

Risk factors for postoperative pneumonia and prognosis in lung cancer patients after surgery

A retrospective study

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Abstract

Postoperative pneumonia (POP) is one of the most frequent complications following lung surgery. The aim of this study was to identify the risk factors for developing POP and the prognostic factors in lung cancer patients after lung resection.

We performed a retrospective review of 726 patients who underwent surgery for stages I–III lung cancer at a single institution between August 2017 and July 2018 by conducting logistic regression analysis of the risk factors for POP. The Cox risk model was used to analyze the factors influencing the survival of patients with lung cancer.

We identified 112 patients with POP. Important risk factors for POP included smoking (odds ratio [OR], 2.672; 95% confidence interval [CI], 1.586–4.503; $P < .001$), diffusing capacity for carbon monoxide (DLCO) (40–59 vs $\geq 80\%$, 4.328; 95% CI, 1.976–9.481; $P < .001$, < 40 vs $\geq 80\%$, 4.725; 95% CI, 1.352–16.514; $P = .015$), and the acute physiology and chronic health evaluation (APACHE) II score (OR, 2.304; 95% CI, 1.382–3.842; $P = .001$). In the Cox risk model, we observed that age (hazard ratios (HR), 1.633; 95% CI, 1.062–2.513; $P = .026$), smoking (HR, 1.670; 95% CI, 1.027–2.716; $P = .039$), POP (HR, 1.637; 95% CI, 1.030–2.600; $P = .037$), etc were predictor variables for patient survival among the factors examined in this study.

The risk factors for POP and the predictive factors affecting overall survival (OS) should be taken into account for effective management of patients with lung cancer undergoing surgery.

Abbreviations: AGR = albumin-to-globulin ratio, APACHE II = Acute Physiology and Chronic Health Evaluation II, CI = confidence interval, CICU = cardiothoracic intensive care unit, COPD = chronic obstructive pulmonary disease, DLCO = diffusing capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HR = hazard ratio, OPEN = open thoracotomy, OR = odds ratio, OS = overall survival, PEF = peak expiratory flow, POP = postoperative pneumonia, VATS = video-assisted thoracic surgery.

Keywords: acute physiology and chronic health evaluation II score, lung cancer, overall survival, postoperative pneumonia

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All relevant data are within the paper and its Supporting Information files.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Lung cancer is a major global health problem, as it is the leading cause of cancer-related deaths worldwide.^[1] Surgery is the only curative therapy for early-stage lung cancer. However, some patients may not be offered surgery because of concerns about perioperative mortality. Postoperative complications are well documented to be a poor prognostic factor, with immediate negative effects on recovery and survival after major lung resection for lung cancer.^[2–4] Postoperative pulmonary complications after lung resection surgery are the most frequent complications, with an incidence of up to 25%.^[5–7] Previous studies have shown that postoperative pulmonary complications may be a marker of increased long-term mortality in patients undergoing surgery due to lung cancer.^[5–8] However, studies aiming to specifically address the risk factors for postoperative pneumonia (POP) and the prognostic factors associated with overall survival (OS) in lung cancer patients are largely lacking.

In the current study, we retrospectively investigated the possible risk factors for POP and the potential prognostic factors for survival in lung cancer patients after lung surgery. Identifying more risk and prognostic markers is imperative for better and early prediction of prognosis among patients with the same tumor, node, and metastasis (TNM) stage.

2. Methods

2.1. Patients

This study included lung cancer patients who underwent complete surgical resection at the Department of Cardiothoracic Surgery, The First Affiliated Hospital of Chongqing Medical University from August 2017 to July 2018. During the operations, the patients were on single lung ventilation and under general anesthesia. All patients were subsequently scheduled for extubation in the cardiothoracic intensive care unit (CICU). When the patient's condition was stable, they were transferred to the thoracic surgery ward, unless there were complications requiring them to be admitted to the CICU, such as the need for invasive ventilation. The inclusion criteria were: histologically confirmed primary lung cancer without metastatic tumors and systematic/selective lymph node dissection or lymph node sampling. The exclusion criteria were presenting clinical evidence of chronic inflammatory, hematological, or autoimmune diseases. This retrospective study complied with the tenets of the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University. Informed consent was obtained from all the patients.

2.2. Clinicopathological parameters

All clinical and pathological information was collected from the patients' medical records, including age, smoking history, preoperative measurement of lung function (forced expiratory volume in 1 second [FEV₁], forced vital capacity [FVC], FEV₁/FVC ratio, peak expiratory flow [PEF], diffusing capacity for carbon monoxide [DLCO]), AGR (albumin-to-globulin ratio), resection type, estimated intraoperative blood loss (EIBL), histological findings (adenocarcinoma [ADC], squamous cell carcinoma [SCC], other types), tumor stage, neoadjuvant chemotherapy (nCT), and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, etc. Preoperative pulmonary function was routinely measured at the lung function laboratory of the hospital before the operations. Preoperative blood samples were obtained within the 1 week preceding the surgery. Tumor staging was assessed according to the eighth edition of the American Joint Committee on Cancer TNM staging system 2017. The APACHE II scoring was performed within 24 h of admission to CICU. The set of physiological parameters measured within 24 h of CICU admission was used. Preoperative AGR was calculated using the following formula: serum albumin/globulin levels (g/dL).

2.3. Definition of POP and outcomes

The occurrence of POP was considered within 30 days of surgery. POP was defined as:

- (1) abnormal radiographic findings (new or changing radiographic infiltrates that persisted after physiotherapy or bronchoaspiration),
- (2) fever > 38°C, and
- (3) one of the following criteria: a new rise in the C-reactive protein value or WBC count over the last 24 h (with WBC > 12 × 10⁹/L), an increase and modification of the expectorate—possibly with purulence and positive sputum samples, or positive blood cultures.^[9]

The clinical outcomes were postoperative length of stay (PLOS), length of ICU stay, postoperative antibiotic use time, re-intubation, CICU reentry, 30-day mortality, and 90-day mortality. The primary study outcome was OS, defined as the time from resection to the last follow-up visit or death from any cause. The latest follow-up included in this study was in May 2019.

2.4. Statistical analysis

The median value was used as the optional cutoff value for PEF and AGR. Data are presented as median (interquartile range) or n (%). Logistic regression analysis was used to identify the independent predictive factors for POP, and the Cox risk model was used to analyze the factors influencing the survival of lung cancer patients. A *P*-value < .05 by univariate analysis was chosen as the criterion for submitting variables to the model. All statistical analyses were performed using SPSS software, version 24.0 (IBM Corp, Armonk, NY) and GraphPad Prism software (GraphPad Software, La Jolla, CA). A *P*-value of < .05 was considered significant.

3. Results

3.1. Basic characteristics of the POP and non-POP groups

Seven hundred twenty-six patients who underwent lung surgery were included in the analysis. One hundred twelve patients (15.43%) developed POP during the follow-up period (30 days). The follow-up time ranged from 9 to 21 months. Current or former smokers accounted for 75% of the POP group. There were 35 subjects with DLCO ≥ 80% (31.3%) in the POP group, while the ratio was 58.1% in the non-POP group. Among the POP group, the histological features of lung cancer included ADC (43.8%), SCC (47.3%). Patients in the POP group were classified into the following pathological stages: stage I (54, 48.2%), stage II (22, 19.6%), and stage III (36, 32.1%). Most patients in each group underwent lobectomy. Detailed information about the demographic differences in the perioperative characteristics between patients with and without POP is shown in Table 1.

3.2. Risk factors for POP

Importantly, the multivariate logistic regression analysis revealed the following variables as the independent risk factors for POP: smoking (odds ratio [OR], 2.672; 95% confidence interval [CI], 1.586–4.503; *P* < .001), DLCO (40–59 vs ≥ 80%, 4.328; 95% CI, 1.976–9.481; *P* < .001, < 40 vs ≥ 80%, 4.725; 95% CI, 1.352–16.514; *P* = .015), AGR (OR, 2.108; 95% CI, 1.257–3.535; *P* = .005), resection type (pneumonectomy vs lobectomy, 10.563; 95% CI, 3.828–29.146; *P* < .001; sleeve resection vs lobectomy, 12.832; 95% CI, 2.855–57.676; *P* = .001), EIBL (≥ 200 vs < 100 mL, 2.741; 95% CI, 1.111–6.767; *P* = .029), nCT (OR, 4.817; 95% CI, 1.204–19.265; *P* = .026), and APACHE II score (OR, 2.304; 95% CI, 1.382–3.842; *P* = .001) are related to POP (Table 2).

3.3. Primary study outcome

During follow-up, 88 patients died. We found that age (hazard ratios [HR], 1.633; 95% CI, 1.062–2.513; *P* = .026), smoking (HR, 1.670; 95% CI, 1.027–2.716; *P* = .039), albumin (HR,

Table 1
Baseline characteristics of postoperative pneumonia and non-postoperative pneumonia group.

Characteristic/variables	POP group n=112	Non-POP group n=614
Age (≥65)	53 (47.3%)	88 (14.3%)
Sex (male)	90 (80.4%)	314 (51.1%)
Smoking (current or former)	84 (75.0%)	244 (39.7%)
Respiratory diseases (current or former)	27 (24.1%)	82 (13.4%)
COPD (current or former)	9 (8.03%)	17 (2.8%)
FEV ₁ /FVC		
≥70%	55 (49.1%)	434 (70.7%)
60–69%	31 (27.7%)	122 (19.9%)
50–59%	14 (12.5%)	35 (5.7%)
35–49%	9 (8.0%)	21 (3.4%)
<35%	3 (2.7%)	2 (0.3%)
FEV ₁ (% predicted) (<80%)	35 (31.3%)	85 (13.8%)
FVC (% predicted) (<80%)	9 (8.0%)	21 (3.4%)
DLCO (% predicted)		
≥80%	35 (31.3%)	357 (58.1%)
60–79%	46 (41.1%)	224 (36.5%)
40–59%	25 (22.3%)	26 (4.2%)
<40%	6 (5.4%)	7 (1.1%)
PEF (% predicted) (<99.2)	73 (65.2%)	288 (46.9%)
Albumin (abnormal)	21 (18.8%)	46 (7.5%)
Globulin (abnormal)	5 (4.5%)	19 (3.1%)
AGR (≤1.69)	32 (28.6%)	327 (53.3%)
Surgical approach (VATS)	71 (63.4%)	507 (82.6%)
Resection type		
Lobectomy	81 (72.3%)	538 (87.6%)
Anatomic segmentectomy	1 (0.9%)	49 (8.0%)
Wedge resection	2 (1.8%)	18 (2.9%)
Pneumonectomy	20 (17.9%)	7 (1.1%)
Sleeve resection	8 (7.1%)	2 (0.3%)
EIBL (mL)		
<100	6 (5.4%)	129 (21.0%)
100–199	30 (26.8%)	237 (38.6%)
≥200	76 (67.9%)	248 (40.4%)
Operation time (min) (≥180)	67 (59.8%)	285 (46.4%)
Postoperative mechanical ventilation time (min) (≥120)	85 (75.9%)	397 (64.7%)
Histologic		
ADC	49 (43.8%)	472 (76.9%)
SCC	53 (47.3%)	143 (23.3%)
Other type	10 (8.9%)	49 (8.0%)
Tumor stage		
I	54 (48.2%)	440 (71.7%)
II	22 (19.6%)	84 (13.7%)
III	36 (32.1%)	90 (14.7%)
Lymph node metastasis		
N ₀	68 (60.7%)	486 (79.2%)
N ₁	20 (17.9%)	51 (8.3%)
N ₂	20 (17.9%)	75 (12.2%)
N ₃	4 (3.6%)	2 (0.3%)
nCT	6 (5.35%)	6 (1.0%)
APACHE II (≥10)	75 (67.0%)	288 (46.9%)

ADC=adenocarcinoma, AGR=albumin-to-globulin ratio, APACHE=Acute Physiology and Chronic Health Evaluation, COPD=chronic obstructive pulmonary disease, DLCO=diffusing capacity for carbon monoxide, EIBL=estimated intraoperative blood loss, FEV₁=forced expiratory volume in 1 second, FVC=forced vital capacity, nCT=neoadjuvant chemotherapy, PEF=peak expiratory flow, POP=postoperative pneumonia, SCC=squamous cell carcinoma, VATS=video-assisted thoracic surgery.

1.725; 95% CI, 1.016–2.929; *P*=.044), tumor stage (II vs I, 7.269; 95% CI, 3.727–14.178; *P*<.001; III vs I, 12.730; 95% CI, 6.923–23.409; *P*<.001), and POP (HR, 1.637; 95% CI, 1.030–2.600; *P*=.037) correlated with the OS after lung resection

Table 2
Multivariate logistic regression analyses for postoperative pneumonia.

Variable	OR for POP (95%CI)	<i>P</i>
Smoking (current or former)	2.672 (1.586–4.503)	<.001
DLCO (% predicted)		.001
60%–79% vs ≥80%	1.319 (0.771–2.258)	.313
40%–59% vs ≥80%	4.328 (1.976–9.481)	<.001
<40% vs ≥80%	4.725 (1.352–16.514)	.015
AGR (≤1.69)	2.108 (1.257–3.535)	.005
Resection type		<.001
Anatomic segmentectomy vs lobectomy	0.248 (0.032–1.926)	.183
Wedge resection vs lobectomy	0.613 (0.113–3.220)	.570
Pneumonectomy vs lobectomy	10.563 (3.828–29.146)	<.001
Sleeve resection vs lobectomy	12.832 (2.855–57.676)	.001
EIBL (mL)		.006
100–199 vs <100	1.274 (0.485–3.347)	.623
≥200 vs <100	2.741 (1.111–6.767)	.029
nCT	4.817 (1.204–19.265)	.026
APACHE II (≥10)	2.304 (1.382–3.842)	.001

AGR=albumin-to-globulin ratio, APACHE=Acute Physiology and Chronic Health Evaluation, DLCO=diffusing capacity for carbon monoxide, EIBL=estimated intraoperative blood loss, nCT=neoadjuvant chemotherapy, POP=postoperative pneumonia.

Table 3
Cox proportional-hazards model of overall survival.

Variable	HR (95%CI)	<i>P</i>
Age (≥65 vs <65)	1.633 (1.062–2.513)	.026
Smoking (current or former vs never)	1.670 (1.027–2.716)	.039
Albumin (abnormal vs normal)	1.725 (1.016–2.929)	.044
Tumor stage		<.001
II vs I	7.269 (3.727–14.178)	<.001
III vs I	12.730 (6.923–23.409)	<.001
POP	1.637 (1.030–2.600)	.037

HR=hazard ratio, POP=postoperative pneumonia.

(Table 3). The Kaplan–Meier survival curves showed consistently higher mortality in patients with POP than in those without POP (*P*<.001) (Fig. 1). Surprisingly, there was no difference between these parameters, including DLCO, APACHE II score, and OS of lung cancer patients.

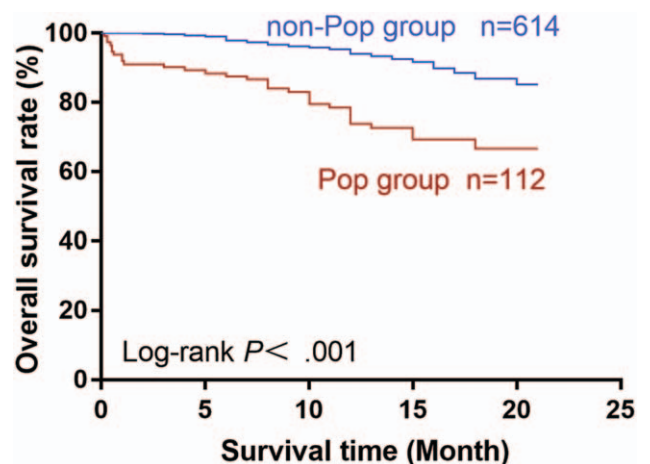


Figure 1. Kaplan–Meier curves for overall survival associated with POP. POP, postoperative pneumonia.

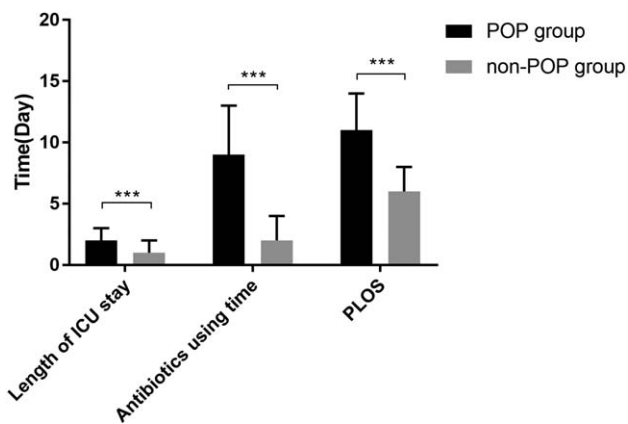


Figure 2. Clinical outcomes between the POP group and the non-POP group. ****P*-value < .001. POP, postoperative pneumonia; PLOS, postoperative length of stay.

3.4. Clinical outcomes of POP

As demonstrated in Figure 2 and Table 4, POP had a significantly longer PLOS (*P* < .001), length of ICU stay (*P* < .001), and postoperative antibiotic use time (*P* < .001). Seven of 726 (1%) patients died within 30 days after surgical resection. The 30-day mortality rate was higher among patients in the POP group than those in the non-POP group (6.3% vs 0, *P* < .001). The prevalences of CICU reentry and re-intubation were higher in the POP group.

4. Discussion

Overall, our study showed a POP incidence of 15.43% (112/726) among cancer patients after lung surgery within 30 days, with a mortality rate of 0.96% (7/726) in the same time period. The high incidence of POP maybe explained by the fact that a higher percentage of patients undergoes pneumonectomy and sleeve resection. On the other hand, there is no unified diagnostic standard for POP, and the incidence may therefore be different in other studies. We have indicated that several variables, including smoking, DLCO, AGR, resection type, EIBL, and APACHE II score, etc were significantly associated with POP after surgery. Furthermore, the clinical outcome of the POP group was worse than that of the non-POP group. POP directly increased hospital mortality and length of hospital stay. On the other hand, age, smoking, POP, etc were prognostic factors for the OS of lung cancer after surgery.

The present study demonstrates that older age was negatively associated with OS after lung resection. However, we failed to find a correlation between age and POP, consistent with the view of Schussler and coworkers.^[9] Simonsen et al^[10] demonstrated

that advanced age (age ≥ 80 years: [OR = 3.64; 95% CI: 2.17–6.12] as compared to patients aged 50 to 59 years) was important risk factor for POP. In their study, 36.1% of patients were older than 70 years. Compared to them, in our study, the frequency of age over 65 years was 19.4%. The contribution of age to POP may differ according to the different distribution of age, characteristics of studied populations, the criteria for defining POP. These maybe potential explanations for this difference.

Current smoking was identified as an independent risk factor for POP. This is consistent with previous finding.^[5] Furthermore, smoking significantly increased the mortality rate of lung cancer patients by 1.67 times. The observed effects of smoking (increasing POP incidence and reducing the OS after lung resection) could be explained by suppressive effect of cigarette smoking on the innate immune system. A previous review provided preliminary evidence quitting smoking after been diagnosed with early-stage lung cancer improves the prognostic outcomes.^[11] Accordingly, preoperative smoking cessation should be vigorously and urgently promoted to reduce or prevent the incidence of POP and improve the prognostic outcomes after lung surgery.

Variables obtained from lung function tests, including FEV₁/FVC, FEV₁, FVC, DLCO, and PEF, are essential for risk stratification prior to major lung resection. Low FEV₁ was found to be significantly associated with early postoperative death.^[12] Berry et al^[13] reported that long-term OS was positively correlated with a better PEF. In contrast, in our study, only DLCO was identified as an independent risk factor for POP. In our study, both the Cox proportional-hazards model and multivariate logistic regression analysis failed to demonstrate a significant association between FEV₁/FVC, PEF, FEV₁, or FVC and POP or OS of patients that underwent lung resection. Patients with impaired DLCO should be informed that they have a higher incidence of POP than those with better DLCO. In accordance with the guidelines for preoperative physiologic evaluation,^[14,15] in our centre, patients with impaired pulmonary function are recommended to undergo a stair-climbing test for additional risk stratification. However, approximately 19% of the patients with poor pulmonary function do not undergo surgery.^[16] Individualized preoperative rehabilitation may be beneficial for patients with impaired lung function.

In the present study, AGR was identified as an independent risk factor for POP, and lower albumin concentration was negatively associated with the OS of lung cancer. No significant difference in terms of serum globulin levels was observed between the POP and non-POP groups. No existing studies have been designed to evaluate the correlation between AGR and POP, and the correlation with systemic inflammation might support this interpretation to some extent. AGR is affected by inflammation and has been widely used to assess the systemic inflammation status of patients with cancers.^[17] Systemic chronic inflammation may be a common mechanism linking diverse risk factors to pneumonia.^[18] This may explain the link between AGR and POP. The molecular mechanism of their role needs to be elucidated. A prior study reported that AGR is a prognostic factor for predicting the survival of NSCLC patients.^[17,19] However, there was no substantial interaction between AGR and OS in our model. Since the median follow-up time was relatively short (9–21 months), a longer follow-up study is warranted to confirm this finding.

The extent of lung resection is a well-known predictive risk factor for postoperative pulmonary complications.^[20] Consistent with this finding, we found that the resection type was closely associated with POP, especially sleeve resection and pneumonectomy. According to a previous study, 40% to 60% of the patients

Variable	POP group (n = 112)	Non-POP group (n = 614)	<i>P</i>
Re-entry CICU	13 (11.6%)	0	<.001
Re-intubation	15 (13.4%)	0	<.001
30-d mortality	7 (6.3%)	0	<.001

CICU = cardiothoracic intensive care unit, POP = postoperative pneumonia.

on whom pneumonectomy was performed faced postoperative complications, with cardiovascular complications predominating.^[21] In this study, we did not include cardiovascular complications. Melloul et al^[22] reported that pulmonary complications were more frequent after sleeve resection than after pneumonectomy in patients <70 years of age. In our study, POP was also more frequent after sleeve resection than after pneumonectomy. Li et al^[23] investigated the correlation between EIBL and postoperative cardiopulmonary complications in 429 patients with NSCLC who underwent video-assisted thoracic surgery (VATS) lobectomy. Their results showed that EIBL is significantly associated with postoperative cardiopulmonary complications, with an adjusted OR of 3.01 (95% CI: 1.47–6.16). Like them, we found that EIBL was significantly correlated with POP after lung resection. Therefore, surgeons should endeavor to reduce intraoperative bleeding.

APACHE II, established and reported in 1985, is a severity-of-disease classification system and has been extensively used in general ICUs for risk stratification of critically ill patients.^[24–26] It is composed of 12 acute physiological parameters (acute physiology score), patient age, chronic diseases, and surgical procedures. Kuo et al^[27] demonstrated that APACHE II scores could predict short- and long-term outcomes of patients with cancer admitted to the ICU due to sepsis. However, it has not been used in lung cancer patients admitted to the CICU after lung surgery. In the current study, the APACHE II score was identified as an independent risk factor for POP by an adjusted OR of 2.304, although it was not associated with patient survival. We suggest that the APACHE II score should be used as a first-line test to identify patients with a high-risk for POP after lung surgery so that special attention is paid to them.

In practical terms, our findings demonstrate the negative potential impact of POP on the clinical outcomes and OS of lung cancer patients with an HR of 1.64 (95% CI, 1.03–2.60; $P=.037$). The poorer OS of lung cancer patients with POP is also agreement with the results of Andalib et al.^[28] In their study, pulmonary complications were found to be significant prognostic indicators of survival, with adjusted estimates for pulmonary complications (HR=1.54, 95% CI: 1.34–1.77). These findings have clinical utility. Prevention of POP is needed to improve OS among lung cancer patients after lung resection. Since patients with POP have a worse prognosis, careful preoperative assessment and management of the identified risk factors for POP could be beneficial to patients scheduled for lung surgery. Clinicians should thus remain vigilant in preventing and treating POP in these patients.

We acknowledge that this study had several limitations. First, this is a retrospective study, not a prospective one. Therefore, the findings reported here may inevitably be confounded by other factors. Hence, large prospective controlled trials are required to validate the findings reported in this study. Second, all the data were obtained from a single institution, which may not fully reflect the clinical scenario elsewhere. Therefore, more investigation involving a multicenter design is necessary to further confirm our findings. Third, the follow-up duration in our study was relatively short, and a longer follow-up study is warranted to confirm the findings reported in the current study, particularly for those findings involved in predicting the long-term survival rate among the patients who undergo lung resection.

In conclusion, our study provided evidence for several important risk factors for POP and prognostic factors for patients after lung resection. Some of these factors, such as

smoking and impaired lung function, are modifiable before surgery. On the other hand, other factors may need to specific prophylactic measures, including reasonable antibiotic therapy and individualized lung rehabilitation after surgery. This information can be used to aid the decision-making process when patients and providers are choosing treatment for lung cancer, particularly when weighing potential risks and benefits. In summary, our findings provide useful insights into risk assessment, patient counselling, perioperative management, and prognostic analysis for lung cancer patients who underwent lung resection.

Author contributions

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