Original Article

Risk factors for postoperative pulmonary complications in non-adenocarcinoma non-small cell lung cancer patients undergoing surgery after neoadjuvant therapy

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Background: Neoadjuvant therapy followed by surgery is the recommended treatment for patients with locally advanced lung cancer. No studies have examined the risk factors of postoperative pulmonary complications (PPCs) in this group of patients. The addition of immune checkpoint inhibitors (ICIs) can improve the efficacy of neoadjuvant therapy; however, it is unknown whether ICIs will also increase the PPC incidence. Thus, we conducted this study to identify the predictors of PPCs.

Methods: We reviewed the database of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University. Patients with non-adenocarcinoma non-small cell lung cancer (non-ADC NSCLC) who underwent surgery after neoadjuvant therapy were included. The clinical information was collected, the PPCs and mortality were evaluated.

Results: The cohort in this study consisted of 108 patients. Among them, 36 had PPCs, and the incidence of PPCs was 33.3% (36/108). The majority of PPCs were prolonged time to chest tube removal and pneumonia. One patient died within 30 days due to serious postoperative complications. The mortality within 30 days was 0.9%. The addition of ICIs to neoadjuvant therapy did not increase the incidence of PPCs, but the operation time was longer in the ICI group. Multivariate analysis indicated that age, blood urea nitrogen (BUN) level and N2 stage may be superior predictors of PPCs.

Conclusions: The addition of ICIs did not increase the incidence of PPCs but did prolong the operation time. Age, BUN level, and N2 stage were excellent predictors of PPCs in non-ADC NSCLC patients treated with surgery after neoadjuvant therapy.

Keywords: Risk factor; postoperative pulmonary complications (PPCs); neoadjuvant therapy; immunochemotherapy

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and in China (1,2). Surgery is the principal treatment for early-stage or locally advanced lung cancers (3). The reported perioperative mortality is about 4.4%, while the postoperative pulmonary complication (PPC) rate ranges from 20% to 40% (4,5). Numerous risk factors have been reported to increase the risk of PPCs, including impaired pulmonary function, a high inflammation index, and poor immunonutritional status (6-8). Cancer is closely related with inflammation, while cytokines become activated and increase in expression in the process of tumor development. Inflammatory cells are gathered by cytokines (9,10), and cancer cells alter the patient's metabolism and grow rapidly by redirecting nutrients from normal cells. It was previously reported that weight loss and low albumin level are associated with the occurrence of PPCs after lung cancer resection (11).

However, most of the related studies have focused on the patients who received surgery as the initial treatment. For patients with locally advanced lung cancer, neoadjuvant therapy followed by surgery is the recommended treatment. Neoadjuvant therapy includes chemotherapy and immunochemotherapy, with immunochemotherapy demonstrating better performance in the downstaging of locally advanced disease (12-14). During neoadjuvant therapy, patients may experience anemia, hepatic dysfunction, immune-checkpoint inhibitor (ICI)-related pneumonia, etc. The related perioperative mortality and PPCs has not be extensively reported, and whether immunochemotherapy increases the incidence of PPCs remains unclear.

In this study, we reviewed a cohort of patients with locally advanced lung cancer who received neoadjuvant therapy and operation in Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, to address two questions: weather the addition of ICIs to neoadjuvant therapy increases the PPCs and find the risk factors of perioperative mortality and PPCs. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-25/rc).

Highlight box

Key findings

- The addition of immune checkpoint inhibitors in neoadjuvant therapy did not increase the incidence of postoperative pulmonary complications (PPCs) but did prolong the operation time.
- Older age, N2 stage and lower blood urea nitrogen level were excellent predictors for PPCs in patients treated with surgery after neoadjuvant therapy.

What is known and what is new?

- Previous studies have not examined outcomes of patients with locally advanced lung cancer who received operation after neoadjuvant therapy.
- In this study, we examined whether the addition of immune checkpoint inhibitors in neoadjuvant therapy would increase PPCs. We further analyzed the risk factors of PPCs in patients with locally advanced lung cancer who received operation after neoadjuvant therapy.

What is the implication, and what should change now?

- The addition of immune checkpoint inhibitors in neoadjuvant therapy did not increase the PPCs. Newly identified risk factors could predict PPC occurrence in this group of patients and may be a useful tool in clinical practice.

Methods

Patient selection

In this single-center, retrospective, cohort study, we searched the database of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, for patients who underwent lung cancer resection between 2020 and 2021. The study was conducted according to the principles outlined in the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (No. 20251008). All patients signed the informed consent form before participating in the study.

The inclusion criteria were as follows: (I) completion of lung cancer resection at Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University; (II) neoadjuvant therapy administered before surgery, including chemotherapy or immunochemotherapy; (III) most squamous and large cell lung cancer are central lung cancer, which required for neoadjuvant therapy. Thus in our study, only non-adenocarcinoma non-small cell lung cancer (non-ADC NSCLC) patients enrolled; and (IV) physical and laboratory examinations performed within 1 week before surgery. Meanwhile, the exclusion criteria were as follows: (I) incomplete clinical data for analyze; and (II) administration of epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitors (TKIs) as neoadjuvant therapy. In our central, neoadjuvant therapy was applied for most potentially resectable local-advanced

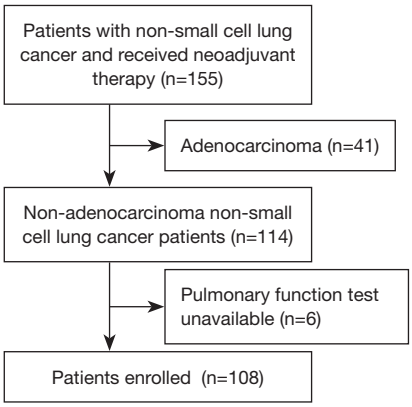

Figure 1 The flow chart of patient selection.

NSCLC. Basic demographic and clinical information were collected, including age, sex, physical and laboratory examination results, comorbidities, surgery type, pathologic diagnosis, PPCs, and mortality within 30 days. The stage of tumor was based on imaging examination, including enhanced computer tomography (CT) scan, positron emission tomography-CT (PET-CT).

Surgical procedures

Seven surgeons and their teams performed all operations with standard operative and perioperative procedures. Enhanced recovery was conducted for all patients after surgery (15). The enhanced recovery included health education, smoking cessation, pulmonary rehabilitation, comorbidity management, nutrition support, and prevention of deep venous thrombosis. Patients were administered prophylactic antibiotics for 2–3 days after surgery.

Evaluation of PPCs

PPCs within 30 days after lung cancer resection were defined as follows: (I) pneumonia (16); (II) atelectasis; (III) long-term mechanical ventilation due to postoperative respiratory failure (mechanical ventilation time >48 hours); (IV) secondary tracheal intubation; (V) persistent air leakage or pleural effusion requiring long-term drainage (>7 days); (VI) bronchopleural fistula; (VII) pulmonary embolism; and (VIII) other pulmonary complications (17,18).

Statistical analysis

We used SPSS 20.0 software (IBM, Armonk, NY, USA) for statistical analyses. Categorical variables were presented as frequency (percentage). Continuous variables following a normal distribution were presented as mean ± standard deviation, whereas those not conforming to a normal distribution were delineated by median and range. Differences between groups were evaluated via one-way analysis of variance and with the *t*-test. Categorical variables were analyzed with the Pearson Chi-squared test and the Fisher exact probability test. Differences were considered statistically significant for P values <0.05.

Results

Of the 108 patients with non-ADC NSCLC included in this study (*Figure 1*), most were male (92.6%), and diagnosed to squamous cell lung cancer (90.7%). More than half of the patients (64.8%) had abnormal pulmonary ventilation function. The mean number of cycles of neoadjuvant chemotherapy was 2.33±0.79. For this is a retrospective study, the type of induction chemotherapy and immunotherapy varied based on the physicians' preferences and patients' financial situation. All patients received platinum-based dual-drug chemotherapy, including paclitaxel, nab-paclitaxel, or docetaxel. Only one patient with adenosquamous carcinoma received pemetrexed treatment, and 53 patients received immunochemotherapy (53/108, 49.1%), which included five different immunotherapy drugs. The mean number of cycles of immunotherapy was 2.36±0.79. The detailed data are summarized in *Table 1*.

The majority of patients received lobectomy (76.9%) and video-assisted thoracic surgery (VATS) (80.6%). One lung lobe was removed in 69 (63.9%) patients. The mean surgery operation time was 171.90±66.15 min, and the mean amount of blood loss was 72.40±66.51 mL. The surgery-related details are provided in *Table 2*.

Among the whole cohort, 36 patients experienced PPCs, and the incidence of PPCs was 33.3% (36/108). The majority of PPCs were a prolonged time to chest tube removal of >7 days and pneumonia. Thirteen patients had more than one PPC, and one patient died within 30 days due to serious postoperative complications. The mortality within 30 days was 0.9% (*Table 3*).

First, we analyzed the relationship between the addition of ICI to neoadjuvant therapy and surgical outcomes. No patient characteristics difference between the two group (Table S1). As shown in *Table 4*, the addition of ICIs did not increase the PPCs. However, the operation time was longer in the ICI group. There was a tendency of increased blood

Table 1 Patient characteristics

Variable	Value
Total patients	108
Age (years)	64.27 [38 to 75]
Sex	
Male	100 (92.6)
Female	8 (7.4)
Cycles of neoadjuvant chemotherapy	2.33±0.79
Neoadjuvant immunotherapy	
Yes	53 (49.1)
No	55 (50.9)
Immunotherapy drug	
Pembrolizumab	20 (37.7)
Tislelizumab	5 (9.4)
Camrelizumab	15 (28.3)
Sintilimab	11 (20.8)
Toripalimab	2 (3.8)
Cycles of neoadjuvant immunotherapy	2.36±0.79
Days between surgery and neoadjuvant treatment	31.12±13.15
Pathology	
Squamous	98 (90.7)
Adenosquamous	3 (2.8)
Large cell lung cancer	2 (1.9)
Other type*	5 (4.6)
Pulmonary ventilation function	
Normal	38 (35.2)
Obstructive	54 (50.0)
Restrictive	8 (7.4)
Mixed	8 (7.4)
Degree of pulmonary ventilation function	
Normal	38 (35.2)
Mild	54 (50.0)
Moderate	10 (9.3)
Moderate-to-severe	1 (0.9)
Severe	5 (4.6)
T stage after neoadjuvant therapy	
T1	41 (38.0)
T2	52 (48.1)
T3	7 (6.5)
T4	8 (7.4)
N stage after neoadjuvant therapy	
N0	44 (40.7)
N1	7 (6.5)
N2	57 (52.8)

Data are presented as number, n (%), mean [range], or mean ± standard deviation. *, including 2 non-small cell lung cancer-not-otherwise specified patients, 2 poor differentiated lung cancer patients, and 1 squamous cell carcinoma combined with sarcomatoid carcinoma patient.

Table 2 Details of surgical operation

Variable	Value
Total patients	108
Surgery type	
Lobectomy	83 (76.9)
Sleeve	12 (11.1)
Pneumonectomy	10 (9.3)
Lobectomy + wedge	1 (0.9)
Lobectomy + segmental	1 (0.9)
Sleeve + wedge	1 (0.9)
Surgical method	
Video-assisted thoracic surgery	87 (80.6)
Thoracotomy	21 (19.4)
Lung lobes removed	
<1 lung lobe	12 (11.1)
1 lung lobe	69 (63.9)
>1 lung lobe	27 (25.0)
Operation time (min)	171.90±66.15
Blood loss (mL)	72.40±66.51
Hospital days after surgery (days)	7.14±5.03

Data are presented as number, n (%), or mean ± standard deviation.

loss in surgery and prolonged hospital stay after surgery in the ICI group. A significant difference was found in different ICIs (Table S2).

We conducted univariate analysis to identify the risk factors of PPCs. The index P<0.05 in univariate analysis was adopted in multivariate analysis. And the factors, such as age, ICI, which regarded as important factors which may affect the PPCs based on clinical practice were also adopted in multivariate analysis. Significant differences in blood urea nitrogen (BUN) level, N stage was found between the PPC and non-PPC groups (P<0.05). In the PPCs group, the patients had lower levels of BUN. No differences were found for age, sex, cycle of neoadjuvant chemotherapy, days between surgery and last neoadjuvant treatment, pulmonary ventilation function, VATS, or other blood test indices (*Table 5*).

In the multivariate analyses, age, N stage, and BUN level were found to be correlated with the occurrence of PPCs in patients with lung cancer who received surgery after neoadjuvant treatment, both chemotherapy and chemoimmunotherapy. Older age, N2 stage and lower levels of BUN increased the PPCs (*Table 6*).

Table 3 Postoperative pulmonary complications in the study population

Item	Number
Total patients	108
Total postoperative pulmonary complication events	
Pneumonia	19
Atelectasis	1
Chest tube time >7 days	15
Empyema	2
Pulmonary embolism	1
Respiratory failure	2
Bronchopleural fistula	1
Total postoperative pulmonary complication patients	36
1 event	23
>1 event	13
Death within 30 days	1

Discussion

Several studies have identified the predictors for PPCs to be pulmonary function, inflammation index, and immunonutritional status (19,20). However, these studies primarily focused on patients who received surgery as the initial treatment, and patients who received neoadjuvant therapy before surgery were excluded. It thus remains unclear what the predictors are for PPCs in patients with locally advanced lung cancer treated with neoadjuvant therapy following surgery.

Surgery after neoadjuvant therapy is the preferred treatment for locally advanced NSCLC, especial for central lung cancer. For most squamous and large cell lung cancer are central lung cancer, thus in this manuscript focused on the non-ADC NSCLC. Meta-analyses have suggested a gain in survival benefit of at least 6% after 5 years (21). Neoadjuvant chemotherapy results in clinical downstaging in approximately 40–60% of the patients and a pathological complete response rate of 5–10% (22,23). When compared

Table 4 Correlation between addition of ICIs in neoadjuvant treatment and surgical outcomes

Variable	ICI treatment	No ICIs	P value
Patients	53	55	
Days between surgery and neoadjuvant treatment	31.26±14.77	30.98±11.50	0.91
PPCs			
Yes	19 (35.8)	17 (30.9)	0.07
No	34 (64.2)	38 (69.1)	
Operation time (min)	185.38±72.04	158.89±57.63	0.04
Blood loss (mL)	73.58±73.51	71.27±59.66	0.07
Hospital days after surgery	8.06±4.56	6.27±5.34	0.07

Data are presented as number, n (%), or mean ± standard deviation. ICI, immune checkpoint inhibitor; PPC, postoperative pulmonary complication.

Table 5 Correlation between postoperative pulmonary complications and parameters

Variable	Non-PPC	PPC	P value
Patients	72	36	
Age (years)	63.75±6.02	65.33±5.99	0.20
Sex			
Male	67 (93.1)	33 (91.7)	P>0.99
Female	5 (6.9)	3 (8.3)	
Cycles of neoadjuvant chemotherapy	2.28±0.774	2.44±0.88	0.33
Days between surgery and neoadjuvant treatment	29.25±9.77	34.86±17.69	0.08
Pulmonary ventilation function			
Normal	23 (31.9)	15 (41.7)	0.45
Obstructive	39 (54.2)	15 (41.7)	
Restrictive	6 (8.3)	2 (5.5)	
Mixed	4 (5.6)	4 (11.1)	
Degree of pulmonary ventilation function			
Normal	23 (31.9)	15 (41.7)	0.34
Mild/moderate	46 (63.9)	18 (50.0)	
Moderate-to-severe/severe	3 (4.2)	3 (8.3)	
T stage after neoadjuvant therapy			0.5
T1	25 (34.7)	16 (44.4)	
T2	36 (50.0)	16 (44.4)	
T3	4 (5.6)	3 (8.4)	
T4	7 (9.7)	1 (2.8)	
N stage after neoadjuvant therapy			
N0	34 (47.2)	10 (27.8)	0.05
N1	6 (8.4)	1 (2.8)	
N2	32 (44.4)	25 (69.4)	
Surgical method			
VATS	56 (77.8)	31 (86.1)	0.44
Thoracotomy	16 (22.2)	5 (13.9)	
Lung lobes removed			
<1 lobe	7 (9.7)	5 (13.9)	0.67
1 lobe	48 (66.7)	21 (58.3)	
>1 lobe	17 (23.6)	10 (27.8)	
White blood cell count ($\times10^9$)	6.55±3.52	6.00±1.95	0.30
Neutrophil count ($\times10^9$)	4.42±3.38	3.71±1.51	0.13
Lymphocyte count ($\times10^9$)	1.53±0.66	1.65±0.67	0.38

Table 5 (*continued*)

Table 5 (*continued*)

Variable	Non-PPC	PPC	P value
Monocyte count ($\times10^9$)	0.52±0.33	0.49±0.17	0.67
Red blood cell count ($\times10^{12}$)	5.63±14.75	3.94±0.59	0.34
Hemoglobin count (g/L)	118.62±20.03	122.08±16.24	0.34
Platelet count ($\times10^9$)	194.77±71.03	203.64±66.85	0.53
Albumin level (g/L)	40.20±3.58	40.07±4.03	0.87
Globin level (g/L)	29.56±6.59	28.38±4.41	0.27
Blood urea nitrogen level (mmol/L)	6.26±2.00	5.45±1.43	0.02
Creatinine level (μmol/L)	79.00±19.31	76.28±14.50	0.41
C-reactive protein level (mg/L)	4.77±7.55	3.76±9.86	0.59

Data are presented as number, n (%), or mean ± standard deviation. PPC, postoperative pulmonary complication; VATS, video-assisted thoracic surgery.

Table 6 Multivariate analysis of the influence parameters of PPCs

Parameters	OR	95% CI	P value
Age	1.137	1.021, 1.266	0.02
Blood urea nitrogen level	0.482	0.316, 0.734	<0.001
N stage after neoadjuvant therapy			
N1 *vs*. N0	0.367	0.031, 4.330	0.4
N2 *vs*. N0	3.663	1.094, 12.261	0.04

PPC, postoperative pulmonary complication; OR, odds ratio; CI, confidence interval.

with immediate surgery, neoadjuvant therapy does not delay surgery or result in an increased hospital stay or rate of perioperative complications (24,25). In the past few years, ICIs, such as programmed cell death protein 1 monoclonal antibody, have been widely applied in both locally advanced and metastatic lung cancer. Several systemic reviews have reported a higher pathological complete response rate for ICIs combined with chemotherapy in patients with early-stage lung cancer (26-30). However, there are ICI-specific adverse events, such as ICI-associated pneumonia and intrahepatic bile duct injury. Thus far, there has been little data focus on the association of ICI supplementation with PPCs and mortality in patients treated with neoadjuvant therapy (28,31-34).

Moreover, few case-controlled studies have reported PPCs in patients treated with chemotherapy or chemo-immunotherapy. It is known to all the neoadjuvant therapy make surgery more complicated. The surgery technical difficulties were related to the inflammatory response, specifically dense adhesions and fibrosis at the fissure or surrounding hilar and mediastinal nodal stations (35). A high rate of tissue fibrosis and inflammation were reported in chemo-immunotherapy patients versus chemotherapy (36). In Checkmate 816 trials, the neoadjuvant chemotherapy and neoadjuvant immunochemotherapy produced similar PPCs rates (46.67% *vs*. 41.61%) (28). However, two research groups reported low PPC rates associated with neoadjuvant immunochemotherapy (37,38). In our study, we found that the addition of ICIs did not significantly increase the PPC rate. Zhao *et al.* reported less blood loss and a similar length of hospital day after surgery in a neoadjuvant immunochemotherapy group (38). In contrast, we found a similar amount of blood loss and longer hospital stay after surgery in the neoadjuvant immunochemotherapy group. Several factors may account for these discrepancies. First, we intentionally selected neoadjuvant immunochemotherapy in patients with central lung carcinoma, and these cancers tend to result in longer surgical times. Second, in Zhao *et al.*'s study, a high rate of sublobectomy was applied in the neoadjuvant immunochemotherapy group. However, in our study, the proportions of the different types of surgery were relatively balanced between the groups. Third, due to the limited number of patients in the neoadjuvant immunochemotherapy group, the results were not particularly robust.

The PPC rate ranges from 3.33% to 58.8% in patients treated with neoadjuvant immunochemotherapy (29,30). In our study, the PPC rate was about 35.8% for patients

treated with neoadjuvant immunochemotherapy. The majority of PPCs were prolonged time to chest tube removal of >7 days and pneumonia, and other PPC types included bronchopleural fistula and pulmonary embolism, among others, which is in line with previous study (39). In this manuscript we explored the predictors of PPCs in neoadjuvant therapy. In multivariate analysis, age, BUN level, and N2 stage were found to predict PPC occurrence (40). In previous studies, the PPC rate was correlated with surgery type, worse pulmonary function, higher inflammation index, and poorer immunonutritional status but not the type of surgery (41,42).

The thoracotomy, pneumonectomy or the extent of operation were regarded as significantly clinical factors for PPCs. But in our research, no relationship was found between those surgery related factors and PPCs. One reason may due to the limit number of patients enrolled in our study. Secondly, benefit from mature thoracic surgery techniques and efficient nursing care, the surgery type was not the main factors for PPCs. Besides, the N2 stage was a strong predictor for PPCs. The mediastinal lymph nodes are defined as N2 lymph nodes. N2 stage means more operation extension should be done. As mention above, fibrosis at the fissure or surrounding often observed in the lymph nodes invaded by tumors after neoadjuvant therapy, which may increase surgical operation time.

Poor pulmonary ventilation function implies a weak strength of respiratory muscles, a blocked airway, and low elasticity of thoracic lung tissue, which contribute to coughing difficulty and could result in pneumonia and prolonged chest tube removal time. However, no strong relationship was found between PPCs and pulmonary ventilation function in our cohort. The respiratory rehabilitation carried out during neoadjuvant therapy partly account for it.

The inflammation index also could predict PPC occurrence in our study. For example, tumors in an environment rich in neutrophils are prone to metastasis (43). Another inflammation index, C-reactive protein, is associated with a shorter overall survival and progression-free survival (44). However, in our cohort, no clinical significance between inflammation indices and PPC occurrence was found, which may be explained by the different inclusion criteria applied in our study. Previous research has focused on PPCs in patients treated with surgery but not neoadjuvant therapy. In our cohort, all patients were administered neoadjuvant chemotherapy before surgery, with about half of these patients being treated with ICIs. During neoadjuvant therapy, adverse events cannot be ignored. Therefore, the accuracy of these inflammation indices would be disrupted.

Many studies have examined the clinical relevance of applying single immune or nutritional indices for predicting PPCs. Globulin level and lymphocyte ratio reflect the immune status of patients (45). BUN is a decomposition product of proteins. Low BUN level is an important risk factor for sarcopenia (46). Besides, for chronic inflammation result to low albumin, thus the BUN can also reflect the chronic inflammation. In some study, an increase level BUN may negatively affect the mortality of patients with hospital-acquired pneumonia (47). In our study, age and the BUN level performed well in predicting PPCs. During neoadjuvant therapy, nutritional support is consistently applied, and thus compared to inflammation indices, immune or nutritional status is less prone to be disrupted by neoadjuvant therapy.

A few limitations to this study should be noted. First, we employed a retrospective single-center design, and the type of induction chemotherapy and immunotherapy varied based on the physicians' preferences and patients' financial situation. Though we strictly comply to the selection criteria, the selection bias could not be avoided. Second, due to the small sample size, statistical bias was inevitable. A large prospective study was required to verified our conclusions.

Conclusions

The addition of ICIs did not significantly increase the incidence of PPCs, amount of blood loss in surgery operation, and the length of hospital stay after surgery, but it did increase the operation time. Moreover, age, N2 stage and BUN level were effective predictors for PPC occurrence in non-ADC NSCLC patients treated with surgery and neoadjuvant therapy (both chemotherapy and chemoimmunotherapy).

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-25/rc

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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 according to the principles outlined in the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (No. 20251008). All patients signed the informed consent form before participating in the study.

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