed the postoperative recovery and rehabilitation, increased the risk of morbidity, as well as both medical and labor cost. Based on the results, patients

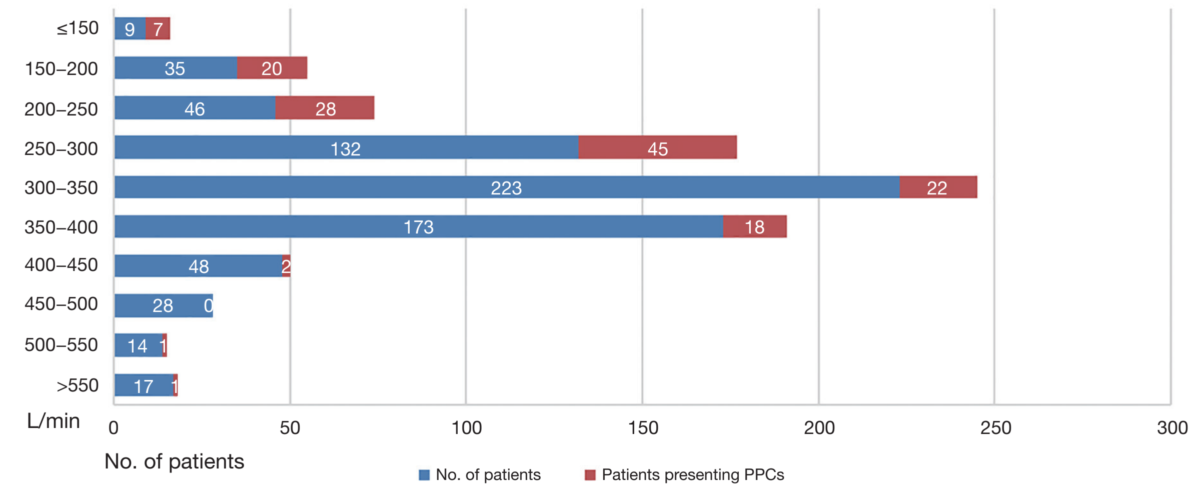
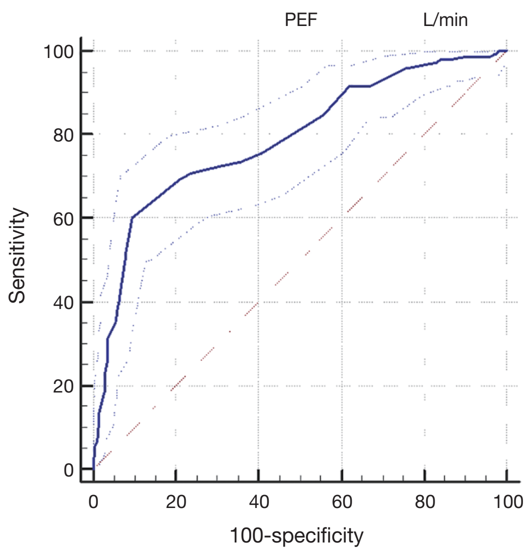


Figure 1 The distribution of peak expiratory flow (PEF) in patients with and without postoperative complications (PPCs).



AUC	95% CI	P value	Cutoff-point value	Sensitivity	Specificity	Youden index
0.789	0.758 to 0.819	<0.001	300 (L/min)	69.4%	79.0%	0.484

Figure 2 Area under the receiver operating characteristics (ROC) curves for the risk of postoperative pulmonary complications as determined by peak expiratory flow (PEF).

in PPCs group had longer LOS including postoperative (P<0.001), total LOS (P<0.001) and more total in-hospital expense (P=0.030) as well as drug cost (P≤0.001), revealing the adverse effect the PPCs brought to the patients. Meanwhile, FEV1 (P=0.007) and PEF value (P<0.001) were found lower in PPCs group and via multivariate logistic regression analysis and PEF was significant independent predictors for the occurrence of PPCs. Moreover, when we selected 300 L/min as cutoff point based on Onodera's original cutoff, with the consideration of balancing the sensitivity and specificity, A PEF ≤300 L/min indicated an 8-fold increase in odds (95% CI: 5.692–12.845, P<0.001) of having PPCs after lung cancer surgery, indicating the potential of a low PEF to predict the occurrence of PPCs

Table 4 Baseline and clinical characteristics between group with PEF ≤300 and PEF >300

Variables	PEF ≤300 (N=222)	PEF >300 (N=503)	P value
Age, mean ± SD	62.5±9.0	61.0±8.7	0.029
Gender (n, %)			0.616
Male	124 (55.9)	291 (57.9)	
Female	98 (44.1)	212 (42.1)	
Smoking status (n, %)			0.606
Current smoking	70 (31.5)	149 (29.6)	
Ex- or non-smokers	152 (68.5)	354 (70.4)	
Cardio-pulmonary function, mean ± SD			
FEV1 (L)	1.86±0.62	2.02±0.69	0.002
FVC (L)	2.84±0.63	2.92±0.65	0.139
PEF	255.5±46.1	383.4±67.4	<0.001
Comorbidities			
COPD	40 (18.0)	74 (14.7)	0.260
Diabetes mellitus	56 (25.2)	139 (27.6)	0.500
Hypertension	26 (11.7)	46 (9.1)	0.287
Coronary heart disease	24 (10.8)	52(10.3)	0.848
Pathological stage (n %)			0.108
Stage I	89 (40.1)	234 (46.5)	
> Stage I	133 (59.9)	269 (53.5)	
Surgical approach (n, %)			0.937
VATS	145 (65.3)	327 (65.0)	
Open	77 (34.7)	176 (35.0)	
Amount of blood loss (mL)	93.6±190.5	82.3±98.7	0.295
Operation time (min)	113.8±50.3	105.2±51.6	0.039
Length of stay, mean ± SD			
Total	11.68±5.35	10.01±4.56	<0.001
Preoperative	5.95±3.05	5.49±3.34	0.073
Postoperative	5.74±4.26	4.51±2.91	<0.001
In-hospital expense, mean ± SD (¥)			
Total	49,140.4±12,234.2	49,094.6±12,771.9	0.964
Material cost	22,649.3±7,403.2	23,582.3±7,101.2	0.108
Drug cost	8,861.5±4,165.8	8,280.9±4,558.7	0.105

PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; CHD, coronary heart disease.

Table 5 Categories of PPCs between group with PEF ≤300 and PEF >300

Categories	PEF ≤300 (N=222)	PEF >300 (N=503)	Total (N=725)	P value
Pneumonia	55 (24.8)	32 (6.4)	87 (12.0)	<0.001
Atelectasis	21 (9.5)	20 (4.0)	41 (5.7)	0.003
Pulmonary embolism	2 (0.9)	2 (0.4)	4 (<1.0)	0.590
Air leak	14 (6.3)	23 (4.6)	37 (5.1)	0.328
Mechanical ventilation >48 h	12 (5.4)	12 (2.4)	24 (3.3)	0.036
Empyema	6 (2.7)	8 (1.6)	14 (1.9)	0.380
Chylothorax/bronchopleural fistula	4 (1.8)	4 (0.8)	8 (1.1)	0.257
Respiratory/heart failure or ADRS	7 (3.2)	9 (1.8)	16 (2.2)	0.249
Re-intubation	2 (0.9)	2 (0.4)	4 (<1.0)	0.590
Back to ICU or needing tracheotomy	4 (1.8)	7 (1.4)	11 (1.5)	0.744

Data are presented as n (%). PPC, postoperative pulmonary complication; PEF, peak expiratory flow.

after lung cancer lobectomy. Furthermore, when the patients were divided into two groups based on whether the PEF value ≤300 L/min, patients with PEF value ≤300 L/min had high PPCs rate as well as pneumonia, atelectasis and mechanical ventilation >48 h than those with PEF >300 L/min. This would significantly explain the strong correlation between a low PEF and PPCs for surgical lung cancer patients.

There are some limitations which can hardly be avoided including its non-randomized nature and single-center design and potential selection bias. All study participants were selected from March 1st, 2017 and December 31th, 2017 by a small group of surgeons in a single regional center. Secondly, we selected patients who underwent lung cancer lobectomy, which meant that those with other surgical type, such as wedge resection, segmental resection or pneumonectomy were not involved, for excluding the confounder caused by surgical types. But on the other side, selection bias was generated, which inevitably limited the generalization of the conclusions. Furthermore, just like other index of lung function (FEV1, e.g.,), age, sex and height gender may be associated with PEF, which makes it necessary for us to perform further study to investigate. Moreover, in the study, we tried to investigate the correlations between some variables and PEF. However, the relative low values of correlation coefficient suggested the relevant correlations were uncertain. Further study is needed to be performed to deeply discuss the issue. Last not the least, for those patients with low PFE value, more researches should be performed for reducing the relatively high risk of PPCs after surgery. We recommend that more attention should be given to some interventions, for example, perioperative pulmonary rehabilitation which may enhance or improve the lung function, and sequentially lead to reduce PPCs rates.

In conclusion, the study we presented identified a significant correlation between a low PEF value and PPCs in surgical lung cancer patients undergoing lobectomy, indicating a low PEF as independent risk factor for the occurrence of PPCs and a PPC-guided (PEF value ≤300 L/min) risk assessment could be meaningful for the perioperative management of lung cancer candidates waiting for surgery.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the university's clinical trials and biomedical ethics committee (No. 2016-121) and written informed consent was obtained from all patients.

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