Peer Review File

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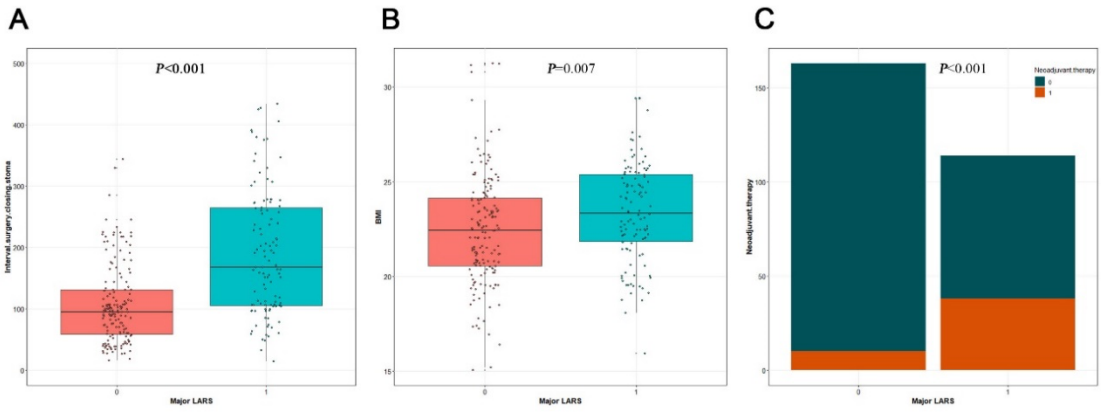
Reviewer A:

Comment 1: Thank you for a very well written and designed study on an important subject and common problem affect patients post low rectal cancer surgery LARS.
Reply: Thank the review's nice comments.
Changes in the text: None

Comment 2: You have highlighted weakness of the study and ai agree a randomised prospective study will help if your machine learning tool is really working.
Reply: Thank you for your insightful comments on our study. We are considering the feasibility of conducting a prospective study (eg. RCT, observational study) to validate the model, which will be our next project.
Changes in the text: None

Comment 3: I will be interested to know and recommend for you to add figures for the key findings; interval time of closure after primary surgery? what BMI, neoadjuvant (any difference between short and long course radiotherapy?)
Reply: Thank you for your thoughtful comments and recommendations. We appreciate your interest in our study and your suggestion. We acknowledge the potential benefits of further population stratification or subgroup analyses in improving the applicability of the model. However, it is essential to clarify that our study primarily focuses on predicting bowel function following stoma reversal. We agree that providing additional details, such as the interval time of closure after primary surgery, BMI, and potential differences in neoadjuvant therapy between short and long-course radiotherapy, would enhance the completeness of our findings. We will carefully consider your recommendation and work on incorporating relevant figures to better illustrate these key aspects (Supplementary Figure 1). We appreciate your constructive feedback, which contributes significantly to refining the clarity and depth of our research.
Changes in the text: we have added figure as advised (see Supplementary Figure 1).



Supplementary Figure 1: Comparison of the interval time of closure after primary

surgery, BMI, and neoadjuvant therapy status between major LARS and non-major LARS Groups in the training set. A: the interval time of closure after primary surgery (mean time of 107 days for non-major LARS groups versus 205 days for major LARS groups; P<0.001). B: BMI (mean BMI of 22.4 kg/m^2 for non-major LARS groups versus 23.4 kg/m^2 for major LARS groups; P=0.007). C: neoadjuvant therapy status (10 for non-major LARS groups versus 38 for major LARS groups; P<0.001).

Reviewer B

Comment 1: Rewrite the abstract with more effective text. In particular, please add a KEY FINDINGS section to the results section. Also, in the results section, please describe what facility the treatment was performed at. Also, isn't the purpose of this study to create a predictive model using machine learning algorithms?

Reply: We have incorporated modifications into the abstract as suggested. Particularly, we have added a KEY FINDINGS section to the results and provided information about the facility where the treatment was performed. Indeed, the primary objective of this study is to create a predictive model utilizing machine learning algorithms and we have highlighted the method of machine learning of the revised manuscript. We believe these revisions enhance the clarity and effectiveness of the abstract. We appreciate your time and expertise in reviewing our work.

Changes in the text: we have modified our text as suggested (see Page 2, lines 44-49).

Comment 2: Please describe what type of rectal cancer was treated. For example, middle or low or cases less than 15 cm from the anal verge. Please state whether the surgery is for total nerve preservation.

Reply: The mid-low rectal cancer in this study were located less than 10 cm from the anal verge. It is crucial to note that TME procedures were routine operations for mid-low rectal cancer and all procedures were performed by experienced senior surgeons, and total nerve preservation was performed during the surgery. We have revised the relevant sections of the manuscript to explicitly mention the specific type and location of rectal cancer treated. Furthermore, we have clarified that all surgical interventions were carried out with a dedicated commitment to total nerve preservation. These modifications aim to provide a more detailed and precise description of the study cohort and surgical approach.

Changes in the text: we have modified our text as suggested (see Page 4, lines 95-100).

Comment 3: Why did you exclude <1year?

Reply: LARS is acknowledged for its time-dependent manner, which generally occurrs within a variable interval of 6-18 months after surgery or the closure of a diverting stoma[1]. This period is essential for the neo-rectum to undergo “rehabilitation”. If the symptoms persist beyond this timeframe without improvement, the syndrome is generally considered irreversible. The short-term symptoms of LARS, often arising from the irritability of the neo-rectum in the early postoperative phase, usually alleviate within **6-12** months after the restoration of bowel continuity. Conversely, long-term symptoms persisting beyond 12 months are more likely associated with permanent

changes[2,3]. Our study excluded patients with less than 1 year of follow-up primarily to ensure a stable assessment of bowel function. This decision was made to evaluate patients' bowel function after the closure of the diverting stoma, allowing for a more accurate assessment and mitigating the potential interference of unstable bowel function with the precision of predictive results. We hope this explanation provides clarity on our study design decisions.
Changes in the text: we have modified our text as advised (see Page 6, lines 140-141).

Comment 4: Why did you include hypertension and diabetes as preditors?
Reply: Thank you for your thoughtful comments. In the context of machine learning models, it is commonly acknowledged that incorporating more features can enhance the reliability of predictions. However, the challenge lies in balancing the inclusion of relevant features without succumbing to overfitting and increasing complexity[4]. The decision to include hypertension and diabetes as predictors stems from the recognition that patient heterogeneity plays a crucial role in the occurrence of LARS. While these factors may not be as prominently significant as more clinically recognized risk factors, they contribute to the overall understanding of the syndrome. Additionally, individual patients undergoing same rectal cancer surgery may experience diverse postoperative bowel functional outcomes. It is essential to note that not every patient possesses all conventional risk factors, and other features may contribute differently to the development of LARS. Our intent is to explore a comprehensive range of variables to capture the nuanced interplay of factors influencing LARS, even if some features are less traditionally emphasized. We hope this clarification provides insight into our rationale for including hypertension and diabetes in our predictive model.
Changes in the text: None

Comment 5: What is the pathological stage based on? (e.g. UICC, etc.)
Reply: Following a meticulous review and scrutiny of postoperative pathological results from all patients, all the tumors were restaged used the 8th AJCC TNM edition.
Changes in the text: we have modified our text (see Page 5, line 119-120).

Comment 6: Why is the distance from the lower margin of the tumor to the anal verge not included as predictors? Shouldn't it be included?
Reply: In response to your inquiry, we want to clarify that the distance from the lower margin of the tumor to the anal verge has been included indirectly through an important predictor – anastomotic height[5]. The anastomotic height inherently reflects the distance from the tumor's lower margin to the anal verge. We have made sure to update the relevant figures and tables in the revised manuscript to highlight this inclusion and its significance in our analysis. Additionally, we have recalculated and modified the performance metrics of the machine learning model.
Changes in the text: we have modified our text (see Page 5, lines 111-119; Pages 20-22, Figures 2-5; Pages 18-19, Tables 1-2; Pages 8-10, lines 216-263.

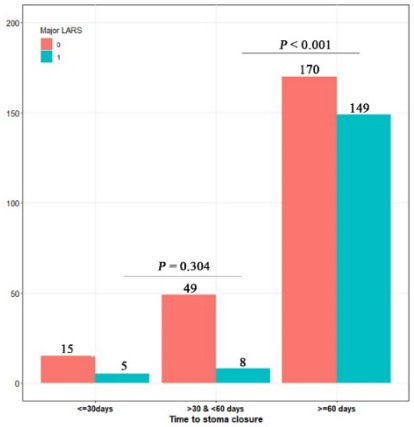
Comment 7: What is the diameter of the endoscope to assess obstruction? Shouldn't this be stated?
Reply: We appreciate your attention on the details. In response to your query, we have thoroughly examined the parameters of the electronic colonoscope used at our institution's endoscopy center. The maximum insertion portion width of the endoscope for assessing obstruction is 12.8 millimeters. We have incorporated this information into the revised manuscript.
Changes in the text: we have modified our text (see Page 5, lines 114-116).

Comment 8: As for the LARS score, shouldn't the original Ann Surg article be cited? (e.g., as originally defined Emmertsen et al.)
Reply: Thank you for your thoughtful feedback. Regarding the LARS score, we appreciate your suggestion to cite the original article where the LARS score was originally defined. In the revised manuscript, we have included this crucial reference.
Changes in the text: we have added this crucial reference in our revised manuscript (see Page 6, line 137).

Comment 9: Shouldn't the present study focus on low or middle rectal cancers? If so, please state so.
Reply: We appreciate your insightful comments. The current study indeed focuses on low and middle rectal cancers. We apologize for any ambiguity in the initial report. In the revised manuscript, we have explicitly stated the focus on low and middle rectal cancers.
Changes in the text: we have modified our text in our revised manuscript (see Page 2, line 39; Page 4, lines 95-96).

Comment 10: We know that the time to stoma closure is important, but the best timing for stoma closure cannot be indicated in this study? If you can, please indicate.
Reply: Thank you for your thoughtful comments. A randomized controlled trials demonstrate that for patients without clinical or imaging indications for anastomotic leakage, temporary ileostomy closure within 8 to 13 days after rectal resection is safe[6]. The prospect of early closure (≤30 days) of prophylactic stomas presents potential advantages over delayed closure (≥60 days), manifesting in reduced contamination issues, a diminished incidence of permanent stomas, and decreased durations of hospitalization, occurrences of bowel obstructions, and medical complications among patients undergoing early stoma closure[7,8]. Nevertheless, caution is warranted in interpreting these findings, as emphasized by the associated trial sequential analysis[9]. The optimal timing for stoma closure remains inconclusive based on our findings, necessitating further dedicated prospective studies to unequivocally elucidate the relationship between temporary ileostomy, Low Anterior Resection Syndrome (LARS), and the timing of closure. Supplementary Figure 2 illustrates the relationship between distinct intervals of stoma closure and the occurrence of major LARS in our study cohort.
Changes in the text: we have modified our text in our revised manuscript (see Page

13, lines 343-345). we have added figure as advised (see Supplementary Figure 2).



Supplementary Figure 2: Relationship between the timing of stoma closure and major LARS.