

1/09/2025

World Journal of Gastrointestinal Surgery

Dear Editorial Board,

We are submitting our revised manuscript titled '**Impact of statin therapy on postoperative outcomes following colorectal cancer surgery: A narrative synthesis**' for publication consideration in World Journal of Gastrointestinal Surgery. We appreciate the reviewers' and editorial office's comments, all of which have been specifically addressed in the revised version of the paper. We hope that these changes will make this paper suited for publication in the journal. Please find below the reviewer and editorial office comments in bold and the author's responses in non-bolded font.

This manuscript is not under publication consideration elsewhere. Disclosures are stated in the manuscript. All authors have reviewed the manuscript and have agreed to its submission for publication.

Regards,

Corresponding Author.

Reviewers' comments:

Reviewer #1:

1. While evidence on anastomotic leak rates is inconclusive, the balanced discussion - noting conflicting findings and possible confounding factors - is a strength, as it avoids overinterpretation.

- We thank the reviewer for recognizing and appreciating our balanced approach to discussing the outcomes.

2. The results have practical significance for perioperative management strategies, particularly in high-risk surgical populations with cardiovascular comorbidities.

- We are grateful that the reviewer highlighted the practical significance of our findings. The authors agree that identifying such potential benefits in high-risk surgical populations is clinically important and a key motivation for our synthesis.

3. The authors appropriately position their findings as hypothesis-generating, underlining the need for prospective randomized trials. This approach enhances credibility and clinical applicability.

- We appreciate the reviewer's recognition of our hypothesis-generating approach.

4. By integrating surgical risk factors (e.g., rectal vs. colon resections, emergency vs. elective surgery) and systemic-level care variations into the analysis, the paper provides a more nuanced understanding than prior overviews.

- We thank the reviewer for noting the integration of risk factors and variations. Our aim was to provide a comprehensive synthesis reflecting real-world variability and expanding on the depth of prior reviews.

5. The topic is clinically relevant, and the balanced presentation will be useful for both clinicians and researchers interested in perioperative pharmacological adjuncts in CRC surgery. Overall, the work meets the standards for publication in the World Journal of Gastrointestinal Surgery without the need for substantive revision.

- We sincerely appreciate the reviewer's positive assessment of the manuscript's relevance and its utility.

Reviewer #2:

1. Overall Structure and Clarity: The manuscript is well-structured, but certain sections could be more concise, especially in the methodology section. The discussion of study inclusion criteria and study designs could be streamlined to focus more on the key elements.

- We thank the reviewer for emphasis on the clarity of our text. In the revised manuscript, the text under the methodology section relating to the inclusion criteria and study design was made to be concise.

2. There are some formatting issues, particularly with inconsistent spacing and paragraph breaks. Please review the document carefully and ensure consistent formatting throughout to improve readability.

- We appreciate the reviewer's comment. In the revised manuscript, we have thoroughly reviewed and ensured consistent formatting across the text.

3. Literature Review Depth and Breadth: While the review covers relevant studies on the impact of statins in CRC surgery, the inclusion of newer studies or related reviews would strengthen the discussion. More recent literature should be referenced to provide a timely and up-to-date perspective.

- We thank the reviewer for highlighting the importance of including recent evidence. Our review incorporates the most up-to-date studies available in

literature, including Loffler et al. 2024, Bahl et al. 2024 which represent the latest contributions to this topic. Currently, similar studies have not yet been published in 2025, highlighting the limited amount of studies in current literature.

4. The manuscript mentions conflicting results in studies regarding the effects of statins on anastomotic leak and postoperative mortality. The authors should explore the reasons behind these discrepancies, particularly in terms of differences in study design, statin types, dosage, and therapy duration. Addressing these factors in the discussion would provide more clarity.

- We appreciate the reviewer's comments. In our revised text for the discussion, we have expanded to consider possible explanations for these differences, including study design (retrospective cohorts and their population sizes), lack of variability in statin type (lipophilic versus hydrophilic), as well as differences in doses and duration of therapy, which were underreported across majority of the included studies. Furthermore, we have also highlighted that the lack of stratification by statin subtype and period of administration represent key limitations in current literature.

5. Literature Support for Postoperative Complications: The manuscript mentions that approximately one-third of patients undergoing CRC surgery experience postoperative complications (such as anastomotic leak, small bowel obstruction, surgical site infections, etc.). It would be helpful if the authors provide references to support this claim, which would enhance the clinical significance of the study.

- We sincerely thank the reviewer for this valuable comment. We have addressed this point in the revised manuscript by incorporating appropriate references in the Introduction section to support the statement. In addition, we have elaborated on the major risk factors that increase the likelihood of such complications.

6. Clarification of Tumor Recurrence Rate: The manuscript states that surgical resection itself may lead to tumor recurrence, with a recurrence rate of 25-45% at 5 years post-surgery. This statement is somewhat unclear. The authors should provide more detailed clarification on the source of this recurrence rate and how it is calculated to avoid any ambiguity.

- We appreciate the reviewer's comment on this detail. For this, we have thoroughly reviewed the original reference and have stated the parameters from which the original authors derived the statistics from.

7. Clarification of Statin Types Used in Studies: Several studies are cited showing that statin use reduces the incidence of anastomotic leak, sepsis, and short-term mortality in CRC patients. However, the types of statins used in these studies are not specified. The authors should clarify which statins (e.g., atorvastatin, simvastatin) were used in the studies mentioned and discuss how different statins might influence the results.

- We thank the reviewer for their observation on this detail. In many of the included studies of this narrative synthesis, the type of statin was not specified, as the data were stated to be extracted from registries or prescription databases which recorded statin use as a class rather than by individual administered agent. In response, we have clarified this limitation in the discussion, emphasizing that the heterogeneity in statin subtype may influence the inferences drawn from this synthesis and further underscore the need for future trials to report and analyze stratified statin types.

8. Clarification of Liushen Li et al. Meta-analysis: The manuscript cites a meta-analysis by Liushen Li et al. indicating that statins reduce cancer-specific mortality in CRC patients. However, the cited meta-analysis does not specifically focus on rectal cancer, which could be misleading. The authors should clarify this point and provide more context about the relevance of this meta-analysis to the current review.

- The authors appreciate the reviewer's comment to clarify this text. In response to their suggestion, we have elaborated on the relevance of the reference of this meta-analysis and to avoid any misleading interpretation we have mentioned that although Liushen Li et al's analysis did not stratify outcomes by colon versus rectal cancer, the findings remain relevant given that rectal cancer represents a subset of CRC, hence providing important context while also emphasizing the vital need for future stratified studies based on tumor location.

9. Study Quality Assessment: The authors mention using the Newcastle-Ottawa Scale (NOS) to assess the quality of the included studies, but there is limited discussion on how the quality of individual studies might impact the overall conclusions. The authors should provide a more detailed evaluation of the quality scores and how they influence the findings.

- We thank the reviewer for this comment. In the revised manuscript, we have expanded our discussion of the Newcastle-Ottawa Scale (NOS) results by interpreting Table 1 and explaining how study quality impacts the findings. Specifically, we noted that higher-scoring registry and propensity-matched studies provide stronger evidence, while lower-scoring single-center studies with smaller samples and limited follow-up may reduce generalizability. These differences were considered when drawing our overall conclusions.

10. Figures and Tables: Tables 1 and 2 summarize the results from the various studies, but the interpretation of some of these data could be clearer. The authors should expand on the explanation of these tables, highlighting key findings and discussing the discrepancies between studies.

- We thank the reviewer for this insightful comment. For Table 1 in the revised manuscript, we have expanded our discussion of the study quality assessment using the Newcastle-Ottawa Scale (NOS). Specifically, we have compared the differences in quality scores across the included studies and highlighted how

variations in study design, sample size, and adjustment for confounders may influence the robustness of the findings. We have also acknowledged the limitations of lower-scoring studies (e.g., single-center design, smaller cohorts, or incomplete follow-up) and emphasized that these factors were considered in interpreting the overall conclusions of our synthesis.

- In the revised manuscript, we have expanded the explanation of Table 2 under the Anastomotic Leakage section and highlighted the key findings. We clarified that the discrepancies likely stem from differences in study size, definitions of statin exposure, and completeness of follow-up, which can significantly influence the reporting of rare complications such as anastomotic leaks.

11. Formatting Issues: Please review the manuscript for spacing and consistency. Some sections have inconsistent spacing, which can distract the reader. For instance, ensure there is a space between sentences where needed.

- We appreciate the reviewers comment on improving the structure of the manuscript. To address this, we have reviewed and edited the visible inconsistencies within the text.

12. Language Expression: Some sentences could be simplified for clarity. For example, the sentence “Additionally, surgical resection itself may also precipitate tumor recurrence, with an estimated recurrence rate of 25-45% at 5 years post surgery” could be rephrased to make the meaning clearer. The authors should aim to express complex ideas in a more straightforward manner.

- We thank the reviewer for highlighting this detail. In the revised text in the introduction, we have clarified this specific text to express the idea in a less complex manner. The authors would also like to bring to attention that we have further expanded details on the recurrence rate as per the reviewers comment.

13. Explanation of Figures and Tables: The figures and tables are useful but would benefit from more detailed explanations in the manuscript text. The authors should clarify how to interpret the data presented and address the differences in results across the studies.

- We thank the reviewer for this helpful suggestion. In the revised manuscript, we have elaborated further on the interpretation of Table 1 under the Quality Assessment section, emphasizing how differences in NOS scores across studies reflect variations in study design, sample size, and follow-up, and how these impact the reliability of findings.
- In the revised manuscript, we have expanded the explanations for Table 2 (Anastomotic Leakage) and Table 3 (Mortality) to better guide interpretation and address discrepancies across studies. For Table 2, we highlighted that larger registry-based studies reported no significant increase in leak rates, whereas the smaller single-center study by Bahl et al. suggested higher leak rates, likely due to limited sample size and incomplete follow-up. For Table 3, we provided a concise summary at the end of the *Mortality* section under Results and Discussion. This summary integrates both the data presented in the table and the narrative already provided in the text, highlighting the key differences across studies and clarifying how study design and sample size influence the interpretation of mortality outcomes.

Editorial Office's comments:

1. Some descriptions need to be supported by relevant references

- We thank the editors for pointing this out. We have carefully reviewed the manuscript and added references to support any previously unreferenced statements.

2. The authors should provide more detailed clarification on the source of this recurrence rate and how it is calculated

- In the revised manuscript, elaboration on the calculation of this statistic by the original authors of the referenced study has been included.

3. Clarification of statin types used in studies

- We appreciate the editors commenting on this detail. In the revised manuscript, we have mentioned the lack of stratification of statin types in the included studies of this narrative synthesis.

4. The authors should provide a more detailed evaluation of the quality scores and how they influence the findings

- We expanded the Quality Assessment section to explain how NOS scores impacted the strength and interpretation of outcomes.

5. The authors should expand on the explanation of these tables, highlighting key findings and discussing the discrepancies between studies

- We revised the text accompanying Tables 1-3 in the previous discussion to reference the tables to summarize the findings.

6. Manuscript title: Except for capitalization of the first word, all other words are represented in lowercase

- The title has been revised according to journal style, with only the first letter of the first word being capitalized.

7. Authors and institution(s): Author names should be written out first and typed in bold, followed by a comma and the complete name of the affiliated institution, city, province/state, postcode and country typed in non-bold

- Authors names and affiliations have been reformatted per the journal's style guide.

8. Author contributions: The 'Author contributions' passage describes the specific contribution(s) made by each author. The author's names will be listed in the following format: full family (sur)name, followed by abbreviated first and middle names.

- Author contributions have been revised to reflect the required format.

9. There are issues with the references:

- References have been cross-checked in the revised manuscript.

10. Authors should provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor, and upload it to the destination of "Image File"

- Figure 1 has been recreated in PowerPoint with editable components and uploaded as a separate file as requested.