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## Peer Review File

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### Reviewer A

First, we would like to congratulate the authors on their article entitled: “Effect of laterality on the postoperative survival of non-small cell lung cancer patients undergoing pneumonectomy”.

Please find our comments below per section.

#### General

- The manuscript is well-written, well-structured, and easy to read, with proper vocabulary and grammar.

#### Abstract

- Straight and to the point, nothing to comment.

#### Introduction

- You can shorten the introduction significantly. I would leave out the historic part about pneumonectomy, as this does not contribute to the goal of this manuscript.

Reply: Thanks so much for your comments. We have already modified the relevant content.

Changes in the text: Line: 94-95.

- Just shortly comment on the epidemiology of pneumonectomy as it presently is, and then state your goal/aim.

Reply: Thanks so much for your comments. We have made modifications to this section according to your suggestions.

Changes in the text: Line: 102; Line: 107-109.

#### Methods

- You can leave out the background information on SEER, as this should be common knowledge for the reader.

Reply: Thanks so much for your comments. We have already deleted the relevant content.

Changes in the text: Line: 126-127.

- Why have you chosen to include patients from 2004-2015? Data of 10-20 years ago, which might not represent current practice (i.e. improvements in surgical techniques, anesthesia strategies, ERAS implementation etc.). For OS, you could make a cutoff at 3, or 5 years follow-up, allowing for patient inclusion up until 2019/2021.

Reply: Due to the change in the staging standards after 2016 of NSCLC (the 8<sup>th</sup> edition), those data is temporarily unavailable in the SEER database. Therefore, we could only include data from 2004 to 2015. The advancement of medical technology has indeed

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brought many improvements for lung cancer surgery, but we still believe that NSCLC patients after pneumonectomy, as a special condition, the influence of laterality is still an important prognostic factor, even after improvements in surgical techniques or anesthesia strategies. We are also evaluating the prognosis and risk factors of patients after pneumonectomy in the author's hospital (Shanghai Pulmonary Hospital), in order to further assess the short- and long-term outcomes of patients after pneumonectomy in recent years (until around 2021).

Changes in the text: Line: 136.

- Covariate selection based on univariate regression analysis is an outdated method of selection. Instead consider using forward, backward, or stepwise regression for example, or even better, Bayesian Model Averaging.

Reply: The stepwise logistic regression analysis was used in the multivariate logistic regression analysis of this study.

Changes in the text: Line: 167.

- Please add surgery approach if possible (open vs minimally invasive).

Reply: We are aware that thoracotomy and minimally invasive surgery (VATS) have a significant impact on the short-term recovery of patients undergoing pneumonectomy, but unfortunately, there is no specific information on surgical approaches in the SEER database. We are currently building a multicenter clinical and pathological information database for patients undergoing pneumonectomy to further evaluate the impact of minimally invasive techniques, particularly uniportal VATS or RATS, on short-term prognosis. The authors will conduct further research on this topic in the future.

Changes in the text: Line: 340.

## Results

- Do you have the causes of death? Would be interesting to see what the causes of death were, especially in the first six months when the mortality rate was significantly higher in the right-sided group.

Reply: Thanks so much for your comments. We believe that the cause of death during the perioperative period is indeed essential, but there is no specific indication and information of the cause of death in the SEER database. According to our center's own retrospective data of NSCLC patients after pneumonectomy, most of the mortality causes are due to heart and lung failure, with little correlation with oncology.

Changes in the text: Line: 338.

- Consider shortening the text, while referring to you figures and tables more. Just state the most important findings in the text.

Reply: Thank you very much for your comment. We have made revisions to this section.

Changes in the text: Line: 185-186; 197-198.

- Please show how the mortality rate changed over time. It might be probable that more patients died in 2004 compared to 2015, and how were the differences between left and right pneumonectomy over time? Does the difference remain significant?

Reply: Thanks very much for your comments. We further analyzed the 0-3 months and 4-6 months mortality rates of patients who underwent left- and right-sided

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pneumonectomy in 2004 and 2015, as detailed in S-Tab.1. Although the overall perioperative mortality data in 2004 was higher than that in 2015, there was no significant change in the overall trend of the difference between the left and right sides. Therefore, we believe that although the perioperative mortality rate of patients after pneumonectomy has improved with the advancement of medical technology, the impact and differences caused by laterality have not undergone significant changes.

S-Tab. 1 The 0-3 and 4-6 months mortality rates of patients after pneumonectomy in 2004 and 2015

	Year 2004	Year 2015	<i>P</i> -value
0-3 months mortality all	11.09%	8.65%	0.874
0-3 months mortality of right side	15.38%	14.35%	0.744
0-3 months mortality of left side	7.64%	6.70%	0.793
4-6 months mortality all	10.47%	8.51%	0.863
4-6 month mortality of right side	5.88%	4.69%	0.759
4-6 month mortality of left side	6.55%	5.47%	0.784

Changes in the text: Line: 192-196.

#### Discussion

- Please elaborate further on how you think the timeframe of this study impacts the usability of the results.

Reply: During the first six-month timeframe after operation, NSCLC patients who undergo right-sided pneumonectomy should receive more detailed follow-up, including timely chest X-ray re-examination and chest drainage management.

Changes in the text: 259-262.

- You found results that have been found repeatedly before, why is this manuscript “new and relevant”?

Reply: Previous studies have mainly focused on the long-term effects of laterality on postoperative outcomes in NSCLC patients undergoing pneumonectomy, with limited research on short-term effects. Currently, no studies have been found to specifically explore the specific time range of laterality's impact on postoperative outcomes. Therefore, we believe that this is a relatively novel aspect of this research.

Changes in the text: Line: 328-331.

- Could you elaborate on preventive measures that could be taken for patients that undergo right pneumonectomy specifically, apart from optimized screening and patient selection?

Reply: In addition to preoperative screening and optimization of long-term follow-up after pneumonectomy, there should be a higher frequency of chest X-ray re-examination in the short term after right-sided pneumonectomy to facilitate timely assessment of mediastinal displacement. At the same time, more attention should be paid to postoperative drainage management.

Changes in the text: Line: 259-262.

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## Reviewer B

This is a study that investigated the laterality and postoperative outcomes in patients who underwent pneumonectomy. Unfortunately, this study lacks novel findings, not as expected. Although propensity score matching was performed, the study population included patients with a wide range of conditions.

Reply: Thanks so much for your comments. If the 90-day postoperative high-risk period is considered for all NSCLC patients after pneumonectomy, there is reason to believe that there should be a longer risk period and close follow-up period for patients undergoing right-sided pneumonectomy. The main endpoint of this study is overall survival; therefore, we mainly evaluated the overall perioperative survival of patients after pneumonectomy. The authors were unable to further obtain detailed data on tumor-specific survival in the database and therefore were unable to further evaluate the impact of oncologic and non-oncologic factors on mortality. Our center is currently promoting a prospective designed database focusing on NSCLC patients undergoing pneumonectomy to further evaluate the high-risk prognostic factors and specific impacts of laterality in those groups of patients.

Changes in the text: Line: 338-343.

## Reviewer C

The article examines the impact of laterality (whether the surgery is on the right or left side) on postoperative survival in patients with NSCLC who undergo pneumonectomy. Using data from the SEER database, the study finds that patients undergoing right-sided pneumonectomy have a significantly higher risk of mortality within the first six months post-surgery compared to those undergoing left-sided pneumonectomy. However, interestingly after this six-month period, the influence of laterality on overall survival diminishes, suggesting that the long-term prognosis is similar regardless of the side of the surgery. The study underscores the importance of thorough preoperative evaluation and extended postoperative monitoring, particularly for patients undergoing right-sided pneumonectomy.

The introduction provides a thorough historical context and rationale for the study, tracing the evolution of surgical approaches to lung cancer and establishing the significance of the research question and identifying the gap in current knowledge regarding the impact of laterality on outcomes after pneumonectomy. While the introduction discusses the clinical importance of understanding the effect of laterality, it could provide more detail on why this specific aspect was chosen over other potential factors affecting postoperative outcomes.

Reply: Thanks so much for your comments. The authors further elaborated in the introduction section. With the advancement of medical technology, the proportion of pneumonectomy has gradually decreased. However, recent studies still suggest that

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laterality remains an important prognostic factor for patients after pneumonectomy. Therefore, this study focuses on this issue.

Changes in the text: Line: 94-97.

Methods: the use of the SEER database with a large number of patients and a propensity score is a significant strength. While the methods section lists the variables used in the analysis, it does not provide detailed definitions or discuss how these variables were chosen or validated. Why did you choose marriage status and race for propensity score? I don't think that these data were relevant. Of course, based on the SEER database, you could not include pulmonary function, and cardio-pulmonary comorbidities. Even mentioned in limitations, these 2 points are a major limitation of such database

Reply: Thanks very much for your comments. Race and marital status may have a relatively weak impact on the prognosis of patients undergoing pneumonectomy, but in conducting PSM analysis, we included all baseline variables for the completeness of the study. Indeed, cardiopulmonary function is an important short-term and long-term prognostic factor for patients after pneumonectomy, but unfortunately it was not included in the SEER database, and we have also stated this in the limitations section.

Changes in the text: Line: 338-340.

Results: The results are presented with clear statistical analyses, including both univariable and multivariable logistic regression, which enhance the credibility of the findings. The results include a detailed breakdown of mortality rates and survival outcomes, with a clear differentiation between short-term and long-term impacts. In tables, chemotherapy and radiotherapy is adjuvant? It should be arranged in the table.

Reply: Thanks so much for your comments. The information on chemotherapy and radiotherapy in the SEER database may not necessarily be all about postoperative adjuvant therapy, but may include preoperative induction therapy and neoadjuvant combined adjuvant therapy. Unfortunately, in the SEER database, there is no detailed distinction between the order of treatment, drug regimen, and radiation dose.

Changes in the text: Line: 339.

Discussion: The discussion could delve deeper into the mechanisms underlying the observed differences in outcomes between right- and left-sided pneumonectomies. The discussion does not sufficiently explore alternative explanations for the findings, such as differences in surgical techniques or postoperative care.

Reply: Thank you for your suggestions. In this research (Line: 266-277), we elaborated on the mechanism differences in outcomes between right- and left-sided pneumonectomies from three aspects. We were also well aware of the impact of cardiopulmonary function on the short-term and long-term clinical outcomes of patients after pneumonectomy, but due to the lack of specific information on patients' performance status in the SEER database, we cannot conduct further analysis on these crucial parameters. We are constructing a prospective designed database of patients undergoing pneumonectomy to further evaluate the prognostic factors and clinical practice guidelines for these high-risk patients.

Changes in the text: Line: 339: Line: 266-277

**Reviewer D**

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I have some comments and suggestions on this manuscript.

The first part of the Introduction section is not related at all with the topic under investigation. Dealing not this paper with a historical review, your lines 49-58 can be removed from the text. Why not just focusing on the risk of mortality after pneumonectomy? You could start your Introduction in line 67 helping the reader being focused on the topic under analysis.

Reply: Thanks so much for your comments. The authors have made modifications to the Introduction section and deleted irrelevant parts.

Changes in the text: Line: 94-97.

Your reference 2 is not dealing with the Graham procedure. Please remove from the references list.

Reply: Thanks so much for your comments. We have adjusted this section according to your constructive suggestion.

Changes in the text: Line: 96.

You could include in the Introduction that the authors in your reference 10 conclude that postoperative mortality of right pneumonectomy is much higher compared to the left up to 3 months after the procedure. Since the higher risk period has been not confirmed in many papers it is interesting to discuss it and that is the problem you are discussing in your analysis.

Reply: Thanks so much for your comments. We have adjusted this section according to your suggestion. The high-risk period after right-sided pneumonectomy is indeed our main research topic.

Changes in the text: Line: 107-109.

Matching cases and controls by PS is biasing your conclusions. From the original population you have excluded around 20% of records, and from left side cases around 40%. Thus, your conclusion statement can be applied just to highly selected patients according to several criteria. You can avoid excluding cases from the analysis calculating the PS, them to balance patient baseline characteristics in right and left cases groups by weighting each individual in the analysis by the inverse probability of receiving each type of resection (doi: 10.1093/ckj/sfab158).

Reply: Thanks so much for your constructive suggestions. Patients who underwent left- and right-sided pneumonectomy have already undergone careful preoperative selection and evaluation before operation, so we screened them from the overall group of patients in the database who underwent this surgery. PSM does exclude some patients, but we evaluate and screen patients with similar tumor characteristics from an oncological perspective to balance preoperative clinical and pathological information indicators. In addition, due to the weighted uncertainty of the main factors (such as laterality or tumor size) involved in the study, we were unable to analyze the enrolled patients using the inverse probability method. We do hold the view that PSM is helpful in research populations screening and variable matching in this research.

Changes in the text: Line: 341-343.

The main outcome in your series is death by any cause. Your study would be much better including the cause of death in the analysis and performing a survival analysis in

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the presence of competing events (death by cancer and death due to postoperative complications).

Reply: Thans so much for your suggestion. We do believe that perioperative causes of death are important, but unfortunately, there are no specific causes of death included in the SEER database. OS is an important aspect of prognostic analysis for cancer patients. The main population of this study was NSCLC patients; therefore, OS was chosen as the primary endpoint. Our center is currently building a database on the clinical and pathological characteristics of patients after total lung resection, further analyzing the diagnosis and treatment strategies for the prognosis of these patients and the specific factors related to death. According to our center's retrospective data on non-small cell lung cancer patients after lung resection, the majority of deaths within six months are due to cardiopulmonary failure.

Changes in the text: Line: 338.

### **Reviewer E**

In this manuscript the Authors describe the results of a study analyzing the mortality after right and left pneumonectomy for stage I to III non-small cell lung cancer. The data obtained from the SEER database were analyzed, and after propensity score matching the mortality of 1.911 patients for each side of pneumonectomy were analyzed at 3, 6, and 9 months.

The results of the study show that overall survival after right pneumonectomy was significantly worse, confirming previous results on this topic. However, the mortality after right pneumonectomy was significantly higher only during the first six months after surgery. In fact, the side of pneumonectomy did not influence mortality from 7 to 9 months after surgery.

These results are probably due to the higher incidence of surgical complications after right pneumonectomy in the early postoperative period, and to the higher pathophysiological impact of a pneumonectomy on this side.

The manuscript may be of some interest, since based on a large series of patients and due to the fact that the results obtained are quite original. However, the study has significant limitations due to the lack of information concerning the causes of death. In fact, data describing the different causes of mortality in the subsequent periods of follow-up could allow to better understand the pathophysiology of different types of pneumonectomies and improve treatment and prevention of complications. The Authors should discuss further this issue.

Reply: Thanks so much for your comments. We do agree that perioperative causes of death are essential for this study, but unfortunately, there is no specific data on the cause



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of death included in the SEER database. OS is an important aspect of prognostic analysis for cancer research. The main population of this study was NSCLC patients; therefore, OS was selected as the primary endpoint. Our center is currently building a database on the clinical and pathological characteristics of NSCLC patients after pneumonectomy, further analysis on the prognosis and treatment strategies for these patients and the specific factors related to postoperative death will be conducted in the future. Previous studies have mentioned that the cause of death within 30 days after pneumonectomy is mainly due to cardiac or pulmonary failure. We further elaborated on this issue in the Discussion section.

Changes in the text: Line: Line: 338.

Moreover, the Authors should also further address the limitations of the study related to the fact that, despite the use of propensity score matching, differences between the two study groups may still be present, in particular concerning tumor size and stage, an issue that may influence not only oncological results but also the complexity of surgery and therefore the incidence of postoperative complications and mortality.

Reply: Thanks so much for your constructive suggestion. This study used PSM to balance differences of clinical and pathological variables between two groups of patients. Due to the fact that this study involves patients undergoing pneumonectomy, which is already the most complex and thorough surgical method among pulmonary resection. The authors believe that the indicators with difference between two groups after PSM have limited impact on the study. We have stated this in the limitations section, and in addition, the authors are constructing a prospective multicenter database for NSCLC patients undergoing pneumonectomy to further evaluate prognostic factors and treatment strategies for patients at different stages.

Changes in the text: Line: 340-343.