

Peer Review File

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Reviewer A

The authors have presented an alternative to traditional TNM staging for prognostication of rectal cancer after surgery. Overall an interesting read. These are my comments:

1. Title

- if the authors have only included patients with rectal cancer then it should read :

"Construction and validation of a nomogram for predicting disease-free survival after radical resection of RECTAL cancer using perioperative inflammatory indicators" instead of "colorectal"

Reply 1: Thank you for your feedback. We have made the necessary modification to the title as per your suggestion. The revised title now reads: "Construction and validation of a nomogram for predicting disease-free survival after radical resection of rectal cancer using perioperative inflammatory indicators".

Changes in the text: we have modified our title as advised (see Page 1, line 3)

2. Introduction and knowledge gap

- I see the benefit of having an alternative predictive scoring system to the traditional TNM staging, but perhaps the authors can elaborate how their positive results may potentially change clinical practice. Do they plan to increase the surveillance intensity of the patients they have identified as high risk based on their nomogram? Or even consider adjuvant treatment ?

Reply 2: Thank you for your insightful feedback. In our revised manuscript, we have elaborated on how the implementation of our nomogram could potentially impact clinical practice. Specifically, we have outlined plans to utilize the nomogram for risk stratification in postoperative rectal cancer patients, with a focus on intensifying surveillance for high-risk individuals and considering timely interventions such as adjuvant treatment.

Furthermore, we are currently conducting ongoing prospective studies to assess the practical application of the nomogram in real-world clinical settings. These efforts aim to analyze the clinical utility and value of the nomogram in enhancing patient care and outcomes. We believe that our positive results and the utilization of the nomogram have the potential to significantly influence clinical practice by improving risk assessment and guiding personalized treatment strategies.

Changes in the text:we have modified our introduction as advised (see Page 5, line 72-79)

3. Methods

- I find the exclusion criteria too restrictive and not generalizable to the majority of rectal cancer patients.

- The authors have included stage 1 - 3 rectal cancer patients in their study population. (I note

about 40% are stage 3) but have also excluded patients who have gone for neoadjuvant treatment. Perhaps the authors can elaborate why the stage 3 rectal cancer patients did not undergo neoadjuvant treatment as per current guidelines?

- The authors have excluded other complications as well. I would presume this would include anastomotic leaks (AL). AL is well documented to have a negative impact on DFS and survival. Perhaps the authors could have studied if this is also an independent risk factor for a poorer DFS.

Reply 3 (1) : Thank you for reviewing our study and providing feedback. Regarding the issue you raised about excluding stage 3 rectal cancer patients who received neoadjuvant treatment in our study, we would like to offer the following explanation:

Study Purpose and Design: The exclusion of stage 3 rectal cancer patients who received neoadjuvant treatment in our study was based on specific research purposes and design considerations. Our study aims to investigate changes in inflammatory markers during the perioperative period, and neoadjuvant treatment may significantly impact these markers (see reference below). Therefore, to avoid the influence of neoadjuvant treatment on preoperative inflammatory markers, we chose to exclude patients who received such treatment.

Clinical Practice and Individualized Treatment: We fully acknowledge that in clinical practice, some stage 3 rectal cancer patients may undergo surgery directly without receiving neoadjuvant treatment. This individualized treatment decision may be influenced by factors such as the patient's condition, physician recommendations, and patient preferences.

Study Limitations and Future Perspectives: We will clearly state the reasons for excluding patients who received neoadjuvant treatment and discuss the limitations of this choice in the study. We will also explore the potential impact of this exclusion on the generalizability of the results. Future research could further investigate changes in inflammatory markers during the perioperative period under different treatment strategies to provide a more comprehensive understanding.

We hope the above explanation addresses your concerns. If you require more information or have further questions, please feel free to let us know. We are more than willing to discuss and make adjustments. Thank you for your review and valuable feedback.

Reference: Zhang R, Hu C, Zhang J, Zhang Y, Yuan L, Yu P, et al. Prognostic significance of inflammatory and nutritional markers in perioperative period for patients with advanced gastric cancer. *BMC Cancer*. 2023 Jan 3;23(1):5.

Changes in the text: we added the reasons and discussed the limitations of this choice in the study (see Page 14, line 263-267)

Reply 3 (2) : Thank you for your insightful feedback regarding our study. We appreciate your suggestion to investigate whether anastomotic leaks (AL) could be an independent risk factor for a poorer DFS.

During the revision process, we did include anastomotic leaks in our study due to their well-documented negative impact on DFS and survival outcomes. However, the LASSO algorithm ultimately excluded anastomotic leaks from the model.

The exclusion of anastomotic leaks by the LASSO algorithm was based on several factors,

including statistical significance, model selection criteria, and the focus of our study on specific research questions. While we acknowledge the importance of studying anastomotic leaks as a potential independent risk factor for DFS, the algorithm prioritized other variables with stronger associations with the outcome.

Your input is invaluable to us, and we are committed to enhancing the robustness and relevance of our study.

Changes in the text: we include anastomotic leaks in the study (see Page 7, line 102)

Reviewer B

1. Authors should add a statement here to indicate if the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013), available at: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects> (22). Suggesting wording: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

97 malignant tumors. This study was approved by the ethics committee o

98 ersity Affiliated Hospital (No. XYFY2023-KL256-01) and the requirem

99 med consent was waived for the retrospective analysis.

Reply: Thank you for the guidance. I have included the statement as suggested.

Changes in the text: we have modified our text (see Page 7, line 113-114)

2. You used studies while citing only one reference. Please check.

Studies have shown that inflammatory reactions play an important role in tumor occurrence, development, and metastasis, thereby affecting patient prognosis (3). Various studies have indicated that high levels of preoperative inflammation indicators suggest an increased risk of postoperative metastasis and recurrence in patients (4).

Reply: You are correct. I cited only one reference in the text. Thank you for pointing that out. I have now added the appropriate references for each mention of studies in the text.

Changes in the text: we have modified our text (see Page 5, line 69-71)