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# Effect of Perioperative Factors on Short-Term Outcomes in Patients with Non-Small Cell Lung Cancer Over 60 Years of Age

Wenzhi Zhu[1,*], Jiaonan Yang[1,*], Xiaoyi Wang[2], Xinqiang Ji[2], Hongyu Tan[1]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Anesthesiology, Peking University Cancer Hospital & Institute, Beijing, People's Republic of China; [2]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Medical Record Statistics, Peking University Cancer Hospital& Institute, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hongyu Tan, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Anesthesiology, Peking University Cancer Hospital & Institute, No. 52 Fucheng Road, Haidian District, Beijing, 100142, People's Republic of China, Tel +86-13693564036, Email galaxyspark@163.com

**Background:** People in China have gradually entered old age society, and the number of lung cancer cases is expected to increase annually among the elderly. This study aimed to retrospectively explore the association between perioperative factors and short-term outcomes in elderly patients with non-small cell lung cancer (NSCLC).

**Methods:** A total of 490 elderly patients with NSCLC between January 1, 2003, and December 31, 2009, were selected. Perioperative factors were grouped and analyzed according to postoperative complications (PPCs) and length of hospital stay. A logistic regression analysis model was used to screen for the independent predictors of patient prognosis. The primary endpoint was postoperative complications and the secondary endpoint was postoperative hospital stay.

**Results:** Of all patients, 344 (70.2%) developed postoperative complications, and the average length of stay after surgery was 14.0 ±5.6 days. Perioperative fentanyl equivalents>28.7μg/kg and duration of surgery>4.4h were associated were associated with an increased risk of postoperative complications ($P < 0.05$); intraoperative blood loss (IBL) > 200 mL was associated with extended hospital stay ($P < 0.05$).

**Conclusion:** This study suggested that Perioperative factors may affect the short-term prognosis of elderly NSCLC patients after surgery. Perioperative fentanyl equivalents>28.7μg/kg, surgery duration, and IBL may be independent predictors of short-term outcomes in elderly patients.

**Keywords:** perioperative factor, NSCLC, outcome, opioid, the elderly

## Introduction

Lung cancer, with an estimated 2.2 million new cases and 1.8 million deaths, is the second most commonly diagnosed cancer and the leading cause of cancer-related deaths worldwide in 2020.[1] The incidence of lung cancer was 14.3% in men and 7.8% in women, and there were approximately 815,563 new cases of lung cancer and 714,699 deaths in 2020 in China, with lung cancer being the most frequently occurring cancer.[1,2] According to literature, lung cancer is a more prevalent malignancy in the elderly.[3] Currently, Chinese society is gradually aging. As the population ages, lung cancer cases in the elderly show an increasing trend, and the age of onset of lung cancer is approximately 60 years.[4] Therefore, lung cancer among elderly patients has become an increasingly common public health issue among oncologists.

Although lung cancer is categorized as small cell lung cancer and non-small cell lung cancer (NSCLC), NSCLC accounts for approximately 85% of all lung cancers, and surgical resection remains the single most consistent and successful cure for patients diagnosed with early stage of NSCLC regardless of age.[5] Nevertheless, all thoracic surgeons face challenges owing to the degraded physiological function, variety of comorbidities, and high risk of postoperative



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complications in the elderly.[6] Therefore, perioperative management seems particularly important to some extent. Prior research has shown that perioperative management has a significant impact on short-term patient outcomes. Several underlying risk factors have been previously examined. For example, the type of surgery, intraoperative blood transfusion, anesthesia procedure, etc., correlate with postoperative complications and length of hospital stay.[7] Also, our previous study revealed that perioperative anesthesia factors impact long-term survival and postoperative pulmonary complications in patients with NSCLC.[8] For further research, this study retrospectively analyzed the influence of perioperative factors on the short-term outcomes of elderly patients with NSCLC, aiming to identify the predictors that affect the postoperative short-term prognosis of the elderly and to provide evidence for the development of perioperative management strategies.

# Methods

## Patients

This study had a retrospective cohort design and was approved by the Clinical Research Ethics Committee of the Peking University Cancer Hospital (Approval No.2019YJZ22-GZ02). The study was conducted in accordance with the Declaration of Helsinki. The electronic medical records system of Peking University Cancer Hospital was employed to screen patients who underwent lung resection between January 1, 2003, and December 31, 2009. The eligibility criteria were as follows: (1) pathologically confirmed NSCLC; (2) underwent segmentectomy, lobectomy, or total pneumonectomy; and (3) over 60 years of age. The exclusion criteria were as follows: (1) presence of other primary malignant tumors, (2) recurrent lung tumors, and (3) no follow-up or missing data. Informed consent was obtained from all patients.

## Surgery and Anesthesia Methods

Double-lumen endotracheal intubation and contralateral lung ventilation were performed under general anesthesia. Anesthesia was induced with intravenous anesthetics (propofol and/or etomidate) and opioids (fentanyl or sufentanil), and maintained with inhalational anesthetics (sevoflurane or isoflurane) and opioids (fentanyl and/or sufentanil). Combined epidural-general anesthesia with local anesthetics (lidocaine and/or ropivacaine) was also administered according to the decision of the anesthesiologist. Segmentectomy, lobectomy, or total pneumonectomy were performed using standard posterolateral thoracotomy. Mediastinal lymph node dissection was performed on the basis of the tumor. After the surgery, a patient-controlled analgesia pump was provided for postoperative analgesia, which was performed using ropivacaine for epidural analgesia or opioids (morphine or sufentanil) for intravenous analgesia.

## Data Collection

The collected data included demographic characteristics (age, sex, height, and weight), preoperative information (comorbidity, American Society of Anesthesiologists classification, tumor location, lymph node metastasis according to imageological examination, and history of smoking), anesthesia-related information (anesthesia technique, anesthetic administration, intraoperative fluid infusion, perioperative total amount of fentanyl equivalents, perioperative glucocorticoids, and nonsteroidal anti-inflammatory drug administration), surgical information (surgical procedure, mediastinal lymph node dissection, duration of surgery, and intraoperative blood loss), and postoperative information (postoperative pulmonary complications, grade of tumor cell differentiation, and postoperative hospital stay). The fentanyl equivalent conversion was sufentanil 0.1ug, remifentanil 1ug, or 110ug morphine for 1ug fentanyl.

## Follow-Up and Endpoints

All patients were followed-up until the date of discharge. The primary endpoint was postoperative complications, defined as the composite outcome of postoperative pneumothorax, pleural effusion, atelectasis, pneumonia, and arrhythmia. All postoperative complications were diagnosed based on the Society of Thoracic Surgeons and European Society of Thoracic Surgeons joint definitions.[9] The secondary endpoint was postoperative hospital stay, defined as the length of hospital stay after surgery.

## Statistical Analysis

Continuous data with abnormal distributions were presented as median (interquartile range [IQR]) or mean (±SD). Categorical data are presented as number (%). Continuous variables were compared using the independent samples *t*-test or Mann–Whitney *U*-test. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test. Univariate statistical analysis was performed by dividing the cohort into two groups according to postoperative complications (with and without) or postoperative hospital stay (>14d and ≤14d). Only variables with a p-value < 0.1 in the univariate analysis, were used in the multivariable logistic regression analysis to identify the predictors of postoperative complications and extended hospital stay. Postoperative complications were compared based on the variables screened by multivariable logistic regression analysis. Odds ratios (ORs) were calculated from these models, together with their 95% CIs. For continuous variables, cutoff points between layers were chosen according to the receiver operating characteristic (ROC) analysis or mean values. The analysis was performed using IBM SPSS version 19. For all tests, a 2-tailed P-values < 0.05, was considered significant.

# Results

## Basic Information

Over a 7-year period, 502 patients aged > 60 years underwent lung resections. Twelve cases were excluded, of which seven cases were complicated with other primary malignant tumors and five cases had missing clinical data. A total of 490 patients were enrolled in this study. Of the 490 patients, 344 (70.2%) experienced one or more postoperative complications, and the mean postoperative hospital stay was 14.0 ± 5.6 days (Table 1 and Figure 1). No in-hospital death occurred in this cohort.

**Table 1** Baseline and Perioperative Data

| Variable | Mean(±SD), Median (IQR) or n (%) |
|---|---|
| Age (yr) | 67 (63, 71) |
| BMI (kg/m$^2$) | 23.9 (22.1, 25.6) |
| Gender | |
| Female | 160 (32.7%) |
| Male | 330 (67.3%) |
| Preoperative complications | |
| Coronary heart disease | 41 (8.4%) |
| Hypertension | 136 (27.8%) |
| Arrhythmia | 99 (20.2%) |
| Cardiac diastolic dysfunction | 51 (10.4%) |
| Diabetes | 52 (10.6%) |
| COPD | 27 (5.5%) |
| Smoking | 272 (55.5%) |
| ASA | |
| I | 97 (19.8%) |
| II | 360 (73.5%) |
| III | 32 (6.5%) |
| Lymph node metastasis | 186 (38.0%) |
| Anesthea | |
| General anesthesia | 311(63.5%) |
| Combined epidural-general anesthesia | 179 (36.5%) |
| Duration of surgery (h) | 4.4±1.2 |
| Total intraoperative fluid volume (mL) | 2250 (1750, 2750) |
| Intraoperative blood loss (mL) | 200 (100, 300) |
| Perioperative etomidate administration | 384 (78.4%) |
| Perioperative fentanyl equivalents (μg/kg) | 13.6 (0.3, 43.6) |

(*Continued*)

**Table 1** (Continued).

| Variable | Mean(±SD), Median (IQR) or n (%) |
|---|---|
| Perioperative NSAIDs administration | 185 (37.8%) |
| Perioperative glucocorticoids administration | 261 (53.3%) |
| Surgical procedure | |
| Segmentectomy or Wedge resection | 34 (6.9%) |
| Lobectomy | 455 (92.9%) |
| Total pneumonectomy | 1 (0.2%) |
| Mediastinal lymph node dissection | 434 (88.6%) |
| Tumor grade | |
| Undifferentiation | 60 (12.2%) |
| Poor differentiation | 75 (15.3%) |
| Moderate differentiation | 290 (59.2%) |
| High differentiation | 65 (13.3%) |
| Postoperative complications | 344 (70.2%) |
| Pneumothorax | 299 (61.0%) |
| Pleural effusion | 162 (33.1%) |
| Atelectasis | 7 (1.4%) |
| Pneumonia | 2 (0.4%) |
| Arrhythmia | 31 (6.3%) |
| Postoperative hospital stay (d) | 14.0±5.6 |

**Notes**: The results are presented as the mean ± standard deviation (SD), median (IQR), or number (%).

## Univariable Analysis for Postoperative Complications

Univariate analysis was conducted using the independent samples *t*-test or Mann–Whitney *U*-test and the chi-squared test. By comparing the two groups, four factors ($P < 0.10$) were screened: sex, anesthesia technique, perioperative fentanyl equivalents, and duration of surgery (Table 2).

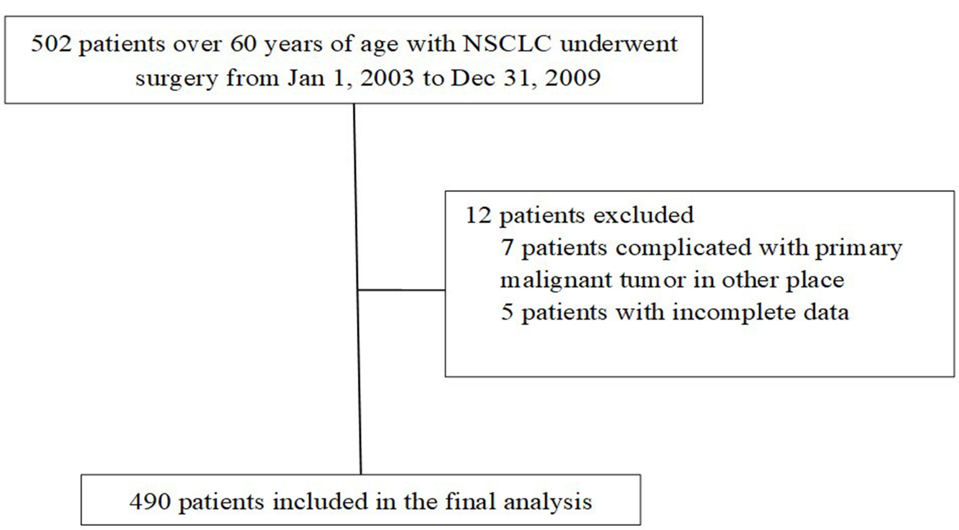


**Figure 1** Flow chart of this study.

**Table 2** Univariable Analysis for Postoperative Complications

| Variables | Postoperative Complications | | $t/Z/\chi^2$ | P value |
|---|---|---|---|---|
| | Yes (n = 344) | No (n = 146) | | |
| Age (yr) | | | 0.973 | 0.615 |
| ≤70 | 261(75.8%) | 106(72.6%) | | |
| 71–79 | 79(23%) | 39(26.7%) | | |
| ≥80 | 4(1.2%) | 1(0.7%) | | |
| Gender (male) | 223(64.8%) | 107(73.3%) | 3.338 | 0.068 |
| BMI (kg/m$^2$) | | | 3.106 | 0.376 |
| <18.5 | 13(3.8%) | 4(2.7%) | | |
| 18.5–24.9 | 218(63.4%) | 93(63.7%) | | |
| 25–27.9 | 78(22.7%) | 40(27.4%) | | |
| ≥28 | 35(10.2%) | 9(6.2%) | | |
| Preoperative complications | | | | |
| Coronary heart disease | 32(9.3%) | 9(6.2%) | 1.316 | 0.251 |
| Hypertension | 94(27.3%) | 42(28.8%) | 0.106 | 0.744 |
| Arrhythmia | 65(18.9%) | 34(23.3%) | 1.227 | 0.268 |
| Cardiac diastolic dysfunction | 36(10.5%) | 15(10.3%) | 0.004 | 0.949 |
| Diabetes | 38(11%) | 14(9.6%) | 0.230 | 0.632 |
| COPD | 22(6.4%) | 5(3.4%) | 1.737 | 0.187 |
| Smoking | 189(54.9%) | 155(45.1%) | 0.151 | 0.698 |
| ASA | | | 2.662 | 0.264 |
| I | 73(21.2%) | 25(17.1%) | | |
| II | 252(73.3%) | 108(74%) | | |
| III | 19(5.5%) | 13(8.9%) | | |
| Lymph node metastasis | 127(36.9%) | 59(40.4%) | 0.531 | 0.466 |
| Anesthesia technique | | | 6.750 | 0.009 |
| General anesthesia | 231(67.2%) | 80(54.8%) | | |
| Combined epidural-general anesthesia | 113(32.8%) | 66(45.2%) | | |
| Duration of surgery (h) | 4.5±1.2 | 4.2±1.1 | 3.325 | 0.001 |
| Total intraoperative fluid volume (mL) | 2250(1700, 2825) | 2100(1750, 2750) | 0.511 | 0.609 |
| Intraoperative blood loss (mL) | 200(100, 300) | 200(100, 300) | 1.271 | 0.204 |
| Perioperative etomidate administration | 78(22.7%) | 28(19.2%) | 0.739 | 0.390 |
| Perioperative fentanyl equivalents (µg/kg) | 29.3(0.3, 46.8) | 0.4(0.2, 31.2) | 5.081 | <0.001 |
| Perioperative NSAIDs administration | 132(38.4%) | 53(36.3%) | 0.187 | 0.665 |
| Perioperative glucocorticoids administration | 183(53.2%) | 78(53.4%) | 0.002 | 0.963 |
| Surgical procedure | | | 4.033 | 0.137 |
| Segmentectomy or Wedge resection | 19(5.5%) | 15(10.3%) | | |
| Lobectomy | 324(94.2%) | 131(89.7%) | | |
| Total pneumonectomy | 1(0.3%) | 0 | | |
| Mediastinal lymph node dissection | 301(87.5%) | 133(91.1%) | 1.242 | 0.265 |
| Tumor grade | | | 0.343 | 0.952 |
| Undifferentiation | 44(12.8%) | 16(11%) | | |
| Poor differentiation | 52(15.1%) | 23(15.8%) | | |
| Moderate differentiation | 203(59%) | 87(59.6%) | | |
| High differentiation | 45(13.1%) | 20(13.7%) | | |

**Notes**: The results are presented as the mean ± standard deviation (SD), median (IQR), or number (%). Statistical significance was set at $P < 0.05$.

## ROC Analysis for Perioperative Fentanyl Equivalents

ROC analysis for perioperative fentanyl equivalents showed an AUC of 0.645 (95% CI = 0.594–0.696; $P < 0.001$) for predicting postoperative complications (Figure 2). According to the ROC curve, the optimal cut-off value was 28.7μg/kg with maximum joint sensitivity (50.6%) and specificity (74.0%).

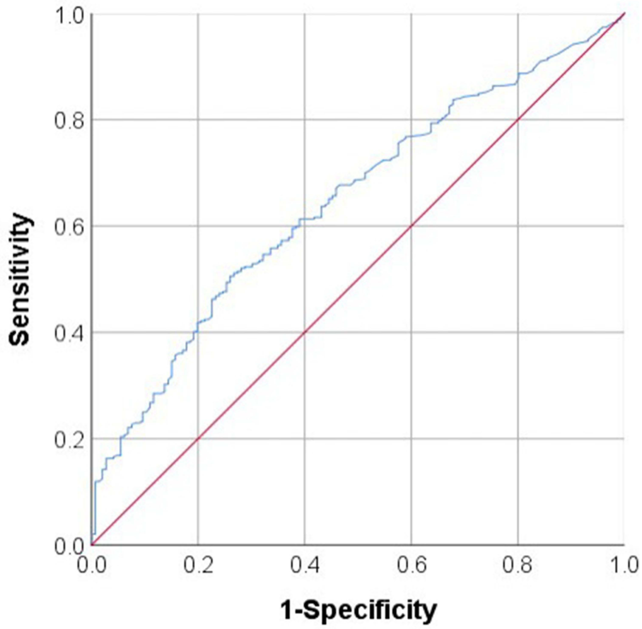


**Figure 2** Receiver operating characteristic analysis on perioperative fentanyl equivalents for prediction of postoperative complications. AUC = 0.645 (95% CI = 0.594–0.696; P<0.001).

## Multivariable Analysis for Postoperative Complications

The cutoff value of perioperative fentanyl equivalents was 28.7μg/kg according to the ROC curve, and the mean duration of surgery was 4.4 hours based on the mean. Four significant dichotomous variables were included in the multivariable logistic regression model, and perioperative fentanyl equivalents >28.7μg/kg (OR= 2.800, 95% CI:1.759–4.456, P < 0.001) and duration of surgery >4.4h (OR= 1.641, 95% CI:1.095–2.459, P= 0.016) were found to increase the risk of postoperative complications (Table 3).

## Impact of Perioperative Fentanyl Equivalents and Duration of Surgery on Postoperative Complications

Postoperative complications were compared based on perioperative fentanyl equivalents and duration of surgery screened by multivariable logistic regression analysis. The incidence of pneumothorax and pleural effusion in patients with perioperative fentanyl equivalents >28.7μg/kg was significantly higher than that in patients with perioperative fentanyl equivalents ≤28.7μg/kg (P < 0.01). There was a higher frequency of pneumothorax in patients with a duration of surgery >4.4h, compared than in patients with surgery duration of surgery≤4.4h (P < 0.05) (Table 4).

**Table 3** Multivariable Logistic Regression Analysis for Postoperative Complications

| Variables | OR (95% CI) | P value |
|---|---|---|
| Gender (male vs female) | 0.676(0.434–1.052) | 0.082 |
| Anesthesia technique (general anesthesia vs Combined epidural-general anesthesia) | 0.868(0.559–1.349) | 0.530 |
| Perioperative fentanyl equivalents (>28.7μg/kg vs ≤ 28.7μg/kg) | 2.800(1.759–4.456) | <0.001 |
| Duration of surgery (>4.4h vs ≤ 4.4h) | 1.641(1.095–2.459) | 0.016 |

**Note**: P<0 0.05 was considered statistically significant.
**Abbreviations**: OR, odds ratio; CI, confidence interval.

**Table 4** Impact of Perioperative Fentanyl Equivalents and Duration of Surgery on Postoperative Complications

| Complications | Perioperative Fentanyl Equivalents | | P value | Duration of Surgery | | P value |
|---|---|---|---|---|---|---|
| | >28.74μg/kg (n=212) | ≤28.74μg/kg (n=278) | | >4.4h (n=247) | ≤4.4h (n=243) | |
| Pneumothorax | 147(69.3%) | 152(54.7%) | 0.001 | 163(66%) | 136(56%) | 0.023 |
| Pleural effusion | 86(40.6%) | 76(27.3%) | 0.002 | 85(34.4%) | 77(31.7%) | 0.521 |
| Atelectasis | 3(1.4%) | 4(1.4%) | 0.982 | 3(1.2%) | 4(1.6%) | 0.687 |
| Pneumonia | 1(0.5%) | 1(0.4%) | 0.847 | 1(0.4%) | 1(0.4%) | 0.991 |
| Arrhythmia | 14(6.6%) | 17(6.1%) | 0.826 | 17(6.9%) | 14(6.6%) | 0.610 |

**Note**: P< 0 0.05 was considered statistically significant.

**Table 5** Univariable Analysis for Postoperative Hospital Stay

| Variables | Postoperative Hospital Stay (d) | | $t/Z/\chi^2$ | P value |
|---|---|---|---|---|
| | >14 (n = 164) | ≤14 (n = 326) | | |
| Age (yr) | | | 0.197 | 0.907 |
| ≤70 | 124(75.6%) | 243(74.5%) | | |
| 71–79 | 38(23.2%) | 80(24.5%) | | |
| ≥80 | 2(1.2%) | 3(0.9%) | | |
| Gender (male) | 116(70.7%) | 214(65.5%) | 1.284 | 0.257 |
| BMI (kg/m$^2$) | | | 3.316 | 0.345 |
| <18.5 | 8(4.9%) | 9(2.8%) | | |
| 18.5–24.9 | 97(59.1%) | 214(65.6%) | | |
| 25–27.9 | 41(25%) | 77(23.6%) | | |
| ≥28 | 18(11%) | 26(8%) | | |
| Preoperative complications | | | | |
| Coronary heart disease | 12(7.3%) | 29(8.9%) | 0.355 | 0.551 |
| Hypertension | 44(26.8%) | 92(28.2%) | 0.105 | 0.745 |
| Arrhythmia | 32(19.5%) | 67(20.6%) | 0.073 | 0.787 |
| Cardiac diastolic dysfunction | 13(7.9%) | 38(11.7%) | 0.004 | 0.949 |
| Diabetes | 17(10.4%) | 35(10.7%) | 1.628 | 0.202 |
| COPD | 11(6.7%) | 16(4.9%) | 0.678 | 0.410 |
| Smoking | 89(54.3%) | 183(56.1%) | 0.154 | 0.695 |
| ASA | | | 2.423 | 0.298 |
| I | 39(23.8%) | 59(18.1%) | | |
| II | 116(70.7%) | 244(74.8%) | | |
| III | 9(5.5%) | 23(7.1%) | | |
| Lymph node metastasis | 60(36.6%) | 126(38.7%) | 0.198 | 0.657 |
| Anesthesia technique | | | 6.588 | 0.010 |
| General anesthesia | 117(71.3%) | 194(59.5%) | | |
| Combined epidural-general anesthesia | 47(28.7%) | 132(40.5%) | | |
| Duration of surgery (h) | 4.6±1.2 | 4.3±1.1 | 2.921 | 0.004 |
| Total intraoperative fluid volume (mL) | 2250(1700, 2825) | 2100(1750, 2750) | 0.296 | 0.767 |
| Intraoperative blood loss (mL) | 200(100, 300) | 200(100, 300) | 1.655 | 0.098 |
| Perioperative etomidate administration | 36(22%) | 70(21.5%) | 0.015 | 0.903 |
| Perioperative fentanyl equivalents (μg/kg) | 29.3(0.3, 46.8) | 0.4(0.2, 31.2) | 2.481 | 0.013 |
| Perioperative NSAIDs administration | 63(38.4%) | 122(37.4%) | 0.046 | 0.831 |
| Perioperative glucocorticoids administration | 90(54.9%) | 171(52.5%) | 0.258 | 0.612 |
| Surgical procedure | | | 1.666 | 0.435 |
| Segmentectomy or wedge resection | 9(5.5%) | 25(7.7%) | | |
| Lobectomy | 155(94.5%) | 300(92%) | | |
| Total pneumectomy | 0 | 1(0.3%) | | |

(*Continued*)

**Table 5** (Continued).

| Variables | Postoperative Hospital Stay (d) | | t/Z/$\chi^2$ | P value |
|---|---|---|---|---|
| | >14 (n = 164) | ≤14 (n = 326) | | |
| Mediastinal lymph node dissection | 146(89%) | 288(88.3%) | 0.050 | 0.823 |
| Tumor grade | | | 1.198 | 0.753 |
| Undifferentiation | 18(11%) | 42(12.9%) | | |
| Poor differentiation | 27(16.5%) | 48(14.7%) | | |
| Moderate differentiation | 100(61%) | 190(58.3%) | | |
| High differentiation | 19(11.6%) | 46(14.1%) | | |

**Notes**: The results are presented as the mean ± standard deviation (SD), median (IQR), or number (%). Statistical significance was set at P < 0.05.

**Table 6** Multivariable Logistic Regression Analysis for Postoperative Hospital Stay

| Variables | OR (95% CI) | P value |
|---|---|---|
| Intraoperative blood loss (>200mL vs ≤200mL) | 1.551(1.032–2.331) | 0.035 |
| Anesthesia technique (general anesthesia vs Combined epidural-general anesthesia) | 0.670(0.429–1.046) | 0.078 |
| Perioperative fentanyl equivalents (>28.7μg/kg vs ≤28.7μg/kg) | 1.375(0.906–2.086) | 0.135 |
| Duration of surgery (>4.4h vs ≤4.4h) | 1.311(0.888–1.934) | 0.173 |

**Note**: P<0 0.05 was considered statistically significant.
**Abbreviations**: OR, odds ratio; CI, confidence interval.

## Univariable Analysis for Postoperative Hospital Stay

The univariate analysis method was the same as described above. The four factors (P < 0.10) identified by univariate analysis were intraoperative blood loss, anesthesia technique, perioperative fentanyl equivalents, and duration of surgery. Considering the correlation between perioperative fentanyl equivalents, the duration of surgery, postoperative complications, and postoperative complications were not included in the univariate analysis as possible risk factors for prolonged postoperative hospitalization (Table 5).

## Multivariable Analysis for Postoperative Hospital Stay

Four significant variables for postoperative hospital stay were included in the multivariable logistic regression model, and the analysis revealed that IBL > 200 mL (OR= 1.551, 95% CI:1.032–2.331, P = 0.035) was an independent predictor of postoperative hospital stay ≥14 days (Table 6).

# Discussion

With an aging society and increasing concerns about health, the number of elderly lung cancer cases is expected to rise in China. In the present study, risk factors for postoperative complications were analyzed in patients who underwent pulmonary resection for NSCLC. The frequency of postoperative complications in this cohort was 70.2%, which was higher than that reported in the literature.[10] A possible explanation is that there was a difference in the studied populations, because the subjects selected were older than 60 years in this study, and postoperative complications occurred more frequently in the elderly than in the young due to organ function decline.[11] Furthermore, the elderly patients in the present study were divided into three subgroups (≤70, 71–79, and≥80 years); however, there was no significant difference in the frequency of postoperative complications and postoperative hospital stay≥14 days between the subgroups in the univariable analysis. These findings suggest that age is not the sole determinant when considering surgery as a treatment option for lung cancer.[12]

The use of opioids is a routine procedure for analgesia during the perioperative period. Whether administered intravenously or neuraxially, perioperative opioids remain an important component of clinical management strategies in thoracic surgeries, and have been demonstrated to be safe in patients having thoracic surgery.[13] Synthetic opioid drugs commonly used in anesthesia, such as fentanyl, sufentanil, and remifentanil, have a high affinity for the μ receptor in the peripheral or central nervous system.[14] High μ receptor expression levels have been observed in human lung, prostate, and colon cancer tissues.[15] There is evidence that when opioids bind to the μ receptors on tumor tissues, neuroendocrine and inflammatory cascades are activated, resulting in an imbalance of the system towards immunosuppression through reduced macrophage and natural killer (NK) cell activity.[16]

In recent years, the impact of opioids on patient prognosis has become an increasing concern. Several studies have shown that opioids play a negative role in the long-term outcomes of lung cancer and have highlighted that opioids enhance tumor metastasis and recurrence by inhibiting cellular and humoral immune functions and stimulating angiogenesis.[17] However, to our knowledge, scientific research regarding the association between perioperative opioid administration and short-term prognosis of lung cancer after surgery has been rarely reported. In the present study, results showed perioperative fentanyl equivalents >28.7μg/kg (OR= 2.800, 95% CI:1.759–4.456, P<0.001) was an independent risk factor for postoperative complications. Similarly, in a retrospective cross-sectional analysis, Sayal et al found an increased risk of postoperative pulmonary complications associated with opioid use.[18] However, the mechanism of action of opioids in the pathogenesis of postoperative complications remains unclear. A possible explanation for this might be that opioids impair macrophages and natural killer cells, decrease the migration of macrophages and neutrophils, and exacerbate inflammatory responses in the lungs and pleural cavity, thereby promoting pneumonia and inflammatory exudation in the pleura.[19] Moreover, opioids may cause respiratory depression and reduced lung ventilation function, increasing the risk of pneumonia and atelectasis.[20]

In our study, increased perioperative opioid use was associated with postoperative pneumothorax and pleural effusion. We considered that the effect of opioids on other postoperative complications was not evident, owing to the small sample size. However, an increase in pleural effusion, partially resulting from opioid immunosuppression, may indirectly affect pleural healing, leading to persistent air leakage. Further studies are required to verify this hypothesis.

Given the high prevalence of opioids, their systemic administration is inevitable. One method is to combine regional or epidural anesthesia to reduce the use of systemic opioids.[21] Another approach to minimize adverse effects is to co-administer a peripheral opioid inhibitor such as naloxone, countering the effects of both exogenous and endogenous opioids.[22]

Surgery duration is another independent prognostic factor that should be considered. This study revealed that a surgery>4.4h (OR= 1.641, 95% CI:1.095–2.459, P= 0.016) might increase the risk of postoperative complications. Prior research has also demonstrated a relationship between prolonged surgery and increased risk of postoperative complications.[23] The duration of surgery depends on many factors, such as the status of the patient, surgical approach, surgeon skill level, and anesthesia management. Furthermore, pleural adhesions in the surgical field prolong the surgical time and increase the risk of postoperative air leak, pneumonia, and atelectasis.[24] On a separate front, prolonged surgery often causes an increased IBL and fluid overload. Excessive intraoperative infusion during pneumonectomy can easily increase the hydrostatic pressure of residual lung capillaries, reduce plasma colloid osmotic pressure, further precipitate pulmonary edema, affect gas exchange, and ultimately lead to postoperative pulmonary complications such as pneumonia, respiratory failure, and reintubation.[25] Moreover, during extended surgery, the distorted shape of the chest wall is prone to mismatch with the underlying lung, resulting in atelectasis, which is also closely related to other lung complications.[26] In this cohort, a prolonged duration of surgery was associated with postoperative pneumothorax. Patients with a surgery frequency of pneumothorax in patients with duration of surgery>4.4h ($P < 0.05$).

In the present study, findings suggested that IBL > 200 mL was associated with a postoperative hospital stay of ≥ 14 days. The mean postoperative hospital stay in our cohort was 14 days, which was chosen as the cutoff value for dividing the groups. A postoperative hospital stay ≥ 14 days meant delayed discharge, which would increase the cost of hospitalization and aggravate the economic burden on patients. Therefore, a larger IBL volume is a negative predictor of short-term prognosis.

Because the volume of IBL is, to some extent, indicative of the complexity of the operation, IBL can affect the outcome of the patient. However, evidence regarding IBL and short-term prognosis of lung cancer is limited. In general, it is reasonable to assume that IBL is likely to increase with tumor progression, because the difficulty of complete tumor resection depends on the degree of tumor invasion.[27] When greater IBL occurs, subsequent blood transfusions are inevitable. Nevertheless, as an IBL-related event, transfusion has been reported as a negative prognostic factor in patients.[28] Additionally, there are several reasons why a large IBL worsens the prognosis. First, a large IBL can lead to prolonged systemic hypoperfusion and impaired oxygen delivery to the vital organs.[7] Second, a large IBL loses a large amount of nutrients, such as red blood cells and albumin, damaging the nutritional status, which is very important for the recovery of patients.[29] Third, a large IBL volume induces infusion overload, which is detrimental to a patient's short-term prognosis.[25]

## Limitations

Our study had some limitations that should be considered. First, it was a single-center, retrospective study. Considering the relatively small sample size, the results of this study need to be interpreted with caution and verified in multicenter prospective randomized trials. Furthermore, other risk factors may have also been identified in a larger cohort. Second, intraoperative ventilator settings were not collected because of incomplete anesthesia records at that time. Studies have indicated that intraoperative ventilator parameter settings affect postoperative complications and recovery.[30]

## Conclusion

In summary, this study focused on the association between perioperative factors and short-term prognosis of patients with NSCLC after surgery. The findings indicated that increased use of opioids, prolonged duration of surgery, and increased IBL were not beneficial in lowering the frequency of postoperative complications or shortening the length of hospital stay. Based on these findings, it is possible to further optimize perioperative management strategies to achieve faster recovery in elderly patients undergoing lung resection.

## Data Sharing Statement

The study datasets are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

This study was approved by the Clinical Research Ethics Committee of the Peking University Cancer Hospital (Approval No.2019YJZ22-GZ02). Informed consent was obtained from all patients.

## Author Contributions

Wenzhi Zhu and Jiaonan Yang contributed equally and share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Wei C, Hongda C, Yiwen Y, Ni L, Wanqing C. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J*. 2021;134(7):783–791. doi:10.1097/CM9.0000000000001474
3. Dohun K, So Young K, Beomseok S, Jong Hyock P. Trend analysis for the choice and cost of lung cancer treatment in South Korea, 2003–2013. *Cancer Res Treat*. 2018;50(3):757–767. doi:10.4143/crt.2017.050

4. Qianqian Z, Zhehai W, Jun G, et al. Comparison of single-agent chemotherapy and targeted therapy to first-line treatment in patients aged 80 years and older with advanced non-small cell lung cancer. *Onco Targets Ther*. 2015;8:893–898. doi:10.2147/OTT.S81837
5. Blanco R, Maestu I, Torre MG, Cassinello A, Nuñez I. A review of the management of elderly patients with non-small-cell lung cancer. *Ann Oncol*. 2015;26(3):451–463. doi:10.1093/annonc/mdu268
6. Chen C, Kolbe J, Christmas T. Surgical treatment of non-small-cell lung cancer in octogenarians: a single-centre retrospective study. *Intern Med J*. 2021;51(4):596–599. doi:10.1111/imj.15268
7. Shuangjiang L, Kun Z, Yutian L, Cheng S, Yanming W, Guowei C. Estimated intraoperative blood loss correlates with postoperative cardiopulmonary complications and length of stay in patients undergoing video assisted thoracoscopic lung cancer lobectomy: a retrospective cohort study. *BMC Surg*. 2018;18(1):29. doi:10.1186/s12893-018-0360-0
8. Wenzhi Z, Shuang L, Xinqiang J, Hongyu T. Impact of anesthetic factors on prognosis of patients with non-small cell lung cancer after surgery. *J Thorac Dis*. 2023;15(9):4869–4884. doi:10.21037/jtd-22-1812
9. Seder CW, Salati M, Kozower BD, Cameron D, Pierre-Emmanuel F, Alessandro B. Variation in pulmonary resection practices between the society of thoracic surgeons and the European society of thoracic surgeons general thoracic surgery databases. *Ann Thorac Surg*. 2016;101(6):2077–2084. doi:10.1016/j.athoracsur.2015.12.073
10. Kim ES, Kim YT, Kang CH, et al. Prevalence of and risk factors for postoperative pulmonary complications after lung cancer surgery in patients with early-stage COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1317–1326. doi:10.2147/COPD.S105206
11. Nozomu M, Masahito I, Shun I, Aika Y, Yoshihito I, Hidetaka U. Analysis of risk factors for postoperative complications in non-small cell lung cancer: comparison with the Japanese National Clinical Database risk calculator. *BMC Surg*. 2022;22(1):180. doi:10.1186/s12893-022-01628-6
12. Guotian P, Shijie Z, Yi H, Zhidong L, Shaofa X. Risk factors for postoperative complications after lung resection for non-small cell lung cancer in elderly patients at a single institution in China. *J Thorac Dis*. 2014;6(9):1230–1238. doi:10.3978/j.issn.2072-1439.2014.07.23
13. Zhenzhen X, Huaijin L, Muhan L, et al. Epidural anesthesia–analgesia and recurrence-free survival after lung cancer surgery: a randomized trial. *Anesthesiology*. 2021;135(3):419–432. doi:10.1097/ALN.0000000000003873
14. Bugada D, Lorini LF, Lavand'homme P. Opioid free anesthesia: evidence for short and long-term outcome. *Minerva Anestesiol*. 2021;87 (2):230–237. doi:10.23736/S0375-9393.20.14515-2
15. Aich A, Gupta P, Gupta K. Could perioperative opioid use increase the risk of cancer progression and metastases? *Int Anesthesiol Clin*. 2016;54:1–16. doi:10.1097/AIA.0000000000000112
16. Zhou Y, Zhang H, Wang Q. Relationship between anesthesia and tumor: can the anesthesia affect the prognosis of the tumor? *Health Care Curr Rev*. 2017;5:184.
17. Gray K, Avitsian R, Kakumanu S, Lashmi V, Tumul C. The effects of anesthetics on glioma progression: a narrative review. *J Neurosurg Anesthesiol*. 2022;34(2):168–175. doi:10.1097/ANA.0000000000000718
18. Sayal P, Bateman BT, Menendez M, Eikermann M, Ladha K. Opioid use disorders and the risk of postoperative pulmonary complications. *Anesth Analg*. 2018;127:767–774. doi:10.1213/ANE.0000000000003307
19. Lo BD, Zhang GQ, Canner JK, et al. Preoperative opioid dose and surgical outcomes in colorectal surgery. *J Am Coll Surg*. 2022;234(4):428–435. doi:10.1097/XCS.0000000000000109
20. Menendez ME, Ring D, Bateman BT. Preoperative opioid misuse is associated with increased morbidity and mortality after elective orthopaedic surgery. *Clin Orthop Relat Res*. 2015;473:2402–2412. doi:10.1007/s11999-015-4173-5
21. Sertcakacilar G, Tire Y, Kelava M, et al. Regional anesthesia for thoracic surgery: a narrative review of indications and clinical considerations. *J Thorac Dis*. 2022;14(12):5012–5028. doi:10.21037/jtd-22-599
22. Chen P, Chen F, Lei J, Benhong Z. Physical compatibility and chemical stability of fentanyl and naloxone hydrochloride in 0.9% sodium chloride injection solution for patient-controlled analgesia administration. *Drug Des Devel Ther*. 2020;14:4179–4187. doi:10.2147/DDDT.S248209
23. Loeffelbein DJ, Julinek A, Wolff KD, Eberhard K, Bernhard H, Rainer H. Perioperative risk factors for postoperative pulmonary complications after major oral and maxillofacial surgery with microvascular reconstruction: a retrospective analysis of 648 cases. *I J Craniomaxillofac Surg*. 2016;44(8):952–957. doi:10.1016/j.jcms.2016.05.007
24. Shuangjiang L, Kun Z, Yanming W, et al. Presence of pleural adhesions can predict conversion to thoracotomy and postoperative surgical complications in patients undergoing video-assisted thoracoscopic lung cancer lobectomy. *J Thorac Dis*. 2018;10:416–431. doi:10.21037/jtd.2017.12.70
25. Shin CH, Long DR, McLean D, et al. Effects of intraoperative fluid management on postoperative outcomes: a Hospital Registry Study. *Ann Surg*. 2018;267:1084–1092. doi:10.1097/SLA.0000000000002220
26. Tusman G, Böhm SH, Warner DO, Sprung J. Atelectasis and perioperative pulmonary complications in high-risk patients. *Curr Opin Anaesthesiol*. 2012;25(1):1–10. doi:10.1097/ACO.0b013e32834dd1eb
27. Lijun Y, Weiwei W. Effect of intraoperative blood loss on postoperative pulmonary complications in patients undergoing video-assisted thoracoscopic surgery. *Turk Gogus Kalp Damar Cerrahisi Derg*. 2021;29(3):347–353. doi:10.5606/tgkdc.dergisi.2021.20657
28. Iqbal N, Haider K, Sundaram V, et al. Red blood cell transfusion and outcome in cancer. *Transfus Apher Sci*. 2017;56(3):287–290. doi:10.1016/j.transci.2017.05.014
29. Mizuno A, Kanda M, Kobayashi D, et al. Adverse effects of intraoperative blood loss on long-term outcomes after curative Gastrectomy of patients with stage II/III gastric Cancer. *Dig Surg*. 2016;33(2):121–128. doi:10.1159/000443219
30. Douville NJ, Jewell ES, Duggal N, et al. Association of intraoperative ventilator management with postoperative oxygenation, pulmonary complications, and mortality. *Anesth Analg*. 2020;130(1):165–175. doi:10.1213/ANE.0000000000004191