

Peer Review File

Article information: <https://dx.doi.org/10.21037/tlcr-24-336>

**Reviewer A**

**Comment 1:** The authors of “Insights into sex disparities in perioperative outcomes of lung cancer patients” present the interesting idea of understanding the sex differences in perioperative outcomes in patients with NSCLC. Although the idea behind the manuscript is good and sex differences are a very important topic, improvements are needed:

1. Make it clear in the title and abstract that this manuscript is about NSCLC patients, not “lung cancer patients” in general.

**Reply 1:** Thank you for your constructive feedback and for recognizing the importance of our study on sex differences in perioperative outcomes among NSCLC patients. In our revised manuscript, we will ensure that the title and abstract clearly specify that our study pertains specifically to patients with non-small cell lung cancer (NSCLC). Thank you for guiding us in this refinement.

**Change 1:** Thank you very much. We have modified our text as advised (see Page 1, line 1 and throughout the article).

**Comment 2.** In the results section in the abstract, it's not sufficient to say that “Women had a lower incidence of complications, shorter postoperative length of stays, and less hospitalization cost. Multivariable regression analysis identified sex as an independent factor of perioperative outcomes...” Present numbers (% , HR, 95% CI) that support your affirmations.

**Reply 2:** Thank you very much for your comment. In the revised abstract, we will include detailed numerical data, percentages, hazard ratios (HR), and their corresponding 95% confidence intervals (CI) to support our statements regarding sex differences in perioperative outcomes among NSCLC patients.

**Change 2:** Thank you very much. We have modified our text as advised (see Page 3, line 38-44).

**Comment 3:** In the conclusions of the abstract, be clearer about what differences exist and how to tackle this. This is what your manuscript is about. We already know that sex differences exist.

**Reply 3:** Thank you very much for your comment. In the revised abstract conclusions, we provided a more explicit statement regarding the nature of the sex differences observed in perioperative outcomes among NSCLC patients. Additionally, we will emphasize practical implications and potential strategies for addressing these differences in clinical practice.

**Change 3:** Thank you very much. We have modified our text as advised (see Page 4, line 48-53).

**Comment 4:** Some of your findings (for example, better surgical outcomes and higher treatment rates in women) go against some findings of the literature (see DOI 10.1016/j.jtocr.2022.100307). Please debate this and explain the reasons in the discussion.

**Reply 4:** Thank you very much for your comment. The study you referenced highlights psychological complications and immune-related adverse events, where females reportedly exhibit worse outcomes compared to males following general treatment for NSCLC. However, our study specifically focuses on perioperative outcomes after surgical intervention. We observed that females had a higher incidence of urinary tract infections compared to males, consistent with findings from other studies.

This discrepancy underscores the multifaceted nature of outcomes in NSCLC patients, influenced by various treatment modalities and patient characteristics. We revised our discussion to address these contrasting findings and highlighted potential factors contributing to sex-specific outcomes in both surgical and non-surgical contexts.

**Change 4:** Thank you very much. We have modified our text as advised (see Page 13-14, line 240-248).

**Comment 5:** The content of your introduction is good, but it is poorly written. I don't see links between phrases and paragraphs. There is enough evidence available to convince the reader that this is an important topic, but your introduction doesn't show that. I suggest rewriting this section, improving it. Also, please update reference 3 as we have GLOBOCAN with 2022

statistics available (DOI 10.3322/caac.21834).

**Reply 5:** Thank you for your valuable feedback. We have thoroughly revised the introduction section to enhance its coherence and improve the flow between sentences and paragraphs. Additionally, we have updated reference 3 to include the latest GLOBOCAN statistics from 2022 (DOI 10.3322/caac.21834).

These enhancements ensure that readers grasp the relevance and urgency of our research from the outset. We appreciate your guidance in refining this critical section of our manuscript.

**Change 5:** Thank you very much. We have modified our text as advised (see Page 6, line 77-101).

**Comment 6.** Give details about the dataset used. It contains data from patients from which institution? What is the profile of the patients there? Why is this different from national datasets? How does this population differ from the national population?

**Reply 6:** Thank you very much for your comment. The dataset used in this study originates from the Western China Lung Cancer Database, which is maintained prospectively by the Department of Thoracic Surgery, West China Hospital. As the largest medical center in southwest China, West China Hospital serves a diverse population, primarily from the southwest region but also includes patients from across the country.

**Change 6:** Thank you very much. We have modified our text as advised (see Page 7, line 110).

**Comment 7.** There are only 1 inclusion and 1 exclusion criteria? Provide a CONSORT diagram and broader details of the covariates used to select the patients to allow reproducibility.

**Reply 7:** Thank you very much for your comment. We have expanded our manuscript to include a CONSORT diagram illustrating the patient selection process. Additionally, we have provided broader details in patient inclusion and exclusion. These updates will help readers better understand the criteria for patient selection and replicate our methodology effectively.

**Change 7:** Thank you very much. We have modified our text as advised (see Page 7, line 112-114).

**Comment 8.** In the methods/results, the distribution of the population needs to be checked first. If the population doesn't fit a normal distribution (which is probably the case), you need to use median and quartiles for descriptive purposes and a non-parametric test for comparison (you are using the T-test, which is parametric and wrong depending on the distribution).

**Reply 8:** Thank you very much for your comment. We have checked the distribution of the quantitative variables using the Kolmogorov-Smirnov test and confirmed the variables included in our analysis fit the normal distribution. We added the description of distribution test in our Methods.

**Change 8:** Thank you very much. We have modified our text as advised (see Page 9, line 139).

**Comment 9.** What was the criteria/methodology for adjustment in multivariable models? Just throwing a lot of covariates there is not the best approach and may lead to equivocal results. I suggest following a stepwise approach or creating multiple adjustments models so you can have sensitivity analysis. Add this information in the text.

**Reply 9:** Thank you very much for your comment. We first performed univariable analysis on these covariates and the significant variables in univariable regression were adjusted in multivariable analysis. We have modified the description of our regression analysis in the manuscript.

**Change 9:** Thank you very much. We have modified our text as advised (see Page 9, line 143-149).

**Comment 10.** In results, what was the level of significance of this study? What p-value should we consider significant? Add this information to the text. Also add information on which kind of regression was performed (logistic? Linear? Cox?), with which R package, same for mediation.

**Reply 10:** Thank you very much for your comment. Two-sided  $P < 0.05$  was determined to be significant. But for mediation analysis, the bias-corrected and accelerated (BCa) bootstrap interval was used to evaluate the significance. We conducted multivariable logistic regression

analysis for categorical outcomes and multivariable linear regression analysis for continuous outcomes. We performed regression with R package 'glm' and the mediation analysis with package 'lavaan'. We added the description in our Methods.

**Change 10:** Thank you very much. We have modified our text as advised (see Page 8-9, line 137-183).

**Comment 11.** This work needs some subgroup and sensitivity analysis to have great statistical power and to achieve points not covered in the literature yet. Consider subgroup via race/ethnicity and stage and sensitivity by year of diagnosis and other relevant characteristics.

**Reply 11:** Thank you very much for your comment. Patients in our cohort were all Chinese, so we did not group via race/ethnicity. We divided the year of surgery into 2014-2015 and 2016-2021, considering the enhanced recovery after surgery in our department started from 2016. We also performed the subgroup analysis via stage and smoking history. Regarding postoperative hospital stays and hospitalization cost, subgroup analysis showed consistent outcomes with our main analysis, proving the statistical power. But for total complications, the stage III group and group with positive smoking history found the sex not the independent risk factor any more. This is the new findings and thank you for your suggestions again. We added the new findings in our article.

**Change 11:** Thank you very much. We have modified our text as advised (see Page 9, line 150).

**Comment 12.** In the discussion, please add a paragraph with clinical implications of the findings and how to use them in clinical practice.

**Reply 12:** Thank you very much for your comment. In the revised discussion section, we have included a paragraph outlining the practical implications of our study's results.

**Change 12:** Thank you very much. We have modified our text as advised (see Page 17, line 323-327).

**Comment 13.** In the discussion, there are only 2 limitations listed. This looks like an underestimation of the limitations of the study. Please rethink the limitations and rewrite this

section.

**Reply 13:** Thank you very much for your comment. We have revisited the limitations of our study and expanded this section to provide a more comprehensive overview.

**Change 13:** Thank you very much. We have modified our text as advised (see Page 18, line 328).

**Comment 14.** In Figure 1, please include what is the reference, does this risk refer to males or females? The same goes for figure 2. In figure 2, the risks and confidence intervals need to be included; we cannot infer only from p-values.

**Reply 14:** Thank you very much for your comment. We added the reference details in figure 1 and figure 2 (In the revised manuscript, Figure 2, Figure3). We also added risks and confidence intervals in figure 2.

**Change 14:** Thank you very much. We have modified our figures.

## **Reviewer B**

**Comment 1:** The study addresses an important topic by examining sex differences in lung cancer outcomes.

Major points:

1. The paper currently uses "sex disparity" to describe its findings. Disparities generally imply an inequality that is avoidable and unjust, often necessitating the inclusion of socioeconomic variables (SES) in the analysis. Without SES consideration, the term "sex difference" would be more accurate to describe variations that are not explicitly linked to inequity.

**Reply 1:** Thank you for your insightful comment. Upon reflection, we agree that "sex difference" more accurately describes the variations observed in perioperative outcomes between male and female NSCLC patients in our research. Moving forward, we used "sex difference" to characterize our findings in the manuscript, ensuring clarity and accuracy in our terminology.

**Change 1:** Thank you very much. We have modified our text as advised (throughout the manuscript).

**Comment 2:** The inclusion of patients across all stages (I-IV) raises concerns regarding the applicability of surgical outcomes, which are typically focused on early-stage (I-IIIa) lung cancer patients where surgery is most beneficial. Evaluating perioperative outcomes in late-stage patients (IIIb-IV), where surgery is less common or beneficial, may not be clinically relevant.

**Reply 2:** Thank you for your response. To enhance the generalizability of the results, we have expanded the sample size by including more patients with all stages. You are correct in noting that surgery is typically performed for stage I-IIIa patients. However, several studies have indicated that pulmonary resection can be associated with long-term survival and should be considered as a therapeutic option in cases of oligometastatic lung cancer (J Thorac Cardiovasc Surg. 2021;161(4):1497-1504.e2. doi: 10.1016/j.jtcvs.2020.02.134; Eur J Cancer. 2021;144:326-340. doi: 10.1016/j.ejca.2020.12.002; Surgery. 2017;161(5):1307-1314. doi: 10.1016/j.surg.2016.11.002). For the patients with stage IIIB or IV in our study, surgery was performed primarily for stage IIIB patients following chemotherapy or other neoadjuvant therapies. Additionally, for stage IV patients with oligometastasis, surgery was also conducted with the aim of achieving improved survival outcomes.

**Change 2:** Thank you very much.

**Comment 3:** The reported smoking rates among females are unusually low and inconsistent with cited literature (ref 8 & 25), particularly studies conducted in Asia which report higher prevalence. A detailed distribution of smoking status, including a category for missing data, should be provided to clarify these discrepancies.

**Reply 3:** Thank you for your comment. The observed discrepancy in smoking rates among females compared to the cited literature may be attributed to differences in study periods. For instance, the reference from J Thorac Oncol, 2010,5(10):1594-601 included patients undergoing lung cancer surgery in 1999, whereas our study covers patients from 2014 to 2021. This temporal difference could reflect evolving trends in female smoking habits over

time.

Additionally, according to recent studies, the overall smoking rate among Chinese females is 1.85% (*Drug Alcohol Depend.* 2024 May 1;258:111258), which aligns closely with the findings of our study.

To address this concern comprehensively, we have provided a detailed distribution of smoking status among all participants in our study, categorizing individuals into current smokers, ever smokers, never smokers, and showing the percentage for missing data. During our analysis, we consolidated current and former smokers into a positive smoking history category. These updates are reflected in Table 1 of our manuscript, enhancing clarity and transparency regarding smoking behaviors among our study cohort.

**Change 3:** Thank you very much. We have modified our text as advised (see Page 16, line 285).

**Comment 4:** - Abstract:

The authors mention early-stage in the introduction, while the study includes all stages. Please rewrite the sentence.

**Reply 4:** Thank you very much for your comment. We have modified the sentence.

**Change 4:** Thank you very much. We have modified our text as advised (see Page 3).

**Comment 5:** Define perioperative outcomes concisely in the methods section.

**Reply 5:** Thank you very much for your comment. We have revised the methods section to provide a concise definition of perioperative outcomes.

**Change 5:** Thank you very much. We have modified our text as advised (see Page 8, line 120-129).

**Comment 6:** -Main Paper:

In the introduction, the authors state that surgery is the standard treatment for early-stage NSCLC patients, while the study includes all stages. Please rewrite the related section (line 74).

**Reply 6:** Thank you very much for your comment. We have rewritten the related section.

**Change 6:** Thank you very much. We have modified our text as advised (see Page 6).



**Comment 7:** In the methods, list all comorbidities (line 101).

**Reply 7:** Thank you very much for your comment. We revised the manuscript to provide a comprehensive list of all comorbidities considered in our study, ensuring transparency and clarity in the selection criteria used for patient inclusion and analysis.

**Change 7:** Thank you very much. We have modified our text as advised (see Page 8, line 125).

**Comment 8:** Patients with lung cancer should not include COPD as a comorbidity. COPD is an independent risk factor for lung cancer (line 101 and table 1).

**Reply 8:** Thank you very much for your comment. While COPD is indeed associated with an increased risk of lung cancer, it is also important to consider its impact on surgical outcomes in patients with existing lung cancer. Including COPD as a comorbidity allows us to assess its influence on perioperative complications, hospital stay, and costs among NSCLC patients undergoing surgery. We will provide further clarification on this in the revised manuscript to address any potential confusion.

**Change 8:** Thank you very much.

**Comment 9:** For perioperative outcomes, list references or logic for selecting the conditions (incidence of postoperative complications, postoperative drainage volume in the first 3 days, etc.) to measure the perioperative outcomes (line 111).

**Reply 9:** Thank you very much for your comment. We appreciate your suggestion to provide references or rationale for selecting specific perioperative outcomes in our study. We will include references to relevant literature and previous studies conducted by our team to justify the inclusion of conditions such as the incidence of postoperative complications and postoperative drainage volume in the first 3 days as key perioperative outcomes.

**Change 9:** Thank you very much. We have modified our text as advised (see Page 8, line 123).

**Comment 10:** For sample size estimation, provide a reference or more logic for using PAL as

the outcome to estimate the sample size (line 118).

**Reply 10:** Thank you very much for your comment. PAL was selected as an outcome for sample size estimation based on its clinical significance and prevalence in NSCLC patients undergoing surgery, as supported by existing literature. We will provide appropriate references and further rationale in the revised manuscript to clarify our choice of PAL for sample size estimation.

**Change 10:** Thank you very much. We have modified our text as advised (see Page 8, line 131).

**Comment 11:** For the multivariable model, please examine the collinearity assumption (line 128).

**Reply 11:** Thank you very much for your comment. We conducted variance inflation factors analysis to assess collinearity among the independent variables included in the model, while the results indicating no significant collinearity issues among the variables. We added the description of this assessment in our methods part.

**Change 11:** Thank you very much. We have modified our text as advised (see Page 9, line 150).

**Comment 12:** Explain why the patients' mean age at diagnosis is so young. Add the study population's background for better understanding.

**Reply 12:** Thank you very much for your comment. The relatively young mean age at diagnosis in our study population can be attributed to several factors. Firstly, our inclusion criteria focused on recent patients (2014-2021), reflecting contemporary trends where lung cancer diagnoses are increasingly occurring at younger ages. Moreover, this trend is supported by our previous study with the same database (Transl Lung Cancer Res. 2023 Mar 31;12(3):446-459.), which have also reported similar age distributions. We appreciate the opportunity to clarify these points and will ensure to provide a detailed background of our study population in the revised manuscript.

**Change 12:** Thank you very much. We have modified our text as advised (see Page 11, line 191).

**Comment 13:** In table 1, check the smoking history for female groups. It appears too low. Does the female group have a higher missing smoking status compared to males? This is not comparable to studies mentioned in references 8 and 25 (line 24).

**Reply 13:** Thank you for your comment. The observed discrepancy in smoking rates among females compared to the cited literature may be attributed to differences in study periods. For instance, the reference from *J Thorac Oncol*, 2010,5(10):1594-601 included patients undergoing lung cancer surgery in 1999, whereas our study covers patients from 2014 to 2021. This temporal difference could reflect evolving trends in female smoking habits over time.

Additionally, according to recent studies, the overall smoking rate among Chinese females is 1.85% (*Drug Alcohol Depend.* 2024 May 1;258:111258), which aligns closely with the findings of our study.

To address this concern comprehensively, we have provided a detailed distribution of smoking status among all participants in our study, categorizing individuals into current smokers, ever smokers, never smokers, and showing the percentage for missing data. The missing rate between males and females were comparable. During our analysis, we categorized current and former smokers into a positive smoking history category. These updates are reflected in Table 1 of our manuscript, enhancing clarity and transparency regarding smoking behaviors among our study cohort.

**Change 13:** Thank you very much. We have modified our text as advised (see Page 16, line 287).

**Comment 14:** In the discussion, rerun the analysis related to smoking status and rewrite the related paragraph (line 246).

**Reply 14:** Thank you very much for your comment. As mentioned in Reply 13, we have addressed the reasons behind the observed smoking prevalence trends in our study. Given these considerations, we will discuss the implications of smoking status in the context of our findings in the discussion section, without rerunning the analysis. We sincerely appreciate your concern and input. We will certainly acknowledge and discuss the implications of

smoking status in our study in the discussion section, reflecting on the insightful points raised by the reviewer.

**Change 14:** Thank you very much. We have modified our text as advised (see Page 16, line 287).

Minor points:

**Comment 15:** In the results, use "female" and "male" consistently (line 155).

**Reply 15:** Thank you very much for your comment. We have carefully checked and revised the manuscript.

**Change 15:** Thank you very much. We have modified our text as advised.

**Comment 16:** For table 1, add mean/SD to age.

**Reply 16:** Thank you very much for your comment. We added the mean/SD to ages. And we updated the presentation of data in Tables.

**Change 16:** Thank you very much. We have modified our tables.

**Comment 17:** Consider reformatting the table 1 for better presentation, especially for variables with different categories (e.g., stage, resection extent, history, pleural adhesion).

**Reply 17:** Thank you very much for your comment. We appreciate your suggestion to reformat Table 1 for better presentation. We have revised Table 1 to enhance its clarity and readability, especially for variables with different categories such as stage, resection extent, history, and pleural adhesion. We believe these changes improve the presentation and accessibility of the information.

**Change 17:** Thank you very much. We have modified Table 1.

**Comment 18:** Table 2 is about the sex difference distribution only and should not be combined with figure 1. Delete figure 1 in the sentence (line 162).

**Reply 18:** Thank you very much for your comment. We have deleted figure 1 in the sentence.

**Change 18:** Thank you very much. We have modified our text as advised.

**Comment 19:** Add abbreviations for all tables and figures.

**Reply 19:** Thank you very much for your comment. We added the abbreviations for all tables and figures as suggested.

**Change 19:** Thank you very much. We have modified our tables and figures.

## **Reviewer C**

### **Comment 1: ABSTRACT**

Result (major revision): For sex disparities to exist, there should be a gap between males and females perioperative for the factors under consideration. The authors stated, “Mediation analysis revealed that age, body mass index, prevalence of chronic obstructive pulmonary disease, predicted diffusion capacity for carbon monoxide, tumor size, pleural adhesion, and surgery duration were identified as mediators for sex disparities in outcomes, while smoking status, surgery type, and resection extent were not.” Therefore, where are the disparities established between men and women based on the outlined mediating factors? Authors can improve their study if they can establish disparities in the perioperative outcomes for the various factors by sex.

**Reply 1:** Thank you very much for your comment. We firstly found that sex differences existed in the incidence of postoperative complication, length of hospital stay and hospitalization cost. Then we uncovered the attributed factors driving sex differences in perioperative outcomes. Thank you very much for your suggestion. We have added more information in related section.

**Change 1:** Thank you very much. We have modified our text as advised (see Page 3-4, line 28-53).

### **Comment 2: INTRODUCTION**

Major revision: I suggest that the authors include the hypothesis of their study in the last paragraph of their introduction.

**Reply 2:** Thank you very much for your comment. We have included the hypothesis of this study.

**Change 2:** Thank you very much. We have modified our text as advised (see Page 7, line 99).

**Comment 3: METHODS**

Major revision: (1) Were there any missing data? If so, how were they handled? (2) Were there patients with unknown or in-situ lung cancer stage?

**Reply 3:**

Thank you for your question regarding missing data.

(1) In our study, there were minimal missing data for certain variables: smoking status, pleural adhesion, postoperative drainage volume in the first 3 days, total postoperative drainage volume, and hospitalization cost, which we showed in Tables 1-2.

We included these missing data directly in our statistical analysis. Specifically, we employed complete case analysis, where cases with missing data were included in the analysis as they were, without imputation. This approach ensures that all available data are utilized without introducing potential biases from imputation methods.

Furthermore, we conducted sensitivity analyses to assess the potential impact on our findings. The analyses showed that the inclusion of missing data did not significantly alter our results or conclusions.

We have revised the methods section to include a detailed explanation of how missing data were handled to provide clarity on this aspect of our study.

(2) We did not include the patients with unknown or in-situ lung cancer stage.

**Change 3:** Thank you very much. We have modified our Methods section (see Page 10, line 162-168).

**Comment 4:** Major revision: Sex is a categorical or dummy variable. Therefore, the authors should clearly state which group was used as a reference in the regression and mediation models.

**Reply 4:** Thank you very much for your comment. We appreciate your suggestion to clarify the reference group. In our analysis, we used males as the reference group. Consequently, the

regression coefficients and mediation effects for the variable "sex" represent the differences between females and males. We have updated the methods section to clearly state this information, ensuring that the reference group is explicitly mentioned.

**Change 4:** Thank you very much. We have modified Methods section as advised (Page 9, line 157; Page 11, line 184-185).

**Comment 5:** Major revision: Figure 1 represents “Multivariable analysis on the association between sex and perioperative outcomes. (a) categorical outcomes; (b) continuous outcomes.” How were the categorical outcomes measured? Also, what type of multivariable analysis was conducted? It is essential for authors to include that in the method section and in the footnote description of the figure.

**Reply 5:** Thank you very much for your comment. In our study, categorical outcomes such as perioperative complications were measured as binary variables (yes/no). The detailed definitions were also showed in the Methods. We conducted multivariable logistic regression analysis for categorical outcomes and multivariable linear regression analysis for continuous outcomes. We have updated the methods section to include these details and added a footnote to the relevant figure to ensure clarity.

**Change 5:** Thank you very much. We have modified our text as advised (see Page 9-10, line 158-160).

**Comment 6:** In Tables 1 and 2, what type of statistical test p-values are being displayed? It is essential for authors to include that in the footnote description of the Tables.

**Reply 6:** Thank you very much for your comment. In Tables 1 and 2, the p-values for categorical variables were calculated using the Chi-squared test or Fisher's exact test as appropriate. And P-values for continuous variables were using Student's t-test since all were in normal distribution. We have updated the footnotes of both tables to include this information.

**Change 6:** Thank you very much. We have modified tables as advised.

**Comment 7:** Major revision (Statistical Analysis): the authors should link their statistical

analyses and tests conducted to the results tables or figures for easy readability and understanding. For example, the authors can state: In Table 1, we conducted .... Or “Baseline characteristics and perioperative outcomes between men and women were compared with Student’s t-test and X2 test when appropriate.” (see Table ...)

**Reply 7:** Thank you very much for your comment. In the revised manuscript, we have clarified the statistical tests conducted and referenced them in relation to the results tables for easier readability.

**Change 7:** Thank you very much. We have modified our text as advised (see Page 8-9, line 142,157,164,177).

**Comment 8:** Additional recommendation: The authors can further improve their study by considering the stratified regression analyses of men and women for each of the perioperative outcomes. This allows us to examine the differences and behavior of factors associated with perioperative outcomes in each subgroup of men and women.

**Reply 8:** Thank you very much for your comment. We agree that stratified regression analyses of men and women could provide deeper insights into the factors influencing perioperative outcomes within each subgroup. In our revised manuscript, we incorporated stratified regression analyses to explore and compare these factors more comprehensively between men and women. We appreciated the opportunity to enrich our analysis in this manner.

**Change 8:** Thank you very much. We have modified our text as advised (see Page 10, line 160-161; page 12, line 211-213).

#### **Comment 9: RESULTS**

Major revision: The analyses result from Tables 1 and 2 are difficult to read directly. For instance, if in Table 1, the columns of males and females present the mean (standard deviation), for clarification, the authors should include them in the column headings. I suggest they should also include the type of statistical test conducted in the tables as part of the footnote description of the tables.

**Reply 9:** Thank you very much for your comment. In the revised manuscript, we ensured



that the column headings clearly indicate the statistical measures presented. Additionally, we included footnotes in each table specifying the type of statistical test conducted for each comparison. These enhancements will provide readers with clearer and more informative presentations of our analyses.

**Change 9:** Thank you very much. We have modified our tables as advised.

**Comment 10:** Minor revision: Page 5, Line 164, there should be space between as and PAL.

**Reply 10:** Thank you very much for your comment. We have revised.

**Change 10:** Thank you very much. We have modified our text as advised (see Page 11, line 197).

**Comment 11:** Major revision: The authors stated, “The perioperative outcomes had little percentage of missing data as follows: postoperative drainage volume in the first 3 days (1.1%), postoperative drainage volume in total (1.2%), and hospitalization cost (3.7%).” I don’t think that is the right place to present the percentage of missing data. It should be presented in the methods as part of the data exclusion.

**Reply 11:** Thank you very much for your comment. We appreciate your suggestion regarding the presentation of missing data percentages. We have moved the information about the missing data percentages from the results section to the methods section, as part of our data exclusion and handling procedures.

**Change 11:** Thank you very much. We have modified our text as advised (see Page 10, line 166-168).

**Comment 12:** Major revision: The odds ratios in Figure 1 have not been well presented and interpreted. Odds ratios compare the outcome of two groups, one group representing the reference. Similarly, in Figure 2, the interpretation of the results of male vs female for each outcome is not clear. The comparison of males and females is the core objective of the study and should be clear and concise.

**Reply 12:** Thank you very much for your comment. We acknowledge that clearer presentation and interpretation of odds ratios and comparisons between males and females

are crucial. In Figure 1, we revised the presentation of odds ratios to explicitly state the reference group for each comparison. In Figure 2, we included risks and their corresponding confidence intervals alongside the p-values. This addition will provide a more comprehensive and informative view of the differences between males and females for each outcome.

**Change 12:** Thank you very much. We have modified our figures.

**Comment 13:** Major revision: The estimated confidence intervals for arrhythmia and gastrointestinal complications in Figure 1 and clinical stage (IV) in Figure 2 are too wide. Also, in Figure 3, some variable's estimated coefficients are almost zero, meaning they have little or no impact on the outcome. These may happen as a result of small samples of some subgroups or extreme values/outliers/influential observations. Such problems can be corrected by transformation or standardization of the variables. The authors should consider this approach before conducting the regression analysis.

**Reply 13:** Thank you for bringing up these important considerations. We carefully reviewed your comments and have taken several steps to address the issues raised.

Regarding Figure 1 (Figure 2 in revised manuscript), we noted the wide confidence intervals for arrhythmia and gastrointestinal complications were primarily due to the small sample sizes in these subgroups. Consequently, we have decided not to present the regression results for these variables in Figure 1, as their statistical reliability in multivariable regression was limited by the sample size.

Similarly, in Figure 2 (Figure 3 in revised manuscript), the wide confidence intervals for clinical stage IV were also influenced by the small number of patients in this stage. Recognizing the distinct tumor progression represented by each stage, we chose to present the stages separately rather than combining them. We have acknowledged this limitation in the Limitations section of our manuscript.

For Figure 3 (Figure 5 in revised manuscript), which depicts mediation analysis results, we observed small coefficients for categorical variables like complications. Despite these small values, the significance of these results can still be interpreted from the figure.

In response to your suggestion about data transformation or standardization, we confirmed

during our initial data examination that there were no extreme values or outliers affecting our regression analyses. Thank you once again for your valuable feedback.

**Change 13:** Thank you very much. We have modified our figures.

**Comment 14:** DISCUSSION

The discussion can be further improved after addressing some of the issues above.

**Reply 14:** Thank you for your feedback on our discussion. Specifically, we will enhance the discussion to incorporate a more thorough analysis of the implications of our findings, particularly in relation to the sex differences observed in perioperative outcomes. This will include a deeper exploration of the clinical significance and the broader implications for clinical practice and future research directions. We are committed to ensuring that the revised discussion section provides a comprehensive and insightful interpretation of our study's results. Thank you once again for guiding us in this process.

**Change 14:** Thank you very much. We have modified our text as advised.