Original Article

Anesthetic predictors for postoperative pneumonia in patients with non-small cell lung cancer

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Background: Postoperative pneumonia (POP) is a preventable complication associated with adverse outcomes. The aim of this study is to explore the anesthetic predictor for POP in patients with non-small cell lung cancer (NSCLC) after surgery.

Methods: A total of 306 patients with NSCLC were selected. Multivariable logistic regression analysis model was used to screen the independent predictors for POP. The primary outcome was POP and the secondary outcomes were intensive care unit (ICU) admission rate, reintubation rate and postoperative hospital stay (PHS).

Results: POP occurred in 102 (33.3%) of 306 patients. Multivariable logistic regression analysis showed that perioperative propofol administration >4.42 mg/kg [odds ratio (OR) =0.543, 95% confidence interval (CI): 0.330–0.895, P=0.02] lowered the risk of POP, while duration of surgery >3 h (OR =1.951, 95% CI: 1.189–3.199, P=0.008) and total intraoperative fluid infusion >1,450 mL (OR =2.428, 95% CI: 1.307–4.509, P=0.005) were associated with the increasing risk of POP. There was a higher ICU admission and reintubation rate in the POP group (P<0.05).

Conclusions: Perioperative propofol administration >4.42 mg/kg may diminish the incidence of POP, while duration of surgery >3 h and intraoperative fluid infusion >1,450 mL increase the development of POP.

Keywords: Anesthetic predictor; postoperative pneumonia (POP); lung cancer

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Introduction

Despite advances in understanding the risk, development, and treatment options for lung cancer, it is still the leading cause of cancer-related death and the second most diagnosed cancer in the United States (1). Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancers, and surgical intervention remains the mainstay of curative treatment option for patients with NSCLC (2). However, the patients undergoing lung cancer surgery are high risk group for pulmonary complications. Among them, the reported incidence of postoperative pneumonia

(POP) after surgery ranged from 2.1% to 40%, with differences among studies attributed to the heterogeneity of the population, the type of surgery, and differences in the definition of POP (3). POP is a preventable complication associated with adverse outcomes including prolonged hospital stay, increased intensive care unit (ICU) occupancy rate as well as reoperation rate, which greatly aggravate the burden of medical expenses of patients (4). To date, there is very limited data available regarding determination of anesthetic factors associated with POP in patients with lung cancer after surgery. In the current study, we retrospectively investigated the potential anesthetic predictors for POP in NSCLC patients after surgery for the purpose of providing clinical evidences for the improvement of perioperative anesthesia strategies and facilitating the recovery of patients. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-107/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The retrospective study was approved by the Institutional Review Board of Peking University Cancer Hospital & Institute, Beijing (approval No. 2019YJZ22-GZ02) and informed consent was waived owing to the retrospective nature of the study. The electronic medical records system of Peking University Cancer Hospital was employed to screen patients who underwent lung resection between January 1, 2019, and May 31, 2019. The inclusion criteria were: (I) pathological diagnosis of NSCLC; (II) patients who underwent segmentectomy, lobectomy or total pneumonectomy; (III) age ≥18 years old. The exclusion criteria were: (I) combined with other primary malignant tumors; (II) recurrent lung tumors; (III) pre-existing chronic respiratory infections before surgery; (IV) no follow-up data or data missing.

Highlight box

Key findings

- Perioperative propofol administration >4.42 mg/kg may diminish the incidence of postoperative pneumonia (POP), while duration of surgery >3 h and intraoperative fluid infusion >1,450 mL increase the development of POP.

What is known and what is new?

- Perioperative factors may affect the short-term prognosis of patients with lung cancer.
- Perioperative propofol administration may diminish the incidence of POP.

What is the implication, and what should change now?

- Anesthetic factors have influence on POP in patients with non-small cell lung cancer. To a certain extent, increasing the use of propofol, shortening the operation time and reducing the amount of fluid infusion are beneficial to improve the short-term prognosis of patients with lung cancer.

Surgery and anesthesia methods

Double-lumen endotracheal intubation and the contralateral lung ventilation were established under general anesthesia. During the one-lung ventilation (OLV), the ventilator was set at a tidal volume of 6 mL/kg, a positive end-expiratory pressure of 5 cmH_2O, an inspiratory-to-expiratory ratio of 1:1.5, FiO_2 of 100%, and a respiratory rate of 12–15/min. Induction was performed with propofol, opioids (fentanyl or sufentanil) and cisatracurium. Anesthesia was maintained with opioids (fentanyl, remifentanil or sufentanil) cisatracurium, inhalational anesthetics (1–2% sevoflurane) or intravenous combined inhalational anesthetics (propofol 2–3 mg/kg/h + 1–2% sevoflurane). Segmentectomy, lobectomy or total pneumonectomy were done through a standard thoracoscopic surgery. Mediastinal lymph node dissection was conducted according to the locations of tumor. During surgery, the depth of sedation was monitored by the Bispectral Index (BIS) and the value of BIS was maintained at 40–60. After operation, patient-controlled analgesia pump was provided for postoperative analgesia, which was performed with opioids (morphine or sufentanil) for intravenous analgesia. Routine postoperative examinations included complete blood count and chest X-ray 24 hours after the surgery. When infectious symptoms appeared, checked blood count and chest X-ray daily.

Data collection

Data collected included demographic characteristics (age, gender, height and weight), preoperative information [comorbidity, American Society of Anesthesiologists (ASA) classification, tumor location, lymph node metastasis according to imageological examination, and former

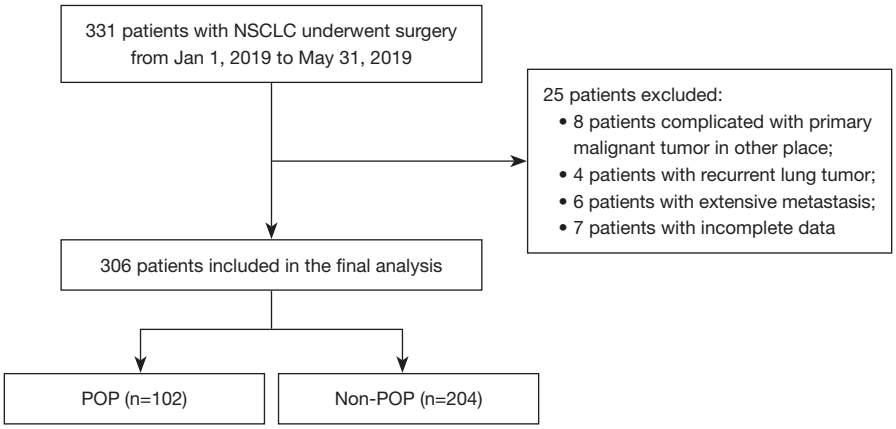

Figure 1 Flow chart of this study. NSCLC, non-small cell lung cancer; POP, postoperative pneumonia.

history of smoking], anesthesia-related information (anesthesia technique, anesthetics administration, intraoperative fluid infusion, perioperative total amount of fentanyl equivalents, perioperative glucocorticoids, and nonsteroidal anti-inflammatory drugs administration), surgical information (surgical procedure, mediastinal lymph node dissection, duration of surgery, intraoperative blood loss), and postoperative information [POP, pathological type, ICU admission rate, reintubation rate and postoperative hospital stay (PHS)]. The fentanyl equivalents conversion was sufentanil 0.1 μg or remifentanil 1 μg for 1ug fentanyl.

Follow-up and outcomes

All patients were followed up until the date of discharge. The primary outcome was POP and the secondary outcomes were ICU admission rate, reintubation rate and PHS.

The POP occurred within 30 days after surgery was defined as: (I) abnormal radiographic findings (new or changing radiographic infiltrates that persisted after physiotherapy or bronchoaspiration); (II) fever >38 ℃; (III) one of the following criteria: white blood cell (WBC) count over the last 24 h (with WBC $>12\times10^9$/L), an increase and modification of the expectorate possibly with purulence and positive sputum samples, or positive blood cultures (5).

PHS was defined as the duration between the date of discharge and the date of surgery.

Statistical analysis

Data were presented as median [interquartile range (IQR)], numbers (%). Continuous variables were compared with the independent samples Mann-Whitney *U* test. Categorical variables were analyzed with the Pearson's chi-squared test or continuity corrected Chi-squared test. Univariable analysis was performed by dividing the cohort into two groups according to POP (with and without) and multivariable logistic regression analysis model was used to identify the independent predictors for POP. A P value <0.10 by univariable analysis was chosen as the criterion for submitting variables to the multivariable logistic regression analysis model to determine the final predictors for POP. Odds ratios (ORs) were calculated from these models, together with their 95% confidence intervals (CIs). The optional cutoff values were chosen according to the receiver operating characteristic (ROC) analysis, median or literature (6). All statistical analyses were performed using IBM Statistics SPSS Version 19. A two-tailed P value of <0.05 was considered significant.

Results

Basic information

There were 331 patients who underwent lung resection from January 1, 2019 to May 31, 2019. A total of 25 cases were excluded, including 8 cases with other primary malignant tumors, 4 cases with recurrent lung tumors, 6 cases with extensive metastasis, and 7 cases with missing clinical data. Finally, 306 patients were enrolled in the study (*Figure 1*). According to the diagnostic criteria, 102 (33.3%) patients experienced POP (*Tables 1*,*2*). There was no in-hospital death in this study.

Table 1 Baseline and perioperative data

Variables	Values
Age (years)	61 [54, 67]
BMI (kg/m^2)	24.6 [22.6, 26.5]
Gender	
Female	189 (61.8)
Male	117 (38.2)
Preoperative complication	
Coronary heart disease	12 (3.9)
Hypertension	93 (30.4)
Diabetes	35 (11.4)
Renal dysfunction	7 (2.3)
Liver dysfunction	22 (7.2)
Chronic pulmonary disease[†]	38 (12.4)
Smoking	102 (33.3)
ASA	
I	21 (6.9)
II	278 (90.8)
III	7 (2.3)
Pathological type	
Adenocarcinoma	258 (84.3)
Non-adenocarcinoma	48 (15.7)
Lymph node metastasis	48 (15.7)
Anesthesia technique	
Inhalation anesthesia	76 (24.8)
Intravenous-inhalation anesthesia	230 (75.2)
Duration of surgery (min)	167 [124, 208]
Total intraoperative fluid volume (mL)	1,700 [1,387, 2,100]
Intraoperative blood loss (mL)	50 [30, 100]
Perioperative propofol administration (mg/kg)	4.42 [2.93, 10.54]
Perioperative etomidate administration (mg)	20 [12, 20]
Perioperative fentanyl equivalents (μg/kg)	19.44 [8.8, 32.82]
Perioperative NSAIDs administration	139 (45.4)
Perioperative glucocorticoids administration	202 (66.0)
Surgical procedure	
Segmentectomy	94 (30.7)
Lobectomy	206 (67.3)
Total pneumonectomy	6 (2.0)
Mediastinal lymph node dissection	227 (74.2)
POP	102 (33.3)

Data are presented as median [IQR] or n (%). [†], chronic pulmonary disease included chronic obstructive lung disease, asthma, bronchiectasis, and interstitial lung disease. ASA, American Society of Anesthesiologists; BMI, body mass index; NSAIDs, non-steroid anti-inflammatory drugs; IQR, interquartile range; POP, postoperative pneumonia.

Table 2 Postoperative pneumonia criteria data

Variables	Values
Radiographic infiltration	135 (44.1)
Fever (>38 ℃)	102 (33.3)
White blood cell >12×10^9/L	105 (34.3)
Positive sputum/blood cultures	4 (1.3)
Purulence	6 (2.0)

Data are presented as n (%).

Univariable analysis for POP

Univariable analysis was performed by the independent samples Mann-Whitney *U* test and Chi-squared test. Four potential factors (P<0.10) were screened for comparison between the two groups, including perioperative propofol administration, duration of surgery, anesthetic technique, and total intraoperative fluid infusion (*Table 3*).

ROC analysis for intraoperative fluid infusion

The ROC analysis for total intraoperative fluid infusion showed AUC of 0.569 (95% CI: 0.503–0.634; P<0.05) to predict POP. According to the ROC curve, the optimal cutoff value was 1,450 mL with the maximum joint sensitivity (83.3%) and specificity (30.4%) (*Figure 2*).

Multivariable analysis for POP

Multivariable logistic regression analysis showed that perioperative propofol administration >4.42 mg/kg (OR =0.543, 95% CI: 0.330–0.895, P=0.02) lowered the risk of POP, while duration of surgery >3 h (OR =1.951, 95% CI: 1.189–3.199, P=0.008) and total intraoperative fluid infusion

Table 3 Univariable analysis for postoperative pneumonia

Variables	Postoperative pneumonia		Z/χ^2	P value
	Yes (n=102)	No (n=204)		
Age (years)	62 [53, 68]	61 [54, 67]	0.110	0.91
Gender (male)	38 (37.3)	79 (38.7)	0.062	0.80
BMI (kg/m^2)	24.72 [22.79, 26.84]	24.61 [22.51, 26.36]	0.629	0.53
Preoperative complications				
Coronary heart disease	3 (2.9)	9 (4.4)	0.098	0.76
Hypertension	29 (28.4)	64 (31.4)	0.225	0.64
Diabetes	10 (9.8)	25 (12.3)	0.368	0.54
Renal dysfunction	3 (2.9)	4 (2.0)	0.018	0.89
Liver dysfunction	5 (4.9)	17 (8.3)	1.200	0.27
Chronic pulmonary disease[†]	15 (14.7)	23 (11.3)	0.736	0.39
Smoking	33 (32.4)	69 (33.8)	0.066	0.80
ASA			0.314	0.85
I	6 (5.9)	15 (7.4)		
II	94 (92.2)	184 (90.2)		
III	2 (2.0)	5 (2.5)		
Pathological type			1.001	0.32
Adenocarcinoma	83 (81.4)	175 (85.8)		
Non-adenocarcinoma	19 (18.6)	29 (14.2)		
Lymph node metastasis	16 (15.7)	32 (15.7)	0.000	>0.99
Anesthesia technique			4.630	0.03
Inhalation anesthesia	33 (32.4)	43 (21.1)		
Intravenous-inhalation anesthesia	69 (67.6)	161 (78.9)		
Duration of surgery (min)	184 [155, 220]	157 [119, 203]	3.759	<0.001
Total intraoperative fluid volume (mL)	1,800 [1,500, 2,200]	1,600 [1,300, 2,087]	1.965	0.049
Intraoperative blood loss (mL)	50 [25, 75]	50 [30, 100]	0.584	0.56
Perioperative propofol administration (mg/kg)	3.95 [2.68, 9.40]	4.94 [2.95, 10.73]	1.656	0.10
Perioperative etomidate administration (mg)	20 [14, 20]	20 [12, 20]	0.022	0.98
Perioperative fentanyl equivalents (μg/kg)	18.95 [8.89, 31.61]	19.72 [8.53, 32.84]	0.475	0.65
Perioperative NSAIDs administration	50 (49.0)	89 (43.6)	0.798	0.37
Perioperative glucocorticoids administration	71 (69.6)	131 (64.2)	0.881	0.35
Surgical procedure			0.194	0.91
Segmentectomy	33 (32.4)	61 (29.9)		
Lobectomy	67 (65.7)	139 (68.1)		
Total pneumonectomy	2 (2.0)	4 (2.0)		
Mediastinal lymph node dissection	72 (70.6)	155 (76.0)	1.032	0.31

Data are presented as median [IQR] or n (%). Statistical significance was set at P<0.05. [†], chronic pulmonary disease included chronic obstructive lung disease, asthma, bronchiectasis, and interstitial lung disease. ASA, American Society of Anesthesiologists; BMI, body mass index; NSAIDs, non-steroid anti-inflammatory drugs; IQR, interquartile range.

>1,450 mL (OR =2.428, 95% CI: 1.307–4.509, P=0.005) were associated with the increasing risk of POP (*Table 4*).

Clinical outcome for POP

In the POP group, the rate of ICU admission was higher than that in the non-POP group (P<0.05). There was no significant difference in PHS between the two group (P>0.05) (*Table 5*).

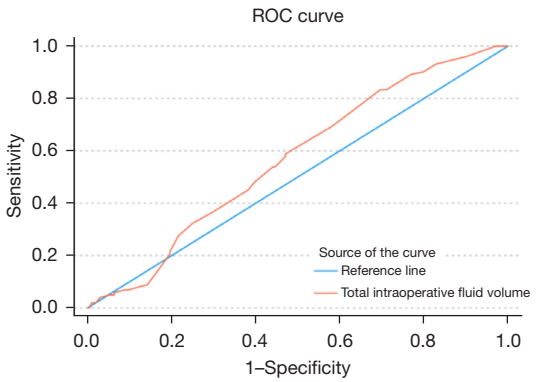

Figure 2 This curve showed ROC analysis on total intraoperative fluid volume for prediction of POP. AUC =0.569 (95% CI: 0.503–0.634; P<0.05). ROC, receiver operating characteristic; POP, postoperative pneumonia; AUC, area under the curve; CI, confidence interval.

Discussion

Of all the 306 patients in this cohort, 102 cases developed POP, with an incidence of 33.3%, which was similar to that reported in the past (7). POP is one of the most frequently observed complications following lung surgery and contributes to worse outcomes and high resource usage. Although the systemic inflammatory response mainly depends on the invasiveness of the surgical procedure, several studies have reported perioperative management has impact on the development of POP, including advanced age, greater American Society of Anesthesiologists (ASA) physical status, high intraoperative blood loss, and so on (8,9). Thus, in terms of making clinical strategies, it is important to identify predictors of POP in patients with NSCLC.

General anesthesia is an indispensable part in most operations for lung cancer and considered as a prognostic factor for POP in prior literatures (10). The possible explanations are mainly involved with the aspiration caused by the increased gastric pressure in the pre-oxygenation stage, the contamination secondary to intubation, and the injury of lung tissue induced by mechanical ventilation (11). Besides, some anesthetic factors also play roles in the development of POP such as nerve block procedure and opioids (12). Of note, anesthesia technique and perioperative fentanyl equivalents were not shown to be

Table 4 Multivariable analysis for postoperative pneumonia

Variables	OR (95% CI)	P value
Anesthesia technique (intravenous-inhalation anesthesia *vs.* inhalation anesthesia)	0.683 (0.367–1.272)	0.23
Total intraoperative fluid volume (>1,450 *vs.* ≤1,450 mL)	2.428 (1.307–4.509)	0.005
Duration of surgery (>3 *vs.* ≤3 h)	1.951 (1.189–3.199)	0.008
Perioperative propofol administration (>4.42 *vs.* ≤4.42 mg/kg)	0.543 (0.330–0.895)	0.02

P<0.05 was considered statistically significant. OR, odds ratio; CI, confidence interval.

Table 5 Clinical outcomes

Outcomes	Postoperative pneumonia		Z/χ^2	P value
	Yes (n=102)	No (n=204)		
ICU admission	20 (19.6)	4 (2.0)	26.907	<0.001
Reintubation	11 (10.8)	3 (1.5)	11.462	0.001
PHS (d)	5 [4, 7]	5 [4, 7]	0.543	0.59

The results are presented as median [IQR] or n (%). Statistical significance was set at P<0.05. ICU, intensive care unit; PHS, postoperative hospital stay; IQR, interquartile range.

potential predictors of POP in this study (P>0.05), perhaps due to the small sample size, and further experimental confirmation is needed.

However, perioperative propofol administration is a previously less-mentioned factor associated with POP. This study also found that the intraoperative dosage of propofol was closely associated with POP after lung resection, and perioperative propofol administration >4.42 mg/kg (OR =0.543, 95% CI: 0.330–0.895, P=0.02) significantly decreased the risk of POP. Propofol is a main intravenous anesthetic agent and has inflammatory-modulating effects (13). A randomized controlled trial by Wakabayashi *et al*. revealed that propofol can reduce inflammatory responses in lipopolysaccharide (LPS)-induced alveolar type II cell injury through the downregulation of CD14, and potently suppress the surgical stress-induced inflammatory perturbation at the local milieu of the airway (14). Likely, Hsiao *et al*. found propofol exhibited anti-inflammatory and anti-oxidant actions during mechanical ventilation, thus preventing apoptosis of alveolar cells (15). In this context, perioperative propofol administration >4.42 mg/kg represented continuous infusion of propofol and a choice of intravenous-inhalation anesthesia, and also indicated that propofol was more protective than sevoflurane during surgical stress in some sense. Nevertheless, both sevoflurane and propofol have shown anti-inflammatory effects in previous researches (16). So far, it remains unclear whether sevoflurane or propofol exerts a stronger inhibition effect on inflammatory response (17,18).

The finding of this study showed duration of surgery >3 h was another risk predictor for the development of POP. Duration of surgery is referred to the time of incision until the end of surgery, which is closely associated with the duration of mechanical ventilation. Prolonged surgery time means longer duration of mechanical ventilation and OLV so that patients are more susceptible to the infection of bacteria, which originally exists in secretions from the upper respiratory tract and enters the distal end of the trachea (19). Meanwhile, with the prolonged operation time, inappropriate fluid management increases the risk of pulmonary edema, which furthers the development of pneumonia (20). Furthermore, prolonged surgery time usually causes an increase in blood loss, and leads to the loss of immune cells and albumin (21). A previous study has demonstrated that the incidence of POP was 40% for surgical procedures lasting more than 3–4 h (22). In another retrospective study of 585 patients, the observations also suggested that the risk of postoperative respiratory infection increased significantly with prolonged surgery time (23). As a result, in high-risk patients, it is wiser for surgeons to choose a less ambitious and brief procedure.

The other independent risk factors for POP identified in this study were total intraoperative fluid infusion. Total intraoperative fluid infusion >1,450 mL was associated with the increasing risk of POP. Intraoperative fluid infusion has been studied to determine the effects on postoperative pulmonary complications (PPCs) in previous studies (24-26). Fluid overload can precipitate pulmonary edema and impair gas exchange, leading to postoperative pulmonary complications such as pneumonia, respiratory failure, and reintubation (27). A study by Arslantas *et al.* showed that the occurrence of PPCs was seen more frequently if the intraoperative infusion rate of fluids exceeded 6 mL/kg/h (28). Moreover, Hikasa *et al.* found Intraoperative fluid dosing at the liberal and restrictive margins of observed practice was also associated with increased PPCs (29). Although the aforementioned studies presented that a larger amount of fluid infusion was a risk factor of PPCs, there was few researches addressing the link between fluid infusion and POP, and well-designed randomized control trials are necessary to investigate on this.

As far as clinical outcomes are concerned, ICU admission and reintubation rate were higher in POP group compared with non-POP group. ICU admission for patients who are at high risk of subsequently requiring physiological support is considered a standard of care in many healthcare systems (30). However, ICU beds are costly and of limited resource. ICU admission and reintubation will greatly increase the economic burden of patients. Notably, in present study, there were no significant difference in PHS between the POP and non-POP group, which may attribute to proper antibiotics administration for infection control and timely physiological support therapy for recovery of patients.

Limitations

This study has several limitations. Firstly, as a retrospective cohort, experimental results need to be interpreted with caution, and prospective trials are needed to confirm the findings. Secondly, given single-institute study with a small sample size, there were biases in patient selection. Thirdly, prior research has found forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <0.7 is a risk factor for POP in pneumonectomy (31). Due to incomplete

pulmonary function tests in this cohort, pulmonary function data were lacking in this study. Additionally, the total dose of sevoflurane administered was also lacking, which might lead to confounding biases. Finally, the study did not investigate the long-term survival of patients with POP.

Conclusions

Taken together, the results of this study suggested that anesthetic factors have influence on POP in patients with NSCLC. Perioperative propofol administration >4.42 mg/kg, duration of surgery ≤3 h and total intraoperative fluid infusion <1,450 mL may decrease the incidence of POP and benefit the short-term prognosis of patients. It is obvious that the real value of research is in improving the quality of life of patients and helping clinical staffs generalize the findings to surgical procedures.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-107/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-107/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-107/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-107/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The retrospective study was approved by the Institutional Review Board of Peking University Cancer Hospital & Institute, Beijing (approval No. 2019YJZ22-GZ02) and informed consent was waived owing to the retrospective nature of the study.

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