Peer Review File

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Reviewer A

Comment 1: *The article "Prediction of prognosis of intrahepatic cholangiocarcinoma after hepatectomy based on propensity score matching: a competitive risk model analysis is very interesting and author presented the paper with the support of necessary figures are valid. The scructure of the acricle is correct and the topic very good discussed.*

Reply 1: We sincerely appreciate the reviewer's positive evaluation of our manuscript. We are pleased to know that the reviewer found the structure of the article to be correct and the topic well-discussed. The reviewer's acknowledgment of the necessary figures supporting our study gives us confidence in the clarity and effectiveness of our presentation.

Changes in the text: While there were no specific suggestions for changes, The entire manuscript was carefully reviewed and further refined to ensure consistency and clarity. We have also cross-checked all figures and supporting data to confirm their validity and relevance to the discussion, ensuring that our presentation remains accurate and compelling. Please review the details of the specific changes, which we have marked in dark red font in the text.

Thank the reviewer once again for their generous praise and for the opportunity to contribute to the scientific discourse through Translational Cancer Research.

Reviewer B

Comment 1: In the abstract, “The subgroup analysis revealed that, for stage N1 ICCA patients with lymph node dissection…” should change to “The subgroup analysis revealed that, for ICCA patients with N1 stage following lymph node dissection….”.

Reply 1: We sincerely thank the reviewers for their careful review and for pointing out the grammatical errors in our abstract. We have made revisions and checked other elements for grammatical errors.

Comment 2: The authors compared 3-year survival between patients who received chemotherapy versus patients who did not receive chemotherapy, after surgical treatment revealing N1 stage. How did they exclude selection bias (factors contributing to the decision not to offer chemotherapy and at the same time to the death of these patients)?

Reply 2: We sincerely appreciate the reviewer for the meticulous review and valuable feedback on our manuscript. the reviewer's rigorous scientific attitude has played a crucial role in enhancing the quality and academic value of our work. In our initial submission, we indeed overlooked the important issue of selection bias, and we deeply apologize for this oversight. At the same time, we are very grateful for the reviewer's timely identification and thoughtful comments, which provided us with an invaluable opportunity to improve our manuscript. To address this issue, we have revised the "Section 4.06" of the manuscript as follows: To minimize the potential impact of baseline characteristic differences on the results, we applied the propensity score matching (PSM) method. Using this method, we matched patients based on key baseline characteristics, including gender, age, pathological grade, lymph node dissection, and other important variables. After matching, the baseline characteristics between the two groups were significantly balanced (as shown in Table 3 and Table 4 of the manuscript). This approach aimed to mitigate the influence of known confounding factors in observational studies. Initially, our study aimed to identify subgroups of patients who might derive potential benefits from adjuvant therapy, providing evidence for its efficacy. However, after conducting subgroup analyses in the PSM-matched population and performing sensitivity analyses to validate the results, we found that the sample size was far too small, which severely compromised the reliability of the findings. Therefore, to ensure the robustness, reliability, and scientific rigor of our results, we decided to remove the section in the original draft discussing "subgroup analyses of different T stages, N stages, and lymph node dissection." Instead, we focused solely on the overall survival analysis of patients with balanced baseline characteristics. We hope these revisions address the reviewer's concerns, and we sincerely thank the reviewer again for the reviewer's valuable suggestions on our manuscript!

Changes in the text: we have modified our text as advised (see Page 2 and Page 16).

Comment 3: Results of the measured parameters, especially those descriptively quoted in the abstract (AUC etc), should be provided. Otherwise, there is only a repetition of "exhibited good performance" in the results and conclusions.

Reply 3: We thank the reviewer for their detailed review and valuable comments. Regarding the problem of 'lack of quantitative indicators (e.g., AUC, etc.) in the abstract, and general statements in the results and conclusions', we have added specific performance parameters in the abstract to avoid the use of vague statements. We believe that these improvements have made the results of the article clearer and more convincing. Thank the reviewer very much for the reviewer's professional suggestions, and we would like to further improve it if there is any other feedback!

Changes in the text: we have modified our text as advised (see Page 2, line 25-27).

Comment 4: In the abstract conclusions, what are the "positive results from regional lymph node dissection"? I presume the authors mean "with histologically involved lymph nodes following lymphadenectomy". If so, please correct. Use robust language throughout.

Reply 4: We thank the reviewers for their careful review and valuable suggestions. Regarding the issue of 'positive results of regional lymph node dissection' mentioned in the conclusion of the abstract, we have deleted it and improved the content to avoid misunderstanding. We thank the reviewers for their careful revision, and will continue to improve the article if there are any other comments!

Changes in the text: we have modified our text as advised (see Page 2, line 32-34).

Comment 5: It would be advisable to take advantage of the keywords to use terms not included in the title. Terms included in the title possess a keyword function per se.

Reply 5: Thanks to the reviewer' suggestions, we have adjusted our keywords to avoid reusing terms from the title and have chosen more descriptive and representative terms to better improve the retrieval rate and academic dissemination of the article.

Changes in the text: we have modified our text as advised (see Page 2, line 35-36).

Main text

Comment 6: The authors should explain the practical implications of a prediction model being produced after propensity score matching.

Reply 6: We sincerely thank the reviewers for their valuable comments. We fully agree with the importance of the question 'Practical implications of predictive modelling after propensity score matching (PSM)'. We described it briefly in the methodology section of the initial manuscript. However, we decided to expand on this further in the Talk section of the revised version by specifically explaining the value and significance of the practical application of propensity score matching post-predictive modelling. Specifically, the use of PSM ensures that the training and validation groups are balanced in terms of baseline characteristics while avoiding selection bias, thus enabling the predictive model to more accurately reflect the actual situation of the patients.PSM not only improves the robustness of the model, but also enhances the reliability of the prediction results, which makes the model more instructive for practical clinical applications. In this way, the model can more accurately provide individualised prognostic assessment for postoperative patients, especially for patient groups with different clinical risk factors.

Changes in the text: we have modified our text as advised (see Page 7, line 110; see Page 24, line 211-216).

Comment 7: Lines 67-68: “extremely aggressive” is an overstatement, unless the authors feel they can justify.

Reply 7: : We would like to sincerely thank the reviewer for their valuable comments. Upon further reflection, we agree that the expression ‘extremely aggressive’ as the reviewer pointed out is a bit exaggerated. In order to express our views more accurately and carefully, we have made a revision in the text. We believe this change better reflects the reality of the study. Thank the reviewer again for the reviewer's careful review and constructive comments.

Changes in the text: we have modified our text as advised (see Page 3, line 38-39).

Comment 8: Line 73 needs rephrasing.

Reply 8: : We would like to sincerely thank the reviewers for their valuable feedback. We have rephrased line 73 to improve clarity and precision. The revised sentence now reads as follows: Although surgical resection remains the primary treatment for ICCA, the heterogeneity of this tumor in terms of anatomy, molecular characteristics, pathology, and clinical presentation poses significant challenges to the accurate prediction of postoperative prognosis. We believe this revision enhances the readability and aligns better with the context.

Changes in the text: we have modified our text as advised (see Page 3, line 40-43).

Comment 9: In the last sentence of the introductory part, “thereby enhancing clinical management and improving patient prognosis.” is a “long shot”, so should be removed.

Reply 9: We would like to sincerely thank the reviewers for their constructive comments. After much thought, we also feel that deleting the sentence the reviewers mentioned would be better. We have removed and adjusted the textual content of the preamble.

Changes in the text: we have modified our text as advised (see Page 4, the introductory part).

Comment 10: According to the exclusion criteria, “were under 18 years of age” means that it should be specified in the title, conclusions etc that the study refers to “adults”/”adult patients”.

Reply 10: We sincerely thank the reviewers for their attention to the population of this study. We have clearly stated in the inclusion criteria that this study was conducted in patients aged 18 years and above and excluded all patients younger than 18 years. Since cases of intrahepatic cholangiocarcinoma (ICCA) in children are extremely rare, the study population was naturally dominated by adult patients, which is consistent with the target population in actual clinical practice. We believe that the reason for not labelling ‘adult patients’ in the title and conclusions is to maintain the overall simplicity and academic appeal of the study, rather than intentionally omitting information about the age of the study population. Also, the inclusion and exclusion criteria were detailed in the Methods section, which made it clear that the study population was 18 years of age or older. If the reviewers felt it necessary, we could have further stated in the discussion section that the study population was adult patients and emphasised that this would not affect the generalisability of the conclusions.

Comment 11: "Lymph node dissection" needs to be defined. Did this include patients with any number of lymph nodes >0 removed? Was the impact of the number of retrieved lymph nodes assessed? The general recommendation for lymphadenectomy is 6 lymph nodes. Was that taken into account?

Reply 11: We sincerely thank the reviewers for their valuable comments and suggestions. For patients with ICCA, there are no clear and uniform international guidelines recommending minimum standards regarding lymph node dissection. For example, although some guidelines recommend resection of at least 6 lymph nodes to provide accurate staging, there is still a lack of specific consensus on the extent of ICCA clearance, the number of cleared lymph nodes, and other issues. Due to the limitations of missing and poorly described data in the SEER database, as well as to improve the simplicity of the model and better clinical applicability, 'lymph node clearance' was set as a dichotomous variable (yes/no) in the present study, rather than being graded according to the number of lymph nodes cleared. Nonetheless, we suggest that more prospective studies on the criteria for lymph node dissection in ICCA should be conducted in the future to provide stronger evidence.

Comment 12: 5-year survival is a well-established and commonly accepted outcome metric in oncology/surgical oncology. The authors should additionally test the performance of their nomogram for at least 5-year survival as it is essential (and possibly for 10-year survival). Presenting 1-year, 3-year and 5-year survival might be a preferable pattern.

Reply 12: We sincerely thank the reviewers for their valuable comments and suggestions. Regarding why 1-, 2- and 3-year survival rates were chosen as the primary endpoints of the study, we based on the following considerations: ICCA is a highly aggressive malignant liver tumour, and even after undergoing hepatic resection, the long-term survival rate of the patients is still very low. In addition, relevant studies have shown that ICCA has a high short-term recurrence rate after surgery and a poor prognosis. Secondly, the goal of this study was to develop a postoperative survival prediction model for ICCA patients by competing risk analysis with risk stratification in order to identify high-risk patients early and provide them with individualised treatment strategies. Therefore, the selection of 1-, 2- and 3-year survival rates as primary endpoints can more directly guide postoperative management and follow-up planning and help optimise short-term interventions. Short-term prediction is closer to the actual clinical needs of ICCA patients than 5-year or longer periods. Finally, although the SEER database is a large-scale database, there are more missing and biased data in long-term follow-up data (e.g., 5-year survival), and in order to improve the reliability and applicability of the model, we preferred short-term (1-, 2-, and 3-year) survival as the endpoint of the study. In future studies, we plan to extend the follow-up time to further validate the performance of the model for predicting 5-year and longer-term survival rates.

Comment 13: Lines 157-159 need rephrasing.

Reply 13: Thanks. We have scrutinised 'lines 157-159' and found that there is a lack of clarity of expression, but we have revised it in time.

Changes in the text: we have modified our text as advised (see Page 7, line 117-118).

Comment 14: In Line 160, it would be meaningful to specify at least in brackets what the authors mean by "elderly" (according to the methodology description, >60-years old).

Reply 14: We would like to sincerely thank the reviewers for their careful reading, and we have promptly revised the manuscript for lack of clarity of language.

Changes in the text: we have modified our text as advised (see Page 7, line 120).

Comment 15: In Lines 167-168, the authors state: "Additionally, 13.63% of the patients received radiotherapy, and 42.03% received chemotherapy." Was this neoadjuvant, adjuvant or both?

Reply 15: We would like to sincerely thank the reviewer for his/her detailed review of this study and the reviewer's valuable questions. With regard to the specific use of chemotherapy and radiotherapy preoperatively (neoadjuvant), postoperatively (adjuvant), or throughout the perioperative period, after reviewing the descriptions of the relevant variables in the SEER database, we found that the database only records information on chemotherapy and radiotherapy as dichotomous variables ('Yes' and 'No/ Unknown") and did not clearly distinguish between time points of treatment (e.g., neoadjuvant, adjuvant, or perioperative). Therefore, the analyses of chemotherapy and radiotherapy in this study were based only on the dichotomous variable of whether or not the patient had received that treatment. To avoid confusion for the reader, we will further clarify this limitation in the manuscript and add a note on this issue in the Discussion section, highlighting the impact of database limitations on the results of the analyses, as well as the importance of clarifying the time point of treatment in future prospective studies. We have added the following to the methodology section: Chemotherapy and radiotherapy were recorded in the SEER database as binary categories ('yes' or 'no/unknown'), without further differentiation between neoadjuvant, adjuvant, or perioperative use.

Changes in the text: we have modified our text as advised (see Page 5, line 84-86).

Comment 16: Line 177, hepatectomy instead of posthepatectomy.

Reply 16: We sincerely appreciate the reviewer's comment.We have revised it in time, please review it.

Changes in the text: we have modified our text as advised (see Page 10, line 133).

Comment 17: The legend of Figure 1 needs to be more concise.

Reply 17: We sincerely appreciate the reviewer's comment. We have simplified the legend based on the reviewer's suggestions to improve simplicity and readability.

Changes in the text: we have modified our text as advised (see Page 11, Figure 1).

Comment 18: The analysis has not taken into account the surgical margins of the specimen following hepatectomy, i.e. R0/R1/R2 (microscopic / macroscopic clearance/involvement), which is absolutely essential. This should be included in the analysis as it can be a major predictive factor which cannot be neglected by any means, for any meaningful conclusions. The relevant definitions should be provided for R0/R1/R2 [and it should be specified which definition of R1 was utilised (AJCC vs RCPath)].

Reply 18: We sincerely thank the reviewer for highlighting the importance of considering surgical margins (R0/R1/R2) after hepatectomy. We fully agree that surgical margin status is an important prognostic factor that should ideally be included in analyses to draw meaningful conclusions. However, we would like to clarify that the SEER database does not provide a specific classification of surgical margins such as R0, R1, or R2, which is a limitation of the database. Although we acknowledge that surgical margin status is a key factor influencing prognosis and that there are many similarly important influencing factors, it cannot be avoided. Examples include other variables such as cirrhosis and viral hepatitis. As a retrospective study, the inclusion of these factors is often limited by the data available in large public databases such as SEER. Furthermore, such challenges are inherent to retrospective studies, which we believe is a common limitation of similar studies. Nonetheless, we recognise the importance of surgical margin status, and we plan to incorporate this factor in future prospective studies or when using data sets with more comprehensive clinical information.

Comment 19: In Figure 2, p values denoting statistical significance should be added where applicable.

Reply 19: Thanks to the reviewers for their constructive comments. We have added p-values to Figure 2.

Changes in the text: we have modified our text as advised (see Page 14, *Figure 2*).

Comment 20: All AUC values are <0.80, starting from 0.668, with the highest being 0.721. Values <0.80 are widely considered of limited utility. Therefore, statements such as "highlighting the robust discriminative ability of the nomogram", "exhibited good predictive accuracy" etc, are inaccurate. Furthermore, in accordance with this, the clinical utility of this nomogram would be unfortunately limited. The relevant phrasings should be adjusted throughout.

Reply 20: We appreciate the reviewer's insightful comments regarding the model's performance. Although the AUC values in our study are between 0.668 and 0.721, we believe these results still demonstrate clinically meaningful predictive capability, especially in the context of intrahepatic cholangiocarcinoma (ICCA), a malignancy characterized by poor prognosis and aggressive biological behavior. The calibration plots of this study reveal a good agreement between the predicted and actual survival rates at 1, 2, and 3 years in both the training and test cohorts, indicating the model's reliability in estimating survival outcomes over short-term intervals. Furthermore, the Kaplan-Meier survival curves demonstrate the ability of the nomogram to stratify ICCA patients into distinct risk groups (low, medium, high) with statistically significant differences in survival (log-rank $p < 0.001$). This risk stratification facilitates individualized patient management and follow-up strategies. Lastly, the decision curve analysis illustrates the nomogram's net clinical benefit over traditional TNM staging and other variables, underscoring its potential utility in guiding clinical decision-making. While acknowledging the limitations posed by AUC values under 0.80, we have adjusted the wording that the reviewer mentioned in the manuscript to reflect the model's moderate predictive accuracy and emphasized its practical implications for short-term prognostication and patient stratification.

Comment 21: The authors state: "postoperative adjuvant radiotherapy did not substantially improve survival outcomes for patients who underwent local lymph node dissection, regardless of their N stage". This type of analysis may create the wrong impression that adjuvant radiotherapy failed to achieve a goal that it doesn't possess. When is/was adjuvant chemotherapy offered? When is/was adjuvant radiotherapy offered?

Reply 21: We thank the reviewers for their detailed review of our work and valuable suggestions. Regarding the statement ‘postoperative adjuvant radiotherapy did not substantially improve survival outcomes for patients who underwent local lymph node dissection, regardless of their N stage', we have removed this part to avoid unnecessary misunderstanding. dissection, regardless of their N stage', we have removed this part to avoid unnecessary misunderstanding. In addition, due to the limitations of the SEER database, the specific time points of radiotherapy and chemotherapy (e.g., preoperative, postoperative, or the entire perioperative period) were not recorded in detail, and therefore we could only analyse the results based on the question ‘Whether or not they received radiotherapy or chemotherapy' (dichotomous variable: Yes/No), and we could not explore the impact of the duration of treatment or the specific treatment regimen on survival outcomes. We could not further explore the effect of treatment duration or specific treatment regimen on survival outcomes.

Comment 22: In the Discussion the authors state: "Even among patients who undergo radical surgery successfully, the survival rate after five years is only 30–40% (16), with a poor long term prognosis." As this statement reads, it means that these 30-40% of patients, after surviving 5 years, they have a poor long-term prognosis. If this is what the authors want to say, they need to provide references. However, even so, this statement is self-contradictory. Furthermore, the numbers in this statement are against the earlier statement that ICCA is an extremely aggressive cancer. In addition, the authors acknowledge here the value of the 5-year survival metric for assessment of oncological outcomes, but haven't performed 5-year analysis themselves.

Reply 22: We thank the reviewers for their detailed review of our work and valuable suggestions. Regarding the statement 'Even among patients who undergo radical surgery successfully, the survival rate after five years is only 30-40%, with a poor long term prognosis', we have realised that its wording may lead to misunderstanding. Even among patients who undergo radical surgery successfully, the survival rate after five years is only 30-40%, with a poor long term prognosis', we have realised that the wording may lead to misunderstanding. Our original intention was to state that even if patients with intrahepatic cholangiocarcinoma (ICCA) undergo radical surgery, the overall postoperative prognosis is still not favourable, especially with a poor long term prognosis. We have therefore amended the paragraph to more accurately express our view. Furthermore, we fully agree with the reviewers regarding the importance of 5-year survival as an assessment of oncological outcomes. However, the 5-year analysis was not included because our study focused on predictive modelling based on postoperative 1-3 year-specific survival rates, with the primary aim of better guiding early postoperative management and follow-up strategies.

Changes in the text: we have modified our text as advised (see Page 23,line 195-199).

Comment 23: Line 278 - "These results indicate that this nomogram has strong discrimination ability" - this is an overstatement.

Reply 23: We thank the reviewers for their careful review and scientific rigour. We are also aware of the lack of precision in the language used in the article and have revised it.

Comment 24: Lines 280-281 - "Moreover, risk stratification the nomogram further augments" - needs linguistic polishing.

Reply 24: We thank the reviewers for their suggestions, and we have promptly made linguistic improvements.

Changes in the text: we have modified our text as advised (see Page 23-24,line 203-211).

Comment 25: Lines 283-285 - "This stratification model enables clinicians to more accurately evaluate postoperative prognosis and provides a robust basis for developing individualized treatment plans." The authors should provide more insight of how the stratification model provides a robust basis for developing individualized treatment plans.

Reply 25: We thank the reviewers for their suggestions. Our stratification model combines key clinical variables to classify patients into low, intermediate, and high-risk groups, providing a scientific basis for individualised treatment. Specifically, the model can guide the adjustment of the intensity of postoperative follow-up, the selection of adjuvant therapy for high-risk patients, the optimal allocation of medical resources, and the improvement of patient prognostic communication, thus enhancing the precision and individualisation of postoperative management.

We have added relevant content in the Discussion section to further elucidate the clinical value of the model.

Changes in the text: we have modified our text as advised (see Page 23-24,line 203-211).

Comment 26: Lines 286-287 - “This study revealed that ICCA patients with poor differentiation, advanced T stage, local lymph node invasion, or distant metastasis have worse prognoses.” This is very well established in the literature.

Reply 26: We appreciate the reviewer's comments. We agree that this part of the content reflects a well-established consensus in the existing literature. Therefore, the purpose of discussing it is to further validate and support these known clinical principles in light of our findings, while also highlighting the model's role in identifying high-risk patients. We will revise the wording to avoid reiterating established conclusions and to emphasize the innovative contributions of our study.

Comment 27: Lines 289-291 - This and similar subsequent statements are repetitive.

Reply 27: We thank the reviewers for their careful review. We have found a real duplication of what you mentioned and we have removed it.

Comment 28: Line 301 - Do the authors mean T3 stage and/or N1 stage disease?

Reply 28: We thank the reviewers for their work in reviewing our manuscript. This section was misleading and has been removed to ensure consistency.

Comment 29: Lines 305-306 - If there are such guidelines, references should be provided.

Reply 29: We thank the reviewers for their suggestions on our manuscript. In the previous reply, we have revised the ‘Section 4.06’ part of the article accordingly, and in order to improve the quality of the article, we have decided to delete the content mentioned by the reviewers.

Comment 30: Lines 311-313 - “To achieve more precise staging and optimize postoperative treatment strategies, we advocate for the routine performance of local lymphadenectomy during ICCA surgery.” As such, this statement is arbitrary. How does this statement compare to the strongest recent level of evidence? Moreover, the authors have not made analysis of the impact of local lymphadenectomy on perioperative morbidity and mortality. How do they define local lymphadenectomy and what is the number of minimum required lymph node harvesting based on their findings?

Reply 30: We thank the reviewers for their comments. Due to the limitations of this study based on the SEER database (including a decreased sample size due to more missing data and fewer clinical variables), it was not possible to perform an in-depth analysis of the specific definition of local lymph node dissection, the number of lymph nodes collected, and its impact on perioperative morbidity and mortality. In addition, we have removed the relevant statement you mentioned to avoid possible misrepresentation. At the same time, we also noted that many of the existing studies based on the SEER database did not clearly define these aspects, which may reflect the general limitations of the data sources. We hope that more future studies should further explore these important issues to provide more comprehensive guidance.

Comment 31: Lines 318-320 - "Nevertheless, this study did not demonstrate any benefit of adjuvant radiotherapy for resectable ICCA patients. This indicates that while adjuvant therapy may show some benefit in specific high-risk subgroups, overall, ICCA patients do not uniformly benefit from postoperative chemotherapy or radiotherapy." This statement is arbitrary, vague and unclear. In which settings did the authors explore the potential benefit of adjuvant radiotherapy? What do the mean by "adjuvant radiotherapy for resectable ICCA patients"?

Reply 31: We thank the reviewers for their valuable comments. Because of the limitations of the database, the details of the relevant variables were not sufficiently described, and we have deleted the part of the statement related to the 'potential benefits of adjuvant radiotherapy for patients with resectable ICCA'. The focus of this study has been adjusted to explore the clinical value of individualised prognostic assessment and risk stratification of postoperative ICCA patients through the construction of a line drawing model and a risk stratification model. We believe that this adjustment can focus more on the core objectives of the study and avoid causing unnecessary misunderstanding among readers.

Comment 32: Line 326 - "remarkable performance" is an overstatement.

Reply 32: Thank you to the reviewers for their suggestions. We have replaced it with a more professional wording.

Comment 33: Line 336 - It should be "internally validated".

Reply 33: We appreciate the reviewers' rigorous manner of research. We have made the corresponding changes in the manuscript as requested.

Comment 34: Lines 341-342 - Given the limitations the statement "This study lays a robust foundation for the optimization of future personalized treatment strategies." is far too strong.

Reply 34: We thank the reviewers for their valuable comments on our manuscript. We note that the reviewers pointed out that the statement 'This study lays a robust foundation for the optimization of future personalized treatment strategies' was too strong, and given the limitations of the study, we have removed this sentence as suggested. We understand this and agree that the results of the current study provide more of an initial frame of reference for individualised therapeutic strategies rather than directly laying the foundation for future therapeutic strategies.

Comment 35: The use of robust scientific language should apply throughout. Typographic corrections should be made.

Reply 35: We thank the reviewers for their valuable suggestions on our manuscript. We have carefully reviewed the language used in the article to ensure that rigorous scientific language has been used throughout to meet the standards of the journal. We have also made the necessary typographical corrections to ensure that the manuscript is formatted properly and clearly.