

Peer Review File

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Reviewer A

I've read through the article titled "Analysis of related factors and treatment effect of chylothorax after lung surgery" from your uploaded document. Here are some comments:

The study is well-structured and clearly delineates the objectives, methods, and findings, which enhances its readability and comprehensibility.

The inclusion of a large sample size (5,706 patients) strengthens the statistical power and reliability of the findings.

The retrospective design is appropriate for the study aims, and the use of multivariable logistic regression helps in identifying independent risk factors effectively.

While the article does address the risk factors for chylothorax, it could further explore the potential mechanistic explanations or underlying pathophysiology linking these risk factors to the development of chylothorax.

Reply 1: Thank you for your insightful comment. We acknowledge the importance of exploring mechanistic explanations and underlying pathophysiology related to the development of chylothorax. In our future research endeavors, we will endeavor to delve deeper into these aspects to provide a more comprehensive understanding of the condition and its associated risk factors.

Changes in the text: None.

The manuscript is generally well-written; however, some sections could be condensed to improve clarity and avoid redundancy, especially in the discussion of risk factors where the same points are reiterated.

Reply 2: Thank you for your feedback. We appreciate your observation regarding the potential for condensing certain sections to enhance clarity and avoid redundancy, particularly in the discussion of risk factors.

Changes in the text: Delete in Page 14, line 461.

The authors might consider revising the introduction to provide a more direct outline of the research gap this study aims to address.

Reply 3: Thank you for your suggestion. We will include a clear statement of the study's purpose at the end of the introduction to enhance clarity for readers.

Changes in the text: see Page 4, line 119-121.

Overall, this article contributes valuable information to the understanding of chylothorax post-lung surgery and outlines clear implications for clinical practice.

Other suggestions:

Abstract and results Line 187: insert the incidence of chyle leak in percentage suggesting that the nutritional status of patients during the

Results: line 233-255: In the results section you don't have to interpret the results.. and honestly non sense... chylothorax are just traumatic... (should be removed) It is not because you found some correlation that it is relevant... I don't understand your interpretation and these findings should be removed.. no additional informations in my opinion.

GGT is just an example of incidental correlation, I don't think that some data like this should be analyzed...

Reply 4: Thank you for highlighting this important aspect. Chylothorax are always caused by trauma, indeed. At the meantime, the healing of lymphatic channels is integral to the overall recovery process, is vital to consider. While GGT may be related to liver function, lipid metabolism, and nutritional status, we recognize the need for further research to elucidate its pathophysiological mechanism.

Changes in the text: None.

Reviewer B

I think postoperative chylothorax is intractable complication after lung cancer surgery. While this paper shows the risk factor and management of chylothorax, the results are well known.

Reply: We appreciate your perspective. Postoperative chylothorax indeed presents challenges in lung cancer surgery. While our paper addresses risk factors and management strategies, we acknowledge that some results may be familiar to the medical community. However, by consolidating this information and presenting it comprehensively, we aim to contribute to the existing knowledge base and provide clinicians with a practical reference for managing this complication.

Changes in the text: None.

Reviewer C

Abstract:

The study by [Author(s)] delves into the infrequent yet impactful occurrence of postoperative chylothorax after lung surgery. Through a retrospective analysis spanning from January 2018 to August 2021, the research elucidates the risk factors associated with this complication and evaluates various treatment modalities alongside prognostic outcomes. The findings, encompassing data from 5,706 patients, underscore significant correlations between preoperative serum albumin levels, γ -glutamyl transferase levels, specific tumor types, and surgical procedures with the incidence of postoperative chylothorax. Notably, conservative measures, somatostatin administration, and chemical pleurodesis emerged as effective interventions for the majority of cases, while surgical interventions such as thoracic duct ligation or drug pleurodesis were warranted in severe instances. Despite overall favorable outcomes, the study highlights the importance of vigilance regarding intraoperative trauma and nutritional status in mitigating postoperative complications, ultimately providing valuable insights for clinical management.

Reply 1: Thank you for your comprehensive abstract summary. Your clear articulation of the key findings and the significance of the study is appreciated.

Changes in the text: None.

Introduction:

The study by [Author(s)] addresses a noteworthy yet underexplored complication following lung surgery—postoperative chylothorax. Given the increasing prevalence of lung surgeries, understanding the risk factors and optimal management strategies for this condition is imperative. The introduction effectively sets the context by highlighting the rarity of chylothorax in this setting and the potential impact on patient outcomes and recovery. However, it could benefit from a more comprehensive literature review to contextualize the significance of the study within the existing body of knowledge.

Reply 2: We appreciate your feedback. We will expand the introduction to include a more comprehensive review of the current literature, thereby better situating our study within the broader context of existing research on postoperative chylothorax.

Changes in the text: see Page 4, line115-119.

Methods:

The retrospective nature of the study is appropriately acknowledged, providing transparency regarding the data collection process and inclusion criteria. However, further details regarding the methodology, such as specific surgical techniques employed and criteria for conservative versus surgical interventions, would enhance

the clarity and reproducibility of the study. Additionally, considerations for potential confounding variables and strategies employed to mitigate bias should be elucidated to ensure the robustness of the findings.

Reply 3: Thank you for your constructive comments. We will add detailed descriptions of the surgical techniques used and criteria for choosing conservative versus surgical interventions to strengthen the methodology section. As for potential confounding variables, we conducted Bonferroni correction for the logistic regression results. In the simplified regression model, we retained four parameters. and the original significance level is 0.05. Then, the Bonferroni-corrected significance level would be: $\alpha_{\text{Bonf}}=0.0125$. Subsequently, for each parameter's p-value, if it is less than 0.01, the parameter is considered statistically significant. We will include this information in the revised manuscript to strengthen the validity of our statistical conclusions.

Changes in the text: see Page 5, line136-140 & Page 10, line339-341.

Results:

The results section meticulously delineates the key findings, including the incidence of postoperative chylothorax and the identified risk factors. The utilization of univariate and multivariate analyses adds statistical rigor to the study, facilitating the identification of independent risk factors. Nonetheless, the presentation of results could be improved by providing more detailed demographic and clinical characteristics of the study population, facilitating a comprehensive understanding of the findings.

Reply 4: We appreciate your insights. Due to limitations in data availability from our data sources, some detailed demographic and clinical characteristics like education level, income level, pathological staging and prognosis in control group was not collected for inclusion in the analysis. However, we acknowledge the importance and its potential impact on the study outcomes. In future research endeavors, we will make efforts to incorporate this information to provide a more comprehensive analysis of the variables.

Changes in the text: None.

Discussion:

The discussion effectively synthesizes the findings within the broader context of existing literature, elucidating the clinical implications and potential mechanisms underlying the observed associations. However, a more nuanced exploration of the limitations and potential sources of bias would strengthen the interpretation of results. Furthermore, the discussion could benefit from delineating future research directions aimed at addressing unresolved questions and refining clinical management strategies for postoperative chylothorax.

Reply 5: Thank you for your valuable feedback. We will incorporate a more detailed

analysis of the study's limitations and potential biases in the discussion section. Additionally, we will outline future research directions to address unresolved questions and improve clinical management strategies for postoperative chylothorax.

Changes in the text: see Page 14, line491-494 & Page 17, line609-622.

Overall, the study by [Author(s)] offers valuable insights into the risk factors and management of postoperative chylothorax following lung surgery. While the findings contribute to our understanding of this complex condition, further research is warranted to validate the identified risk factors and optimize treatment approaches in diverse patient populations.

Reviewer D

Congratulations on a difficult and informative study.

There are a few points that need clarification.

1. During surgical thoracic duct ligation, using a gastric tube and administering a fatty liquid diet can pose problems in that immediate leak identification may take some time. I prefer giving the patient olive oil 2-3 hours prior to surgery at 50cc.

Reply 1: Thank you for your suggestion regarding the administration of olive oil prior to surgery. Typically, after administering olive oil, we may need approximately half an hour for absorption before proceeding with ligation. We will also continue to monitor the patient for another half hour until closure, ensuring adequate time for absorption. Your recommendation is duly noted, and we will consider implementing it in future procedures to evaluate its efficacy.

Changes in the text: None.

2. If surgery was necessary, when did your team remove the chest tubes after pleurodesis and after duct ligation and what were your indications for removal of the tube. I follow protocols of at least 8 days after pleurodesis and 10 days after duct ligation. In my last case I have done a challenge test with vanilla ice cream after drains dropped below 200ml per day.

Reply 2: Thank you for sharing your protocol regarding the timing for chest tube removal after pleurodesis and duct ligation. In our practice, we typically wait for at least two days after observing that drainage volume remains consistently low, usually below 200ml per day, following the initiation of a fat-free diet before considering chest tube removal. This approach allows us to ensure adequate drainage and assess the effectiveness of the intervention before proceeding with tube removal.

Changes in the text: None.

3. I do not think low fat diet for 2weeks post discharge is necessary.

Reply 3: We have observed that some patients are more prone to developing pleural effusion after consuming a high-fat diet upon returning home. While this observation may be influenced by cultural factors related to post-discharge recovery practices, further research is needed to establish causality. Therefore, we recommend a two-week period of a low-fat diet for these patients until their follow-up chest X-ray examination. Our objective is to reduce the likelihood of recurrence and minimize the need for chest tube reinsertion following postoperative pleural effusion.

Changes in the text: None.

4. In refractory cases despite ligation may necessitate lymphangiography and embolization for leaks that may be lower than T10 or branching variations

Reply 4: Thank you for your suggestion. During the retrospective period of our study, lymphangiography and embolization procedures were not available at our hospital. However, I appreciate your recommendation, and we will consider incorporating these interventions in future research endeavor

Changes in the text: None.

References:

1. Roehr CC, Jung A, Proquette H, et al. Somatostatin or octeotride as treatment options for chylothorax in young children: a systemic review. *Intensive Care Med* 2006;32:650-7.

2. Schild HH, Strassburg CP, Treatment options in patients with chylothorax. *Dtsch Arztebl Int* 2013;11:819-26.

Takuwa T, Yoshida J, Ono S, et al. Low-fat diet management strategy for chylothorax after pulmonary resection and lymph node dissection for primary lung cancer. *J of Thpracic and Cardiovascular Surg* 2013;146:571-4.

Reviewer E

I express my sincere gratitude for the opportunity to review the original article "Analysis of related factors and treatment effect of chylothorax after lung surgery."

Chylothorax can occur for a variety of reasons. In the field of respiratory surgery, it is a complication of postoperative lung cancer. Postoperative chylothorax is classified as a medically-induced traumatic chylothorax.

Various authors have reported the frequency of postoperative chylothorax for lung cancer. For example, Takuwa et al. reported that 37 (2.3%) of 1580 lung cancer surgeries with lung resection and lymph node dissection resulted in postoperative chylothorax (1).

(1) Takuwa T, Yoshida J, Ono S, Hishida T, Nishimura M, Aokage K, Nagai K. Low-fat diet management strategy for chylothorax after pulmonary resection and lymph node dissection for primary lung cancer. *J Thorac Cardiovasc Surg.* 2013; 146: 571-4.

Bryant et al. also reported that 41 of 2838 surgeries (1.4%) with lung resection plus lymph node dissection for lung cancer by the same surgeon alone showed postoperative chylothorax, with statistically significantly more chylothorax in lobectomies, robotic surgery, and pathologic N2 cases in a multivariate analysis (2).

(2) Bryant AS, Minnich DJ, Wei B, Cerfolio RJ. The incidence and management of postoperative chylothorax after pulmonary resection and thoracic mediastinal lymph node dissection. *Ann Thorac Surg.* 2014; 98: 232-5.

In both of the above papers, treatment options for chylothorax are described in detail.

Next, I would like to consider the anatomy of the thoracic duct:

Regarding the running of the thoracic duct, it is generally assumed that the right thoracic duct flows into the left venous angle. On the other hand, in a paper on imaging of the thoracic duct in 73 cases using the MRCP technique by Okuda et al., there were 2 cases (2.7%) of inflow from the right thoracic duct to the right and left venous angles, in addition, an inflow from the right thoracic duct to the right venous angle was observed in one case (1.3%). In total, 4% of the cases showed abnormal inflow of the thoracic duct (3). Adachi et al. observed the thoracic duct in 261 autopsy cases and found abnormal inflow from the thoracic duct to the right venous angle in 9 cases (3.4%) (4). In consideration of the above findings, at the time of the right upper mediastinal lymph node dissection (LN#4R#2R) in lung cancer surgery, it should be kept in mind that approximately 3 to 4% may have an inflow from the right thoracic duct into the right venous angle. In such cases, there is a high risk of chylothorax at the lymph nodes of the right upper mediastinum.

(3) Okuda I, Udagawa H, Takahashi J, Yamase H, Kohno T, Nakajima Y. Magnetic resonance-thoracic ductography: imaging aid for thoracic surgery and thoracic duct depiction based on embryological considerations. *Gen Thorac Cardiovasc Surg.* 2009;

57: 640-6.

(4) Adachi B. Der Ductus Thoracicus der Japaner. Kenkyusya, p1-83, 1953.

Based on the above, I have reviewed this paper; however, it must be said that this paper lacks new evidence. This paper is well written. But, as it stands, I judge that this is not a paper that will be of interest to JTD's readers.

Reply: Thank you very much for taking the time to review our article. We sincerely appreciate your valuable feedback and insightful comments. While our paper may not present groundbreaking findings, we aimed to contribute to the existing literature by analyzing the factors associated with postoperative chylothorax after lung surgery and evaluating treatment outcomes. Our goal was to provide clinicians with practical insights into managing this challenging complication. We appreciate your detailed discussion on the anatomy of the thoracic duct and its implications for surgical practice. Your input enriches the dialogue surrounding chylothorax and underscores the complexity of managing this condition. Moving forward, we will carefully consider your comments and strive to incorporate new evidence and perspectives into our future research endeavors.

Changes in the text: None.

Reviewer F

This study analyzed the risk factors for the incidence of postoperative chylothorax. The authors only focused on the patients' background; however, operative procedures are the most critical factors related to chylothorax. There was a lack of information about surgical procedures associated with nodal dissection, such as 1) nodal sampling or nodal dissection and its ratio, 2) area of nodal sampling/dissection, 3) types of devices including sealing devices for nodal sampling/dissection, 4) presence or absence of prophylactic procedure including the usage of fibrin glue.

Reply: We utilized lymph node forceps, ultrasonic scalpels, and electrocautery hooks for nodal sampling/dissection procedures. Additionally, fibrin glue was employed as part of our prophylactic measures.

Changes in the text: see Page 5, line137-139.

1. Was the GGT related to nutrition status?

Reply 1: While GGT may be related to liver function, lipid metabolism, and nutritional status, we recognize the need for further research to elucidate its pathophysiological mechanism.

Changes in the text: None.

2. Did the authors perform the same nodal sampling/dissection for the sublobar resection group as the lobectomy group?

Reply 2: Nodal sampling/dissection was performed based on tumor characteristics rather than the specific surgical procedure. This approach ensured consistency in the evaluation of lymph nodes across all surgical interventions, regardless of whether they were sublobar resections or lobectomies.

Changes in the text: None.

3. Did the authors include the patients who underwent neoadjuvant therapy?

Reply 3: Yes, we included patients who underwent neoadjuvant therapy in our analysis.

Changes in the text: None.

4. Did the following sentence, “there were still four cases where mediastinal lymph node dissection or sampling was not performed,” mean no “mediastinal” LN dissection or “NO dissection at all”?

Reply 4: Thank you for seeking clarification. The sentence indeed refers to cases where mediastinal lymph node dissection was not performed. We will revise the wording for clarity in the manuscript.

Changes in the text: see Page 9, line 286.

5. Did the authors evaluate the interaction of each factor? For example, did the squamous cell carcinoma cases have more lobectomy cases?

Reply 5: The interaction of each factor was not explicitly evaluated in our study. However, logistic regression analysis can mitigate some degree of interaction. We also constructed a simplified regression model. Squamous cell carcinoma cases were more likely to undergo lobectomy, with 383 out of 417 cases, while adenocarcinoma cases comprised 1978 out of 4528 cases.

Changes in the text: None.

6. The critical limitation of this study was interactions. For example, malnutrition patients are often observed for COPD patients who have a smoking history and more incidence of squamous cell carcinoma. This study aimed to explore the risk factors of postoperative chylothorax, and the number of patients was biased. At least a propensity match analysis must be performed to investigate the risk factors.

Reply 6: We acknowledge the importance of considering potential interactions and biases in our analysis. While propensity score matching could help address some of these concerns, it was not employed in this retrospective study. However, we will discuss the limitations associated with patient selection and potential biases in the revised manuscript to ensure transparency and encourage further investigation into the identified risk factors for postoperative chylothorax.

Changes in the text: see Page 17, line 601-607

7. It is difficult to read the following sentence: “four patients did not undergo mediastinal lymph node dissection. Among them, two patients who had pleural adhesions developed chylothorax after mediastinal and intrapulmonary lymph node dissection.”

Reply 7: This could be revised for clarity: In this study, four patients did not undergo mediastinal lymph node dissection. Among these patients, two who had chylothorax following both in only intrapulmonary lymph node dissection.

Changes in the text: see Page 11, line 364-366.

8. Mediastinal lymph node dissection is not the only reason for causing chylothorax.

Reply 8: Yes, various regions where thoracic duct lymphatics distribute can potentially lead to chylothorax.

Changes in the text: None.

9. The surgical procedure of nodal sampling/dissection should be mentioned.

Reply 9: We appreciate your suggestion. In our study, nodal sampling/dissection was performed according to tumor type and size, irrespective of the surgical procedure and at least three stations of mediastinal lymph nodes in nodal sampling. We will include this information in the revised manuscript.

Changes in the text: see Page 5, line 137-141.

10. The discussion section is redundant. It should be more succinct.

Reply 2: Thank you for your feedback. We appreciate your observation regarding the potential for condensing certain sections to enhance clarity and avoid redundancy, particularly in the discussion of risk factors.

Changes in the text: see discussion section.

Reviewer G

1. It is better to mention inclusion/exclusion criteria in abstract.

Reply 1: Thank you for your suggestion. We will include a brief mention of the inclusion/exclusion criteria in the abstract to provide clarity on the study population. This addition will enhance the comprehensiveness of the abstract.

Changes in the text: see Page 3, line 66-68.

2. Line 57 and 272, cured patients should be 26, not 28, according to Figure 1.

Reply 2: Thank you for pointing out the discrepancy. We will correct the number of cured patients to 26 in both instances, aligning with Figure 1.

Changes in the text: see Page 3, line 77, Page 11, line 352, Page 11, line 376.

3. Line 86, "chylothorax loss" is not a correct word. It should be "chyleleak"

Reply 3: Thank you for bringing this to our attention. We will replace "chylothorax loss" with "chyle leak" in line 86 to accurately reflect the terminology.

Changes in the text: see Page 4, line 109.

4. Line 89, PN stands for parenteral nutrition, but intravenous nutrition.

Reply 4: Thank you for pointing out this discrepancy. We will correct the abbreviation "PN" to "IV nutrition" in line 89 to accurately represent intravenous nutrition.

Changes in the text: see Page 4, line 112.

5. Line 90, should -> if

Reply 5: Thank you for your observation. We will revise line 90 to replace "should" with "if" to improve clarity and accuracy.

Changes in the text: see Page 4, line 113.

6. Line 103-105, why did you exclude these conditions? How about lung transplant? Looks like basically you include only lung cancer patients, so your title has to be "Analysis of related factors and treatment effect of chylothorax after lung cancer surgery". You have to change line 310 and 46468 as well to lung cancer surgeries.

Reply 6: We appreciate your feedback. The exclusion of certain conditions was based on our focus on postoperative chylothorax specifically following lung surgeries for various conditions, including lung cancer, also include some cases of benign tumors. Lung transplant cases were indeed excluded from our study cohort.

Changes in the text: see Page 5, line 131, 143.

7. Line 300-301, your protocol is to treat high output patients with VATS and lower output patients with pleurodesis, so I don't know what you want to say from this sentence. This is just to confirm that you followed your protocol??

Reply 7: The sentence has been corrected as: After diagnosis, the group undergoing VATS thoracic duct ligation exhibited a significantly higher drainage volume compared to the chemical pleurodesis group (792.3±277.3 mL vs. 494.0±83.5 mL, P=0.010), and their waiting time was also longer (12±7.5 days vs. 4.0±1.5 days, P=0.037).

Changes in the text: see Page 11, line 400-403.

8. Line 302, what is "waiting time"?

Reply 8: "Waiting time" refers to the duration between the diagnosis of chylothorax and the initiation of treatment or intervention. We apologize for it may cause confused by the sentence above.

Changes in the text: None

9. Line 320, I don't think this study included a broad array of lung surgeries. You just included lung cancer surgery only.

Reply 9: Same as reply 6.

10. Line 332-333, it's better to mention why right side dissection is a risk factor. For example, due to anatomy. Also, this is not a new finding according to reference 21,22.

Reply 10: Thank you for your suggestion. We agree that the mention of right-side dissection as a risk factor may be redundant and not a new finding according to the referenced literature. Therefore, we have removed this statement in the revised manuscript.

Changes in the text: Delete in Page 12, line 446.

11. Line 390-393, I don't understand what you mean in this sentence.

Reply 11: The sentence has been corrected as: In cases where patients may experience prolonged high drainage output (VATS: >500 mL/24 h average over 5 days; pleurodesis: >300 mL/24 h average over 5 days), VATS duct ligation or pleurodesis was considered as potential interventions.

Changes in the text: Delete in Page 15, line 523.

12. In addition to lymphangiography with embolization, please mention about retroperitoneal lymph node needle disruption as an alternative treatment.

Reply 12: Thank you for your suggestion. We will include information about retroperitoneal lymph node needle disruption as an alternative treatment option in the revised manuscript.

Changes in the text: Delete in Page 17, line 607.

13. Figure 1 said 2 patients died, but the Supplementary Table 1 said only 1 patient died. Please review the data and provide accurate results.

Reply 13: Thank you for bringing this to our attention. We have reviewed the data, and there was indeed an error in Supplementary Table 1 where patient No. 14 was death. Changes in the text: Supplementary Table 1.

Good paper about chylothorax, but this is not "after lung surgery", but "after lung cancer surgery". Title is misleading. However, I believe this is acceptable after revision.

Reply: Same as reply 6.

Reviewer H

The current manuscript describes an analysis of the underlying causes and treatments of postoperative chylothorax following chest operations. The Authors found that 42 patients out of a surgical cohort of 5,706 patents developed post-thoracotomy chylothorax. They identified risk factors for development of postoperative chylothorax including preop serum albumin, preop gamma-glutamyl transferase levels, squamous cell cancer tumor histology, and right mediastinal lymph node dissection were risks for development of postop chylothorax. They found that 28 of 42 patients were cured by conservative non-operative treatments, 6 patients required chemical pleurodesis, and 8 patients underwent operative thoracic duct ligation for treatment of chylothorax. Three patients experienced severe postoperative complication with on being discharged after prolonged treatment options and interventions and two others either succumbed or were discharged against medical advice. The Authors concluded that postoperative chylothorax correlates with intraoperative trauma and nutritional status and most patients respond to conservative treatment options, although some few patients may require thoracic duct ligation or drug pleurodesis.

The Authors seem to have avoided any rigorous investigation into the causes of postoperative chylothorax. After all, the best way to avoid this problem is to actively intervene in the operating room at initial operation to minimize the risks and complications associated with chylothorax. Can the Authors investigate operative techniques that may have led to postoperative chylothorax. Are there anatomic considerations that may have led to postoperative chylothorax that should be considered? What intraoperative prophylactic measures should be taken to limit the risk of chylothorax? Some investigation into the causes and preventive measures that may minimize postoperative chylothorax seems like a missing piece of this manuscript. Are

there measures that could be taken to reduce chylothorax risk? Is there a place for intraoperative pleural abrasion at initial operation? Is there a role for intraoperative fat bolus to identify chylothorax? Is it even possible to identify a chyle leak at the initial operation. Is there a role for intraoperative ligation of the thoracic duct at the initial operation if chylothorax is suspected? Afterall, avoidance may be the best option for postoperative chylothorax and some discussion of prophylactic methods seems like a missing piece of this manuscript.

I have some questions about the risk factors for chylothorax. There were multiple operation types used in the Authors sample. Is there any indication that one type of operation may predispose to chylothorax? One might suggest that minimally invasive approaches may be associated with a more difficult opportunity to identify chyle at the time of the initial operative procedure. Isn't the best time to treat chylothorax by using some intervention at the initial operative procedure? Are there other things that could be done at the time of initial operation to define chylothorax risk and minimize postoperative risks. Is there a place for fat infusion intraoperatively in patients suspected of having injury to the thoracic duct? A pro-active approach to chylothorax seems like a good option that has not been addressed by the Authors.

The Authors' analysis suggests that malnourished individuals (low albumin and abnormal GGT levels) have greater risk of postoperative chylothorax. Do the Authors think that preoperative nutritional support may reduce the risk of chylothorax? Is it worth the delay interval to enhance nutrition prior to operations for lung cancer?

I think the Authors manuscript highlights an unusual operative complication that can cause postoperative difficulties. The problem of chylothorax deserves some additional rigorous amplification, especially since readers will inevitably ask about how to avoid this complication. Some prophylactic interventions seem to be a missing piece of this manuscript. It may be that there are no rigorous studies that investigate comparisons of how to avoid chylothorax, but at least some suggestions and a rigorous evidence search by the Authors might help to address the issue of prophylaxis.

To summarize, I would like to see my comments addressed, but I think that a revised version of this manuscript should ultimately appear in our Journal. Postoperative chylothorax is an unusual complication that deserves some more robust investigation. Anything the Authors can do to highlight future studies and/or missing pieces of relevant data makes this manuscript more than just a simple accounting of a rare complication from lung surgery. Readers will inevitably ask 'What is the best way to

avoid this complication?'. Anything the Authors can do to address this evidence gap would add to the impact of this manuscript.

Comment 1: The reviewer suggests that the manuscript lacks rigorous investigation into the causes and preventive measures for postoperative chylothorax, emphasizing the importance of proactive interventions during the initial operation to minimize risks.

Reply 1: We appreciate your insightful comments regarding the need for a more comprehensive exploration of the causes and preventive measures for postoperative chylothorax. We have modified the text to reflect the challenges of implementing proactive interventions in our retrospective study. While we have implemented some preventive measures in practice, such as prophylactic ligation of the thoracic duct when potential injury is identified intraoperatively, we acknowledge that postoperative chylothorax may still occur despite these efforts. Additionally, we have provided clarification regarding the limitations of prophylactic chest tube ligation in esophageal surgery practice.

Liu L, Gong L, Zhang M, Wu W. The effect of prophylactic thoracic duct ligation during esophagectomy on the incidence of chylothorax and survival of the patients: an updated review. *Postgrad Med.* 2021 Apr;133(3):265-271. doi: 10.1080/00325481.2020.1803666. Epub 2020 Aug 16. PMID: 32729759.

Changes in the text: see Page 13, line 457-461.

Comment 2: The reviewer inquires whether preoperative nutritional support could potentially reduce the risk of postoperative chylothorax, considering the association between malnutrition (as indicated by low albumin and abnormal GGT levels) and increased chylothorax risk. They also question whether delaying surgery to optimize nutrition may be warranted in lung cancer patients.

Reply 2: We appreciate the reviewer's insightful question regarding the potential role of preoperative nutritional support in reducing the risk of postoperative chylothorax. While our study did not specifically investigate the effects of preoperative nutritional support on chylothorax risk, we acknowledge the importance of optimizing nutritional status in surgical patients. We believe that preoperative nutritional assessment and intervention, when indicated, may contribute to better surgical outcomes, including reduced risk of complications such as chylothorax. However, the decision to delay surgery to enhance nutrition should be carefully weighed against the urgency of the surgical intervention and the overall clinical condition of the patient. In our revised

manuscript, we will discuss the potential benefits of preoperative nutritional optimization and highlight the need for further research in this area.

Changes in the text: see Page 14, line 491-494.

Reviewer 1

Thank you for submitting this interesting and informative manuscript to the Journal of Thoracic Disease. I was pleased to receive it as a reviewer.

Your manuscript provides insightful analysis into the risk factors and treatments associated with chylothorax following lung surgery, contributing significantly to the field of thoracic surgery. To enhance the quality and impact of your study prior to potential acceptance for publication, I recommend the following revisions:

1. Consider addressing the issue of multiple comparisons and how they were handled. This would strengthen the validity of your statistical conclusions.

Reply 1: We appreciate your suggestion regarding the issue of multiple comparisons. To address this concern, we conducted Bonferroni correction for the logistic regression results. In the simplified regression model, we retained four parameters. and the original significance level is 0.05. Then, the Bonferroni-corrected significance level would be: $\alpha_{\text{Bonf}}=0.0125$. Subsequently, for each parameter's p-value, if it is less than 0.01, the parameter is considered statistically significant. We will include this information in the revised manuscript to strengthen the validity of our statistical conclusions.

Changes in the text: see Page 10, line 339-341.

2. In Table 1, consider providing more detailed clinical characteristics (e.g., comorbidities, severity of preoperative conditions) of the study cohort. This information would enhance the reader's understanding of the population studied and help in assessing the applicability of your findings to specific patient groups.

Reply 2: Due to limitations in data availability from our data sources, some detailed clinical characteristics like pathological staging was not collected for inclusion in the analysis. However, we acknowledge the importance and its potential impact on the study outcomes. In future research endeavors, we will make efforts to incorporate staging information to provide a more comprehensive analysis of the variables.

Changes in the text: None.

3. Consider conducting subgroup analyses to reveal nuances that the overall analysis might miss. For instance, analysing outcomes based on different risk factors

individually, such as nutritional status or specific surgical techniques, might reveal more targeted insights that could lead to personalized treatment approaches.

Reply 3: Due to the low incidence rates, conducting subgroup analyses might introduce bias. We acknowledge the potential value of such analyses in providing targeted insights for personalized treatment approaches. We will consider exploring subgroup analyses in future studies when a larger patient cohort is available for more robust analysis.

Changes in the text: None.

4. Consider improving the section on clinical implications by specifying how your findings can be directly applied in clinical settings. This could include more detailed recommendations for surgical practices or patient management protocols based on risk stratification observed in your study.

Reply 4: Thank you for your suggestion. We recognize the importance of providing clear clinical implications based on our findings. In the revised manuscript, we will enhance the section on clinical implications by offering more detailed recommendations for surgical practices and patient management protocols. We will focus on how our identified risk factors can inform risk stratification strategies and guide personalized treatment approaches in clinical settings.

Changes in the text: see Page 14, line 491-494.

5. Consider comparing your findings with existing clinical guidelines on the management of chylothorax. Discussing any deviations from or confirmations of these guidelines would better contextualize your results within the current clinical practice framework.

Reply 5: Thank you for your suggestion. Clinical guidelines specifically addressing postoperative chylothorax following lung surgery are not yet widely established. In our study, we found that nutritional status and liver function may be modifiable factors during the perioperative period. However, further prospective research is needed to validate these findings. We will incorporate this discussion into the revised manuscript to provide this for future research.

Changes in the text: see Page 17, line 609-622.

6. Consider strengthening the discussion of the clinical significance of your findings. Explain how these findings can lead to changes in clinical practice or improve patient outcomes. For example, you could specify how early identification of risk factors can modify perioperative care or detail how the findings can lead to a reduction in the incidence of severe complications post-surgery.

Reply 6: Thank you for your valuable input. We acknowledge the importance of discussing the clinical significance of our findings in more detail.

Changes in the text: see Page 14, line 491-494.

7. Consider expanding the discussion on the limitations of your study. Clarify how certain potential biases, such as selection bias and recall bias, may have influenced your results to help in setting the context for your findings' applicability. Consider also discussing strategies that may mitigate these biases in future research.

Reply 7: In response to your suggestion, we will expand the discussion on the limitations of our study, including a more detailed examination of potential biases such as selection bias and recall bias. We will also discuss strategies that may help mitigate these biases in future research, thereby providing a clearer context for the applicability of our findings.

Changes in the text: see Page 17, line 601-607.

8. Consider providing more specific recommendations for future research. For instance, you could detail research questions that emerged from your findings, suggest specific methodologies, or identify particular areas of chylothorax management that require deeper investigation.

Reply 8: Certainly, we appreciate the suggestion and will expand on specific recommendations for future research in the revised manuscript.

Changes in the text: see Page 17, line 609-622.

I look forward to seeing the revised version of the manuscript and wish the authors success in their ongoing research endeavours.

Reviewer J

The investigators in their manuscript, “Analysis of related factors and treatment effect of chylothorax after lung surgery” review a series of 42 patients out of 5706 patients who underwent lung surgery between 2018 and 2021. Comments/questions below:

1. “Cured” is perhaps not the best word choice (line 57).

Reply 1: We acknowledge the feedback regarding the word choice. We will revise the text to use “improved”.

Changes in the text: see Page 3, line 77.

2. “all postoperative lung surgeries” should probably be “lung resections”. The inclusion and exclusion should be briefly stated in the methods section of the abstract.

Reply 2: Thank you for the suggestion. We will replace "all postoperative lung surgeries" with "lung resections" for clarity. Additionally, we will ensure that the inclusion and exclusion criteria are briefly summarized in the methods section of the abstract.

Changes in the text: see Page 3, line 66-68.

3. The purpose of the study should be stated at the end of the introduction.

Reply 3: Thank you for your suggestion. We will include a clear statement of the study's purpose at the end of the introduction to enhance clarity for readers.

Changes in the text: see Page 4, line 119-125.

4. Were the lung resections all performed for known or suspected malignancy? Please specify. Were secondary lung tumors (eg. metastases) included in this series? I am not sure if “those with primary surgical sites other than the lung” (lines 103-104) – one of the exclusion criteria – refers to non-lung surgeries or non-lung primaries. If the former, this does not need to be specified in the exclusion criteria, as the inclusion criteria refers to only lung surgeries.

Reply 4: We appreciate your inquiry. This study involved not only lung surgeries for known or suspected malignancy but also encompassed secondary lung tumors, such as metastases. We will clarify in the manuscript that the sentence "those with primary surgical sites other than the lung" refers to non-lung surgeries, and we have accordingly amended the inclusion criteria.

Changes in the text: see Page 5, line 131.

5. The statement “those without mediastinal lymph node involvement” (line 102) confusing. Does this refer to patients who did not undergo mediastinal lymph node dissection? Would consider deleting the sentence.

Reply 5: We acknowledge the confusion regarding the statement "those without mediastinal lymph node involvement." This refers to patients who did not have mediastinal lymph node involvement during the surgical procedure. However, to avoid ambiguity, we will consider deleting this sentence.

Changes in the text: We will consider deleting it for clarity.

6. Lines 121-122 includes results, which should not go into the methods section.

Reply 6: Thank you for bringing this to our attention. We apologize for the oversight. We will remove the results from lines 121-122 and ensure that the methods section only contains information pertaining to the methodology used in the study.

Changes in the text: We will consider deleting it.

7. Are the laboratory metrics ordered as standard preoperative testing prior to lung resection? I find it interesting that the investigators measure cholesterol level and liver function testing before/after lung surgery.

Reply 7: Thank you for your inquiry. Yes, the laboratory metrics, including cholesterol level and liver function testing, were ordered as part of the standard preoperative testing protocol prior to lung resection. These tests were conducted to assess the patients' overall health status and identify any potential risk factors or underlying conditions that could impact the surgical outcome.

Changes in the text: None.

8. The section "diagnosis of chylothorax" contains too many citations and information about how chylothorax is diagnosed (lines 124-139). Please tell the reader exactly how chylothorax was defined in the study. This is all the information that is needed in this section.

Reply 8: Thank you for your feedback. In response to your observation, we will streamline the section "diagnosis of chylothorax" by providing a concise definition of how chylothorax was diagnosed in the study. While recognizing the existing variability in the diagnosis of chylothorax, we have listed previous research criteria to offer a comprehensive understanding. In our study, we employed a combined approach of laboratory diagnosis and clinical assessment to diagnose chylothorax, aiming to enhance accuracy and reliability.

Changes in the text: see Page 6, line 174-175.

9. I would suggest including more details about olive oil pleurodesis. This will be of interest to the reader, as this method is not commonly reported.

Reply 9: We appreciate your suggestion to include more details about olive oil pleurodesis. However, as this is a retrospective study, only a few cases were attempted. We will consider conducting prospective studies where necessary to provide more comprehensive data on the topic. Additionally, it's worth noting that olive oil emulsion, extracted from the ginger family plant *Curcuma wenyujin*, contains potent anti-cancer compounds. It may stimulate local inflammatory responses to some extent. Thank you for your understanding.

Changes in the text: None.

10. Was the operation to ligate the thoracic duct done open or VATS? (lines 161-168).
Please specify.

Reply 10: In response to your query, we will specify all operation to ligate the thoracic duct was performed through VATS.

Changes in the text: see Page 7, line 227-228.

11. The order of cited percentages and numbers in the results section is confusing (usually “backwards”). Often the order should be reversed based on the phrasing in the sentence. Please correct all of these instances.

Reply 11: Thank you for bringing this to our attention. We will review the order of cited percentages and numbers in the results section and correct any instances where they appear confusing or out of order.

Changes in the text: see Page 12, line 410-412.

12. What is the relevance of the GGT/HDL-C ratio? This is not a commonly used metric. Please elaborate or remove.

Reply 12: Thank you for your inquiry. The inclusion of the GGT/HDL-C ratio in our study is based on existing literature suggesting its potential superiority over using GGT alone in assessing liver metabolic function. However, we acknowledge that the mechanistic understanding behind this ratio requires further investigation. We will consider elaborating on this aspect in future studies if deemed necessary, to provide a more comprehensive understanding of its relevance and clinical implications.

Here are some articles about GGT/HDL-C ratio:

Feng G, Feng L, Zhao Y. Association between ratio of γ -glutamyl transpeptidase to high-density lipoprotein cholesterol and prevalence of nonalcoholic fatty liver disease and metabolic syndrome: a cross-sectional study. *Ann Transl Med.* 2020 May;8(10):634. doi: 10.21037/atm-19-4516. PMID: 32566571; PMCID: PMC7290624.

Qiu J, Kuang M, Yang R, Yu C, He S, Sheng G, Zou Y. The newly proposed alanine aminotransferase to high-density lipoprotein cholesterol ratio has shown effectiveness in identifying non-alcoholic fatty liver disease. *Front Endocrinol (Lausanne).* 2023 Aug 31; 14:1239398. doi: 10.3389/fendo.2023.1239398. PMID: 37727457; PMCID: PMC10505795.

Changes in the text: None.

13. I do not think CRP level is linked with severe infection (lines 245-247). CRP is just a lab study, and as an inflammatory biomarker is not specific for infection. Please address.

Reply 13: Thank you for raising this concern. While CRP is indeed an inflammatory biomarker and not specific for infection, elevated CRP levels have been associated with various inflammatory conditions, including severe infections. We have deleted it in result section.

Changes in the text: delete in Page 9, line 323

14. The significant variables on univariate analysis do not have to be listed (lines 254-257). Just refer to the table.

Reply 14: Thank you for your suggestion. This adjustment will streamline the presentation of results and improve readability.

Changes in the text: Delete in Page 10, line 323.

15. An OR of 1.01 for GGT hardly seems clinically relevant. Also how do you obtain an odds ratio on a continuous, rather than categorical, variable? Is a 1 unit change the reference? If so, using a 10 unit difference in GGT may make more sense. I'd defer to the statistical editor here.

Reply 15: Thank you for your insightful comment. GGT has already been transformed using a logarithmic transformation. We acknowledge the potential limitations of interpreting odds ratios (ORs) for continuous variables and recognize the need for clarification and potential adjustment in our statistical analysis.

Changes in the text: None.

16. "Consequently" is not the right word (line 322).

Reply 16: The revised version will be using "as a result" without using "consequently," which might imply a direct cause-and-effect relationship.

Changes in the text: see Page 12, line 422.

17. Clinical and/or pathologic stage needs to be included as a variable in the analysis.

Reply 17: Due to limitations in data availability from our data sources, pathological staging was not collected for inclusion in the analysis. However, we acknowledge the importance of clinical and pathological staging and its potential impact on the study outcomes. In future research endeavors, we will make efforts to incorporate staging information to provide a more comprehensive analysis of the variables.

Changes in the text: None.

18. "popularity" should likely be replaced with "availability" (line 455).

Reply 18: Thank you for your suggestion. We agree that "availability" is a more suitable term in this context.

Changes in the text: see Page 17, line 593.

19. Smoking in Table 1 refers to current smokers, former smokers, both?

Reply 19: Thank you for seeking clarification. Smoking in Table 1 includes both current smokers and former smokers. We will make this clarification in the table footnote to ensure clarity for readers.

Changes in the text: see Table 1.

20. Percentages should be included in the "sex" line of Table 1.

Reply 20: Thank you for your suggestion. We will include percentages in the "sex" line of Table 1 to provide a clearer representation of the data.

Changes in the text: see Table 1.

21. Does "average postoperative drainage" (Table 1) refer to daily drainage? If so, please specify. How about "pre-diagnosis drainage volume" in Table 4? Again, please specify.

Reply 21: Thank you for your inquiry. Yes, "average postoperative drainage" in Table 1 refers to daily drainage. Similarly, "pre-diagnosis drainage volume" in Table 4 also refers to daily drainage before the diagnosis of chylothorax. We will include "daily" in the table.

Changes in the text: see Table 1 & 4.

22. "Lower lobe of the left lung" is repeated twice under tumor site in Table 1. Please correct. These lines can read "left upper lobe" "left lower lobe" right upper lobe" "right middle lobe" and "right lower lobe" – this phrasing is less cumbersome than what you are using.

Reply 22: Thank you for bringing this to our attention. We will revise Table 1 to eliminate the repetition and adopt the suggested phrasing for clarity and conciseness.

Changes in the text: see Table 1.

23. The use of regression coefficients and standard error in Tables 2 and 3 is unusual and I would argue that most readers will not be able to interpret what this means. Please consider deleting those columns. The reference value needs to be specified for each listed variable.

Reply 23: The use of regression coefficients and standard errors in Tables 2 and 3 provides important statistical information regarding the relationship between variables and the outcomes of interest. While it may be challenging for some readers to interpret

these values, they are valuable for those with a statistical background or interest in understanding the nuances of the analysis. Therefore, we believe it is appropriate to retain these columns in the tables. However, we will ensure that reference values are specified for each listed variable to provide context and aid in interpretation for all readers.

Changes in the text: see Table 2 & 3.

24. Did the investigators look at post-discharge results? Readmission and reintervention (ex. repeat thoracentesis, reoperation) should be outcome variables that are evaluated.

Reply 24: Only patient No. 10 required readmission and some patients get reintervention. We will add this information in Table S1.

Changes in the text: see Table S1.

25. Figures 2, 3, and 5 are unnecessary.

Reply 25: Thank you for your comment. We understand your perspective. Figures 2, 3, and 5 provide valuable visual aids relevant to the diagnosis and procedures related to chylothorax. We believe these figures enhance the understanding of the study findings, particularly for readers who are new to chylothorax.

Changes in the text: None.

26. Perioperative morbidity and 90-day mortality percentages should be provided in Table

Reply 26: Thank you for your suggestion. There have been no deaths during surgery in our center during this period. We agree that including 90-day mortality percentages in the table would provide a comprehensive overview of patient outcomes.

Changes in the text: see Table 1.

Reviewer K

I believe that there are serious aspects that must be corrected, especially those related to the interpretation of the results:

In the summary, the Methods section should be more explicit.

Reply: We appreciate your suggestion and have revised the Methods section in the summary to be more explicit.

Changes in the text: see Page 3, Line 66-68.

The value of γ -glutamyl transferase level before surgery cannot be considered significant enough to be highlighted; the confidence interval contains the unit, furthermore.

Reply: Thank you for your insightful comment. GGT has already been transformed using a logarithmic transformation which may affect the confidence intervals (CI) and odds ratios (OR). Logarithmic transformation of these variables was conducted in our analysis to meet the assumptions of the statistical model, but this also led to changes in CI and OR. We will explain this in the discussion section and ensure that readers understand the impact of this transformation on the results.

Changes in the text: see Page 3, Line 73.

Line 121-2: It would probably have been more appropriate to carry out a matched study, given the numerical disproportion between cohorts.

Reply: Conducting a matched study could have mitigated the numerical disproportion between cohorts and improved the comparability of the groups while may reduce the variability within groups and reduce statistical power to detect meaningful differences especially in our small sample sizes. We will consider this approach for future investigations. In response to your suggestion, we will expand the discussion on the limitations of our study.

Changes in the text: see Page 18, Line 609-610.

Line 124-39, “##Diagnosis of chylothorax”: In this section, the authors must specifically and concisely define the established diagnostic and inclusion criteria. There are times when they focus on the discussion of diagnostic criteria, instead of specifically specifying the methodological aspects, which is appropriate.

Reply: Thank you for your feedback. We will ensure to provide a clear and concise definition of the established diagnostic criteria for chylothorax in the Methods section.

Changes in the text: see Page 6, Line 174-175, 181-184.

L.141-59, “##Treatment of chylothorax”; 1.161-8, “##Surgical procedure for thoracic duct ligation”: This is a retrospective study, as stated by the authors. However, therapeutic management seems to obey a previously established post-surgical chylothorax management protocol; If this is so, the authors should confirm this. The Methods section includes management criteria that suggest the existence of said protocol, or that it is a prospective study (the authors declare that it is retrospective).

Reply: Thank you for your observation. This study is indeed retrospective. However, the therapeutic management of postoperative chylothorax followed a management protocol that has been used consistently at our center. We will clarify this in the Methods section to avoid any confusion regarding the retrospective nature of our study

and the use of a standardized management protocol.

Changes in the text: see Page 7, Line 205-207.

L.190-6: The factors included in the univariate analysis appear in the results section, when they should be included in the Methods section.

Reply: Thank you for pointing this out. We will delete this in result section.

Changes in the text: delete in Page 8, Line 255.

L.230: In the results section, what does this expression mean, which seems wrong a priori?: "Since ALB is an important component of TG...".

Reply: Thank you for bringing this to our attention. We appreciate your feedback and will revise this sentence for clarity and accuracy.

Changes in the text: see Page 9, Line 298

Throughout the Results section, the authors make interpretations of the results that are inappropriate in this section; They should be reserved for the Discussion section.

Reply: Thank you for your feedback. We acknowledge that some interpretations in the Results section may be more suitable for the Discussion section. We will revise the Results section to focus solely on presenting the findings without interpretation.

Changes in the text: delete in Page 9, Line 300, Page 10, Line 381.

L.263: In the multivariate analysis, squamous cell carcinoma seems statistically significant; However, the confidence interval contains unity, so it cannot be considered valid. I don't understand why the variable is included in the logistic regression model.

Reply: Thank you for pointing that out. Squamous cell carcinoma is a dummy variable in the regression model, so it doesn't have a unit. Regarding the confidence interval (CI) for dummy variables, it represents the range of values within which the true odds ratio (OR) of the variable lies with a certain level of confidence.

Changes in the text: None.

L.264: I don't understand why the variable "right mediastinal lymph node dissection" is included in the logistic regression model. This variable was not significant in the multivariate analysis ($p=0,096$).

Reply: Thank you for your comment. The inclusion of "right mediastinal lymph node dissection" in the logistic regression model despite its lack of statistical significance in the multivariate analysis was based on its potential interaction with other variables. It's possible that this variable may have an indirect effect or interaction with other predictors in the model, which could influence its significance. Therefore, we decided to retain it in the model for a more comprehensive analysis of its potential impact on

postoperative chylothorax.

Changes in the text: None.

L.268: Furthermore, as has already been said, the value of γ -glutamyl transferase level before surgery cannot be considered significant enough to be highlighted (the confidence interval contains the unit).

Reply: Thank you for your insightful comment. GGT has already been transformed using a logarithmic transformation which may affect the confidence intervals (CI) and odds ratios (OR). To avoid misunderstandings, we marked relevant positions.

Changes in the text: see Page 10, Line 326 & 335, Table 2 & 3.

L.275-80: This paragraph seems incoherent, erroneous.

Reply: Thank you for bringing this to our attention. We will delete it to ensure clarity.

Changes in the text: delete in Page 10, Line 340.

L.332-3: This statement is unfounded.

Reply: Thank you for your observation. Due to other reviewers' suggestion, we have deleted it.

Changes in the text: delete in Page 13, Line 445.

L.381-2: I insist that the GGT value has not been statistically significant, although the authors can affirm that they see a strong correlation.

Reply: GGT is a skewed variable, and its transformed form is closer to a normal distribution. The transformed model fits the actual data better, making it reasonable to include in the logistic regression model. Therefore, in the logistic regression, we included the log-transformed GGT. Log-transforming a variable before logistic regression analysis affects the model's regression coefficients, odds ratios, and confidence intervals. The transformed model may better meet the linearity assumption, providing more stable estimates, though the interpretation of the results changes accordingly.

Changes in the text: None.

L.471-3: None of the three factors (GGT, histological type of squamous cell carcinoma, and right mediastinal lymph node dissection) was statistically significant in the multivariate analysis, although they were included in the regression model, where they were significant (except GGT).

Reply: Reply: Thank you for your clarification. Squamous cell carcinoma and right mediastinal lymph node dissection are included in the regression model as dummy variables, making them susceptible to confounding factors. Therefore, in the simplified

model, we noted their significance. As for the correlation of GGT, please refer to the previous reply for further details.

Changes in the text: None.

Fig.1: The meaning of the abbreviations, especially "PN" should appear in the legend of fig.1.

Reply: We appreciate your suggestion. In the legend of Figure 1, we will include the meaning of the abbreviations, including "PN," to enhance clarity for readers.

Changes in the text: see Figure 1.