Chronic Progression of Lung Cancer Recurrence After Surgery: Warning Role of Postoperative Pneumonia

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Research

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Abstract

Background: The association between the process of postoperative pneumonia and lung cancer recurrence remains elusive in lung cancer surgery. We investigated the association between postoperative pneumonia and lung cancer recurrence development, emphasizing the warning role of postoperative specific pneumonia, in primary lung cancer resection patients.

Methods: We assessed the occurrence of postoperative pneumonia in four to six months (PPFS), seven to twelve month (PPST), and lung cancer recurrence within one year (LRO) in 332 patients. The primary outcome was the development of PPST and LRO according to PPFS occurrence. Relevant risk factors of PPFS, PPST and LRO were identified through multivariable regression analysis.

Results: During follow-up, 151 participants (45.48%) experienced PPFS outcomes. Regardless of the existing of postoperative pneumonia in one to three months (PPOT), PPFS increased the risk of PPST (OR: 2.886, 95% CI: 1.193-6.978, P<0.01 and LRO (OR: 2.793, 95% CI: 1.406- 5.552, P<0.01), and persistent PPST further increased the risk of LRO (OR:16.271, 95% CI: 6.757-39.182, P<0.001). Generalized estimating equation identified chemotherapy or targeted therapy as independent risk factors for PPFS and PPST.

Conclusions: PPFS was associated with increased risk of PPST and LRO. Postoperative pulmonary inflammation assessed 4 months post-surgery also significantly influenced LRO development, indicating a need for close follow-up of lung inflammatory conditions to improve patient outcomes.

Background

Lung cancer is the leading cause of cancer death worldwide, as it is a malignant tumor with a high recurrence rate(1). So far, surgery is still the only curative therapy for early-stage lung cancer(2). The risk factors of postoperative pneumonia is related to many causes, such as age, length of hospital stay and previous antibiotic treatment, etc(3–5).The occurrence of postoperative pneumonia not only affects the outcome of tumor treatment, but also has a significant correlation with the overall survival rate of patients(6, 7).

As reported, during the first 4 years after surgery, the risk of lung cancer recurrence ranged from 6–10% per person-year(8).According to studies, the overall mortality was 6% in the first year after surgery. The risk of having died of lung cancer was 36%(9).On mortality analysis for lung cancer patients, the number of cancer-related deaths has associated with the occurrence of postoperative pneumonia(10–12). Pneumonia is a common complication after lung cancer surgery. there seems to be an association between postoperative pneumonia and LRO in lung cancer surgery patients. Postoperative pneumonia following lung cancer resection is widely accepted as immediate complications, especially postoperative pneumonia referred in thirty days (PPT).Studies about postoperative pneumonia on risk assessment mostly focus on the short term after lung cancer resection. The long-term incidence of pneumonia developing after discharge as following complications has rarely attracted attentions.

No comprehensive study has yet found evidence showing the relationship between the occurrence of postoperative discharged pneumonia and lung cancer recurrence. To address the shortcomings of previous studies, we conducted a longitudinal retrospective analysis to elucidate the relationship between the chronic progression of postoperative pneumonia in patients with lung cancer surgery and the recurrence of lung cancer one year after surgery. Such a study would provide a valuable framework for selecting patients who would benefit from close post-surgical follow-up.

Methods

Patients

This study included lung cancer patients who underwent complete surgical resection in two comprehensive hospitals from January 2015 to April 2020. The inclusion criteria were: histologically confirmed primary lung cancer without metastatic tumors according to the 7th American Joint Committee on Cancer (AJCC) staging manual. On initial diagnosis, all patients aged 18 above received extensive examinations including chest computed tomography (CT), abdominal ultra- sonography, whole-body bone scan and brain magnetic resonance imaging (MRI). The exclusion criteria were presenting clinical evidence of congenital lung disease. Patients diagnosed with fourth stage lung cancer or severe lung dysfunction were not included. In addition, patients lost to follow-up were also excluded from the study.

Data collection

Data on patients from the electronic database of the medical record system were retrospectively reviewed, including age, sex, smoking history, time of quitting smoking, preoperative comorbidities and medications. Intraoperative data included the type of lung cancer surgery, lymphatic metastasis, operation time and intraoperative blood loss. Postoperative data included hospital stay, intensive care unit (ICU) stay, 30 day mortality and in-hospital mortality, wound infection, failed intubation, reoperation due to blood loss and postoperative treatments. Respiratory adverse events (RAE) was defined upper respiratory tract infections (URTI) and lower respiratory tract infections (LRTI), including nasopharyngitis and laryngitis, bronchitis, influenza, respiratory-related opportunistic infections (OIs), interstitial lung disease (ILD),. pulmonary embolism (PE), including deep vein thrombosis(DVT), or collectively venous thromboembolism (VTE)(13). Laboratory data included white blood cell count, neutrophil ratio and albumin level. In addition, we reviewed reports of incidence of preoperative pneumonia, at discharge, and 3 and 6, 12 months post-surgery.

The most recent preoperatively pulmonary imaging report within 30 days was used for Initial evaluation of lung inflammation, and chest imaging reports within the postoperative 30 days as well as during 1–3, 4–6 and 6–12 month follow-ups were used for diagnosis of PPT, PPOT, PPFS and PPST, respectively. The primary outcome was a recrudescent lung outcome that was compared with the occurrence of postoperative pneumonia(14).The inclusion criteria were the following: postoperative pneumonia diagnosed by either pulmonologist or thoracic surgeon according to the Infectious Diseases Society of America/American Thoracic Society guidelines for diagnosing community acquired pneumonia (CAP) in

adults. These guidelines provide criteria for the diagnosis of pneumonia: the presence of clinical features of lung infiltration through chest X-rays and CT scans.

The primary outcome was the development of PPST and LRO according to PPFS occurrence in patients. For this outcome, the risk of PPFS, PPST and LRO was assessed according to occurrence and period of preoperative and postoperative pneumonia. The secondary outcome was the influence of PPFS on recurrence rate, incidence of RAE and mortality in the first year after lung cancer surgery. In addition, risk factors contributing to the development of postoperative PPST and LRO were identified.

Surgical procedures and postoperative follow-up protocol

Results a total of 451 patients who treated with lobectomy and lymph node dissection for lung cancer were enrolled. Surgical procedures include routinely performed lymph node dissection with lobectomy and pneumonectomy. Postoperative follow-up and adjuvant chemotherapy, targeted therapy and radiotherapy were performed in the two institutions. The detection of pneumonia and lung cancer recurrence protocol adhered to the following schedule in this study. Chest X-rays and CT scans were conducted in discharged at 1–3, 3–6, 6–12 months after surgery thereafter. Patients who do not return on time for each treated course were set as patients in loss to follow-up. Brain imaging and bone scintigraphy were scheduled to detect metastasis. Recurrence included both locoregional and systemic diseases according to Chest X-rays and CT scans.

Statistical analysis

Statistical analyses were performed using SPSSAU 2016–2021 (Qing-Si Technology Ltd., Beijing, China). First, we compared participants' baseline characteristics and PPFS. Categorical variables were compared using chi-square or Fisher's exact tests, and expressed as absolute number (percent). The multivariate analyses using a generalized estimating equation(GEE) with the logit function and a multivariable logistic regression analysis to evaluate the association of PPFS with the development of PPST and LRO to account for the correlation of the events. Variables of important, including PPOT, PPFS and PPST potentially affecting LRO were entered into a multivariable logistic model to assess their impact on the chronic development of LRO. Additionally, variables with a P-value < 0.05 in the univariate analysis were preferentially included within the scope of satisfying analysis and increasing the predictive power of the model. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated using logistic regression models. P-values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Of the 406 cases, 74 patients in loss to follow-up were excluded. A total of 332 patients were enrolled (Fig. 1). 203 patients (61.14%) were male. One hundred fifty-one patients (45.48%) developed PPFS during the follow-up period. Participants who treated with chemotherapy or targeted medicine after surgery or suffered intraoperative much blood loss tended to have PPFS. The in-hospital mortality rate

was 0%, and the occurrence of failed intubation and reoperation due to blood loss also never happened. (Table 1, Supplemental Table 1).

Table 1
Clinical characteristics of patients with or without PPFS

	Non- PPFS patients (N = 181)	PPFS patients (N = 151)	P value
Patients characteristics,n (%)			
Age	37(53.62)	32(46.38)	0.867
< 55	144(54.75)	119(45.25)	
≥ 55			
Sex	107(52.71)	96(47.29)	0.406
Male	74(57.36)	55(42.64)	
Female			
Smoking	99(55.00)	81(45.00)	0.848
No	82(53.95)	70(46.05)	
Yes			
Quit smoking	169(55.96)	133(44.04)	0.094
< 0.5 year	12(40.00)	18(60.00)	
≥ 0.5 year			
Medications,n (%)			
Glucocorticoids	66(53.23)	58(46.77)	0.715
No	115(55.29)	93(44.71)	
Yes			
Antibacterials	25(71.43)	10(28.57)	**0.034***
No	156(52.53)	141(47.47)	
Yes			
Bronchodilator	38(47.50)	42(52.50)	0.148
No	143(56.75)	109(43.25)	
Yes			

* Significant difference compared between-groups (p < 0.05)

** Significant difference compared between-groups (p < 0.01)

PPST = Postoperative pneumonia in seven to twelve month

	Non- PPFS patients (N = 181)	PPFS patients (N = 151)	P value
Mucolytic drugs	38(66.67)	19(33.33)	**0.043***
No	143(52.00)	132(48.00)	
Yes			
Postoperative treatments,n (%)			
Chemotherapy or targeted therapy	99(61.49)	62(38.51)	**0.013***
No	82(47.95)	89(52.05)	
Yes			
Radiotherapy	172(55.48)	138(44.52)	0.185
No	9(40.91)	13(59.09)	
Yes			
Perioperative conditions,n (%)			
Blood loss	114(59.07)	79(40.93)	**0.050***
< 200ml	67(48.20)	72(51.80)	
≥ 200ml			
* Significant difference compared between-groups (p < 0.05)			
** Significant difference compared between-groups (p < 0.01)			
PPST = Postoperative pneumonia in seven to twelve month			

PPFS and development of PPST and LRO

The incidence of preoperative pneumonia and PPOT were significantly higher in PPFS patients than in non- PPFS patients (51.43% vs. 48.57%, P < 0.05; 73.78% vs. 26.22%, P < 0.001). Compared to PPFS patients, non-PPFS patients had significantly higher incidences of early recovery (30.39%vs.69.61%, P < 0.001). Early recovery was defined as an absence of postoperative pneumonia diagnostic criteria thirty days after surgery. The prevalence of PPST (81.46% vs.24.31%, P < 0.001) and LRO (49.67% vs. 12.15%, P < 0.001) was significantly higher in PPFS patients than in non-PPFS patients. (Table 2)

Table 2
Preoperative and postoperative pneumonia occurrence, recovery and outcome of patients with or without PPFS.

	Non- PPFS patients (N = 181)	PPFS patients (N = 151)	P value
Preoperative pneumonia,n (%)	96(61.15)	61(38.85)	**0.022***
No	85(48.57)	90(51.43)	
Yes			
PPT	43(68.25)	20(31.75)	**0.015***
No	138(51.3)	131(48.7)	
Yes			
PPOT	138(82.14)	30(17.86)	**P < 0.001****
No	43(26.22)	121(73.78)	
Yes			
Recovery situation,n (%)			
Recovery in 30 days	55(30.37)	96(63.58)	**P < 0.001****
No	126(69.63)	55(36.42)	
Yes			
Lung outcomes,n (%)			
PPST	137(75.69)	28(18.54)	**P < 0.001****
No	44(24.31)	123(81.46)	
Yes			
LRO	159(87.85)	76(50.33)	**P < 0.001****
No	22(12.15)	75(49.67)	
Yes			

* Significant difference compared between-groups ($p < 0.05$)

** Significant difference compared between-groups ($p < 0.01$)

PPT = postoperative pneumonia in thirty days; PPOT = postoperative pneumonia in one to three months; PPFS = postoperative pneumonia in four to six months; PPST = postoperative pneumonia in seven to twelve month; LRO = lung cancer recurrence within one year; RAE = Respiratory adverse events

	Non- PPFS patients (N = 181)	PPFS patients (N = 151)	P value
RAE	178(54.27)	150(45.73)	0.408
No	3(75.00)	1(25.00)	
Yes			
Mortality	181(100.00)	148(98.01)	0.057
No	0(0.00)	3(1.99)	
Yes			
* Significant difference compared between-groups (p < 0.05)			
** Significant difference compared between-groups (p < 0.01)			
PPT = postoperative pneumonia in thirty days; PPOT = postoperative pneumonia in one to three months; PPFS = postoperative pneumonia in four to six months; PPST = postoperative pneumonia in seven to twelve month; LRO = lung cancer recurrence within one year; RAE = Respiratory adverse events			

PPOT were at increased risk for PPST with relative risks of 4.604. PPFS occurrence increased the risk of PPST (OR: 2.886, 95% CI: 1.193 ~ 6.978, P < 0.001) and LRO (OR: 2.793, 95% CI: 1.406 ~ 5.552, P = 0.003) according to the GEE method for analyzing the primary outcome of the study (Table 3). Furthermore, PPST occurrence had significantly higher incidences with LRO (53.29% vs. 4.85%, P < 0.001) compared to non-PPST patients, and associated with the risk (OR: 16.271, 95% CI: 6.757 ~ 39.182, P < 0.001).

Table 3
Risks for development of PPST according to postoperative pneumonia occurrence and stage.

	PPST		**LRO**	
	OR(95%CI)	P value	OR(95%CI)	P value
Non- PPOT	reference	-	reference	-
PPOT occurrence	4.604(1.927 ~ 11.001)	**0.001****	0.669 (0.330 ~ 1.357)	0.265
Non- PPFS	reference	-	reference	-
PPFS occurrence	2.886(1.193 ~ 6.978)	**0.019***	2.793 (1.406 ~ 5.552)	**0.003****
Non- PPST	-	-	reference	-
PPST occurrence			16.271(6.757 ~ 39.182)	**P < 0.001****
* Significant difference compared between-groups (p < 0.05)				
** Significant difference compared between-groups (p < 0.01)				
PPOT = postoperative pneumonia in one to three months; PPFS = postoperative pneumonia in four to six months; PPST = postoperative pneumonia in seven to twelve month; LRO = lung cancer recurrence within one year; ORs = Odds ratios; CIs = Confidence intervals				

Risk factors for PPFS, PPST, and LRO

In the multivariable logistic regression analysis, chemotherapy or targeted therapy was risk factors for PPFS and PPST. Significantly, PPOT was identified as risk factors for PPFS and PPST development while not revealed as an independent risk factor for LRO. PPFS was an independent risk factor associated with the development of both PPST (OR: 8.410, 95% CI: 4.407 ~ 16.049, P < 0.01) and LRO (OR: 3.129, 95% CI: 1.396 ~ 7.010, P < 0.01), after adjusting for other influencing factors (Table 4). Blood loss was the risk factors for LRO (OR: 2.131, 95% CI: 1.135 ~ 4.002, P < 0.05). When introducing PPST instead of PPFS to the multivariable model for LRO, PPST was the most powerful risk factor for LRO (OR: 23.285, 95% CI: 9.347–58.007, P < 0.001).

Table 4
Multivariable logistic regression analysis of risk factors for PPFS, PPST and LRO patients.

Event	Risk factor	OR(95%CI)	P value
PPFS	Chemotherapy or targeted therapy	1.926(1.126 ~ 3.295)	**0.017***
	PPOT	11.860(6.603 ~ 21.303)	**P < 0.001****
PPST	ICU stay	8.985(1.841 ~ 43.864)	**0.007 ****
	Operation time	2.203(1.057 ~ 4.591)	**0.035***
	Chemotherapy or targeted therapy	1.842(1.014 ~ 3.346)	**0.045***
	Antibacterials	3.015(1.020 ~ 8.913)	**0.046***
	PPOT	3.217(1.647 ~ 6.284)	**0.001****
	PPFS	8.410(4.407 ~ 16.049)	**P < 0.001****
LRO	Smoking	2.681 (1.277 ~ 5.628)	**0.009 ****
	Lymphatic metastasis	5.763 (2.666 ~ 12.460)	**P < 0.001****
	Radiotherapy	3.169 (1.186 ~ 8.469)	**0.021***
	Blood loss	2.131 (1.135 ~ 4.002)	**0.019 ***
	PPFS	3.129 (1.396 ~ 7.010)	**0.006 ****
	PPST	15.636 (6.296 ~ 38.833)	**P < 0.001****
* Significant difference compared between-groups (p < 0.05)			
** Significant difference compared between-groups (p < 0.01)			
PPOT = postoperative pneumonia in one to three months; PPFS = postoperative pneumonia in four to six months; PPST = postoperative pneumonia in seven to twelve month; LRO = lung cancer recurrence within one year; OR = Odds ratio; CI = Confidence interval; ICU = Intensive Care Unit			

Discussion

Lung cancer is a common malignant tumor with poor therapeutic effect.. Now comprehensive treatment is recommended as an effective strategy for lung cancer patients11. However, the high recurrence rate one year after lung cancer surgery is still a challenge in clinical treatment. Most studies have focused more on risk factors for overall survival after lung cancer resection. And there is a lack of real-world data available to predict and evaluate the clinical risk of lung cancer recurrence in the first year after surgery. Currently, the FDA attaches importance to the real-world evidence including electronic health records which can add and evaluate information on how factors such as clinical setting and health system characteristics affect the therapeutic effect and even guide the outcomes(12). And this is the first research to provide some real-world evidence to assess the recurrence of cancer within one year after

lung cancer resection. Studies suggest that the first local recurrence rate after lung cancer resection is 27%-36%(14). In this retrospective review, we found that the incidence of LRO reached 29.22%, which was consistent with previous reports. This study has shown a close link between the occurrence of PPST and LRO development with a distinct warning role for PPFS. The PPFS-associated risk for LRO development was independent of preoperative pulmonary conditions and PPOT. PPFS is an important and ongoing clinical turning point, which could be an important time window for critical interventions to modify disease deterioration and progression.

In our analyses, PPFS significantly increased the risk of development of LRO, regardless of the existing of preoperative pneumonia and PPT. Although the preoperative pneumonia and PPT groups had higher prevalence of PPFS than the preoperative non-pneumonia and non-PPT groups, the risk of preoperative pneumonia and PPT on the development of LRO did not differ with regards to patients without preoperative pneumonia and PPT. Poor early recovery of postoperative pneumonia was not associated with the incidence of PPST and PPFS. Although one study found a close link between PPT and the prognosis of lung cancer resection, it focused on overall survival within five years after surgery(5). It did not assess the actual progression of LRO, which limits further direct comparisons to our study. Here, we found that PPOT patients had 3-times higher risk of progression to PPST than non- PPOT patients, whereas there is no increased risk in developing LRO. The risk of PPST and LRO were increased up to 8-times and 3-times higher in PPFS patients, respectively.

The association of the history of chemotherapy and targeted therapy and the occurrence of PPFS and PPST was well-demonstrated. The PPFS and PPST groups with the history of postoperative chemotherapy and targeted therapy had the higher incidence than the non-history groups. The history of chemotherapy and targeted therapy was an independent risk factor for the progress of PPFS and PPST. A previous study has showed that adjuvant chemotherapy after surgery was a high risk factor for postoperative pneumonia(15). Chemotherapy played an important part after lung cancer surgery. Previous studies mainly suggested that chemotherapy was related to the mechanism of alveolar injury and immune function. Chemotherapy increased the presence of inflammatory cell and interleukines in bronchoalveolar lavage systemic inflammatory response in chemotherapy patients is increased, as compared to patients not undergoing neoadjuvant treatment (16). Higenbottam T et al. also reported that the reason chemotherapy agents affect lungs. The drug directly acts on alveolar cells in the metabolic process and induces an immune response to produce many kinds of biochemical substances. Lung damage is not only directly related to the dose of the drug, but also affected by drug-drug, drug-diet, and drug-environment interactions(17).

In addition, relevant clinical studies also showed that the commonly used chemotherapy drugs for lung cancer such as docetaxel, paclitaxel, gemcitabine, and vinorelbine can cause alveolar epithelial cell damage(18, 19). There is research that showed that small-molecule agents that target EGFR are potential cause of pneumonitis in patients with lung cancer. The occurrence of drug-induced pneumonitis associated with gefitinib and erlotinib is 1.2%-1.6%, with a relatively mortality of 22.8%(20). Furthermore, a post-marketing study of crizotinib found that it was associated with pneumonitis in 5.77% of ALK-

positive NSCLC patients, of which 3.45% were pneumonitis of at least grade 3(21). Oshima et al.(22)also reported that there was an increased pneumonia incidence after treatment with EGFR-targeted drugs in patients receiving nilumab. However, the exact underlying mechanism of pneumonia caused by targeted agents is unclear. Some studies believed that the mechanism of lung infection caused by targeted agents is direct toxicity and immune-mediated injury on alveolar epithelial cells and pulmonary capillary endothelial cells, which leads to pneumonia(23). Namba T et al. (24) also reported that targeted drug-related pneumonia may be associated with its inhibition on the expression of heat shock protein 70 ,or may be linked with the release of large amounts of tumor necrosis factor from tumor necrosis. Therefore, we hypothesize that chemotherapy and targeted therapy lead to weakened immune system function in a period of time. Our study found that patients with a history of chemotherapy and targeted therapy are directly related to the incidence of PPFS, but the history of chemotherapy and targeted therapy is not a risk factor for the occurrence of LRO. As many as 48.49% of patients in our study did not have history of chemotherapy or targeted therapy. Therefore, PPFS patients without history of chemotherapy or targeted therapy should be treated with caution to prevent the occurrence of LRO.

Previous studies have shown that smoking and lymphatic metastasis are associated with the recurrence of lung cancer (25–28). We found that the LRO group had a higher incidence of smoking and lymphatic metastasis than the non-LRO group. Our study was consistent with previous reports. Accordingly, it was suggested that smoking and lymphatic metastasis may be the risk factors of the development of LRO. The combination of surgery and radiotherapy was the important treatment for patients with lung cancer after surgery. Notably, our study found that patients with postoperative radiotherapy had a significantly higher incidence of lung cancer recurrence than patients without radiotherapy. This association suggests that radiotherapy was the independent risk factor for the development of LRO, which was differ from several previous studies(29–31).However, recent studies have shown patients who were determined to need radiotherapy had already cancer that had spread to the lymph nodes(32). Some other studies have shown that adjuvant radiotherapy may increase the risk of radiation pneumonia, especially in combination with chemotherapy(33, 34). Considering the interaction between adjuvant radiotherapy and postoperative pneumonia, individuals with adjuvant radiotherapy may exhibit an increased incidence of PPFS, which predisposes patients with lung cancer surgery to develop LRO. The number of patients with adjuvant radiotherapy in this study was too small, and the study did not analyze adjuvant chemotherapy or target therapy combined with radiotherapy. Although our study concluded that postoperative radiotherapy was a risk factor for LRO, a larger sample size should still be conducted for revalidation analysis. In this study, the intraoperative blood loss was also an independent risk factor for the development of LRO. G Ma et al. reported a significant correlation between intraoperative blood loss and postoperative survival in lung cancer patients(35). Studies have shown that massive blood loss during the perioperative period can lead to postoperative hemorrhagic stress response, which may lead to infectious complications(36). Shuang-jiang Li et al. also reported that blood loss can inhibit the cell-mediated immune response by inducing the mitotic response of T lymphocytes and the antigen presentation ability of macrophages(37). Therefore, we hypothesized that large intraoperative blood loss may increase the incidence of LRO by influencing immune system.

There are two possible explanations as to why PPFS is associated with LRO. The first explanation is that t systemic inflammation can accelerate the adhesion of circulating tumor cells to the vascular endothelium of distant organs, which is the first step of forming distant metastases. This was confirmed in a mouse model of the early stages of hematogenous metastasis(38). Numerous studies have demonstrated that these two status of postoperative inflammatory and lung cancer metastasis are inter-related (39–42).The inflammatory status of PPOT may be related to the postoperative wound repair or the prognosis of lung tumors. So, PPOT is not risk factor for predicting LRO. In the absence of PPOT, the recurrence of PPFS combined with the continuous attack state of PPST would form the inflammatory environment, which may cause the accelerated spread of tumor cells and further induce the development of LRO. The second explanation is that when the cause of inflammation persists that is, when the PPOT persists, acute inflammation can be converted into chronic inflammation. Inflammatory cells can release chemicals such as ROS that promote carcinogenic evolution, and many factors released by inflammatory cells may lead to significant inhibition of immune response(43, 44).As an important time window after lung cancer resection, PPFS played an warning role during the chronic inflammation of the development of LRO. Thus, PPFS, which was associated with inflammatory environment, may be a predictive factor for LRO.

In addition to avoiding further LRO, identifying risk factors for lung cancer recurrence in the early stage could guide timely follow-up and application of therapeutic measures in patients at risk for PPST progression after lung cancer surgery-associated PPFS. In this regard, our study has several strengths. This is the first study to encompass comprehensive data sets of real-world evidence of serially assessed lung inflammation and recurrence during the postoperative 12 months in a cohort of lung cancer surgery patients. We describe a detailed overview of the factors associated with the occurrence of PPFS. In addition,our study provides primary evidence that PPFS, regardless of the existing of PPOT, is associated with LRO development, and concomitantly demonstrates the importance of an warning role for PPFS and the intermediary role for PPST, connecting these two diseases. Lastly, we reaffirmed well-known risk factors for LRO, including smoking, lymphatic metastasis, blood loss and radiotherapy. Chemotherapy or targeted therapy was risk factors for PPFS and PPST. These findings may be helpful for identifying patients without treating chemotherapy or targeted therapy who may benefit from close post-surgery follow-up because 40.99%□19.88% of these patients in our study developed PPST and LRO, respectively. Future studies are warranted to confirm whether identifying and treating PPFS may improve LRO and overall prognosis outcomes.

Conclusion

In conclusion, we observed a close relationship between PPST occurrence and LRO development with a warning role for PPFS in lung cancer surgery patients. Thus, all patients with lung cancer surgery should be followed and assessed for the pulmonary inflammation reappeared and expanded 3 months later, especially the patients without history of chemotherapy or targeted therapy. Multidisciplinary and close follow-ups to assess recurrence and metastasis of lung cancer should also be considered when patients without history of chemotherapy or targeted therapy have the proposed risk factors or appearance of

PPFS. Future animal studies are required to molecular relationship between PPFs and LRO, and prospective studies are conducted to develop the management strategies to detect the postoperative intervention in the course of lung cancer recurrence.

Abbreviations

PPT: Postoperative pneumonia in thirty days; PPOT: Postoperative pneumonia in one to three months; PPFS: Postoperative pneumonia in four to six months; PPST: Postoperative pneumonia in seven to twelve months; LRO: Lung cancer recurrence within one year; RAE: Respiratory adverse events; ORs: Odds ratios; CT: Chest computed tomography; ICU :Intensive Care Unit; CIs: Confidence intervals; GEE: Generalized estimating equation

Declarations

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The Second Affiliated Hospital of Shantou University Medical College and Shantou Central Hospital (2021-38). This study has complied with the Declaration of Helsinki. Informed consent was obtained from all the patients.

Consent for publication

Consent for publication about the analyzed result was obtained from all the patients.

Availability of data and material

The dataset generated and analyzed during the current study are not publicly available due to the patients' privacy but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DQL conceptualized the study, analyzed the data and wrote the first draft of the manuscript; JGZ, XHX, KX, XQW, QFZ collected the data. YHZ and XYC revised and edited the manuscript. XYC supervised the work. All authors read and approved the final manuscript.

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Figures

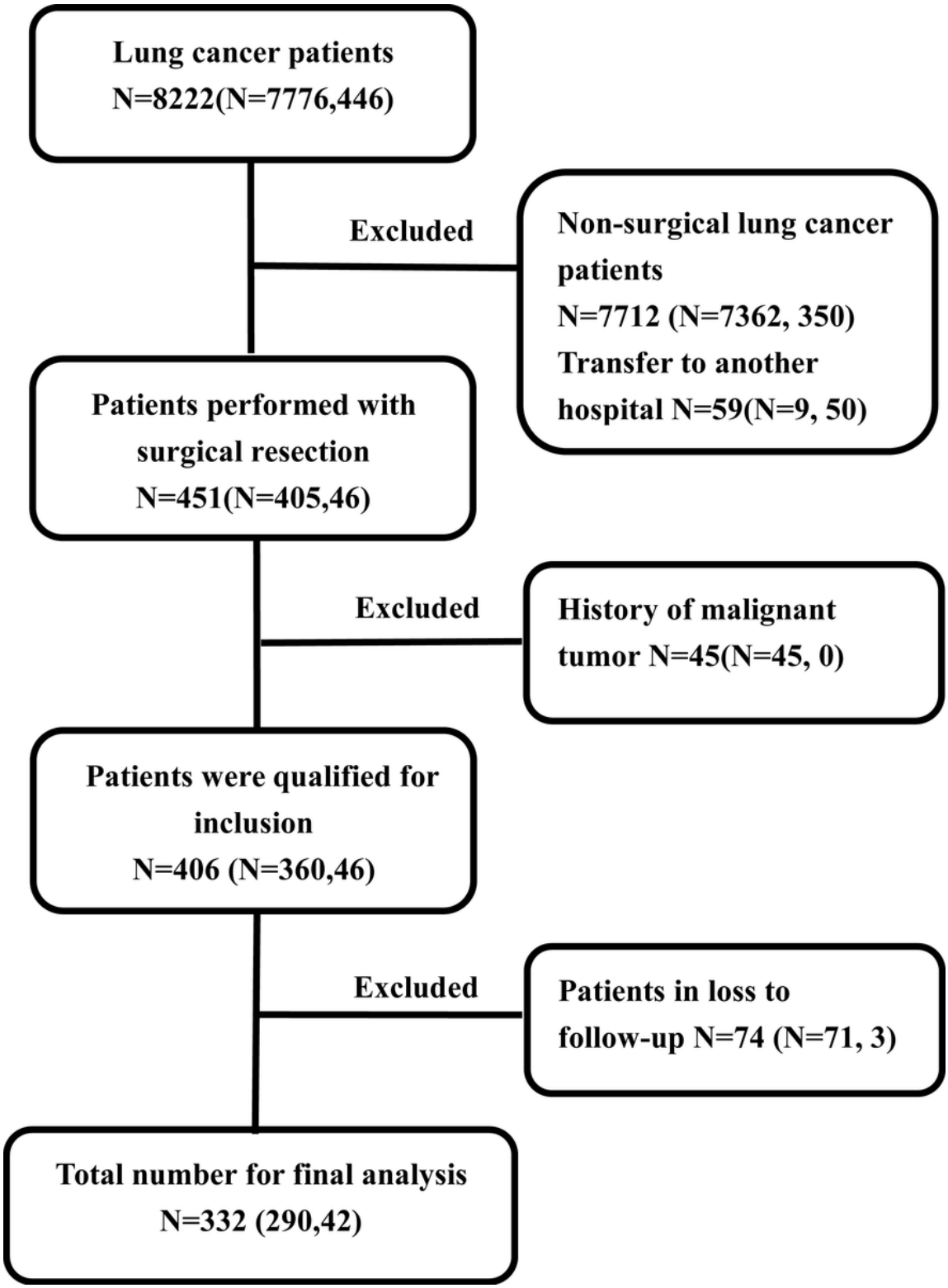

Figure 1

Flow of the retrospective study

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