

Dear Dr. Ma,

Thank you very much for allowing us to submit a revised manuscript titled “Elderly patients over 80 years undergoing colorectal cancer resection: Development and validation of a predictive nomogram for survival” to *World Journal of Gastrointestinal Surgery*. We appreciate the time and effort you and the reviewers have dedicated to providing valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect suggestions provided by the reviewers.

Here is a point-by-point response to the reviewers’ comments.

Reviewer #1:

Specific Comments to Authors: I have reviewed the manuscript carefully. The authors made a great work for contracting the nomogram model to evaluate the risk factors and predict the prognosis of elder CRC patients. And the nomogram showed effect predictive value. However, this research has some controversial or unclear points which need to discuss.

1. In Result, Clinical and surgical characteristics, the article stated that “None of the patients received adjuvant chemotherapy”. However, most cases in this study were stage III and stage IV colorectal cancer patients, please provide the reasons why those patients not received adjuvant chemotherapy. According to clinical practice guidelines for colorectal cancer, elder CRC patients still can receive appropriate adjuvant chemotherapy.

Response: Thank you for your comments. We appreciate your attention to our study. Regarding your concern about the lack of adjuvant chemotherapy in our study, we acknowledge that the current standard of care for stage III colorectal cancer (CRC) patients includes adjuvant chemotherapy. However, the decision to administer adjuvant chemotherapy depends on various factors, including patient age, comorbidities, performance status, and overall health. Each individual stage III CRC patient in our study did not receive adjuvant chemotherapy after collective discussion among the patient, family, attending oncologist, and primary surgeon at the multi-disciplinary meetings. This decision was made based on the clinical assessment and patient choice.

We agree that appropriate adjuvant chemotherapy may benefit elderly CRC patients, and our study does not intend to suggest otherwise. However, our study focused on developing a nomogram to predict overall survival in elderly patients over 80 years undergoing CRC resection, regardless of whether they received adjuvant chemotherapy. We believe the nomogram can still provide valuable information for clinicians to make informed decisions regarding treatment and postoperative care for these patients.

2. In Supplement Table 1, Method of operation, minimally invasive surgery group have better prognosis compared to open surgery group. However, in discussion, authors explained that “laparoscopic colorectal resection was not demonstrated to impact OS in elderly CRC patients”. Please explain this point.

Response: Thank you for your comments. We acknowledge that in Supplement Table 1, the minimally invasive surgery (MIS) group appeared to have a better OS than the open surgery group, and we understand that this may seem contradictory to our statement in the discussion that laparoscopic colorectal resection was not demonstrated to impact overall survival (OS) in elderly colorectal cancer patients. We have amended this in the discussion.

In this study, MIS was found to have a positive impact on OS in elderly CRC patients in the univariate Cox regression ($P = 0.01$). The LASSO regression, however, eliminated the method of operation, indicating that it was not a predictor of OS in CRC patients over 80 years undergoing surgery. In the MIS group, with a total of 160 elderly patients, the majority (90.6%) underwent laparoscopic surgery, while only 15 patients (9.4%) underwent robotic surgery. In the discussion, we aimed to interpret our findings in the context of the existing literature, which has shown conflicting evidence regarding the impact of laparoscopic surgery on OS in elderly CRC patients. Although some studies have suggested a survival benefit associated with laparoscopic surgery in elderly CRC patients, others have not found a significant difference in survival outcomes between laparoscopic and open surgery.

3. In this research, the rate of the anastomotic fistula is 2%. But I think that those patients who not receiver anastomosis operation (such as Hartmann's procedure) should be excluded.

Response: Thank you for your comments. In our study, we included all elderly CRC patients over 80 years undergoing colorectal cancer resection at our institution between 2018 and 2021, regardless of the type of surgery they received, including those undergoing Hartmann's procedure. Among the patients who suffered the complication of anastomotic leak, it was not associated with significantly worse overall survival. Our study aimed to develop a nomogram to predict OS in this elderly population, and identified relevant clinical risk factors that have been shown to have an impact on overall survival. Thank you again for your comments, and we hope this explanation clarifies our approach to including all elderly CRC patients.

4. Lymph node metastasis is one of the prognostic factors in patients with colorectal cancer. The stage III CRC patients should be further analysis.

Response: Thank you for your comments. We agree that lymph node metastasis is an important prognostic factor in CRC patients, and stage III patients are a significant subgroup in this regard. Our nomogram aimed to stratify the clinical risk factors that may significantly impact overall survival. We showed that in the elderly population over 80 years, even those with stage IV CRC may potentially have reasonable overall survival depending on other variables such as age, CCI, BMI, and serum albumin level. The presence of stage IV disease can be ascertained preoperatively on a CT scan, and therefore patients can be counseled on the treatment options appropriately before surgery. Stage III CRC certainly has a significant impact on OS as well. However, the histological confirmation of stage III CRC is determined only after surgery, and therefore this limits the use of this nomogram in preoperative decision-making. We encourage future studies to investigate these important prognostic factors in this elderly population.

5. In Supplement Table 1, Stoma, do stoma group have worse prognosis compared to not-do stoma group, please explain related reasons.

Response: Thank you for your comments. The stoma group was found to be related to a poor OS in elderly CRC patients in the univariate Cox regression, but was excluded in the preliminary multivariate Cox regression and LASSO regression. Moreover, the decision to create a stoma in elderly CRC patients is based on a complex set of factors, including the location of the tumor, the extent of surgery, the patient's comorbidities, and the surgeon's experience and judgment. In our study, we did not specifically investigate the factors contributing to the decision to create a stoma or not, nor did we investigate the impact of stoma-related complications on OS. The patients who underwent stoma formation having a worse prognosis are likely confounded by selection bias. Nonetheless, we appreciate your pointing out this important topic, and we encourage further investigation of the effect of stoma creation on the survival outcomes of elderly CRC patients.

Reviewer #2:

Specific Comments to Authors: The manuscript entitled “Elderly patients over 80 years undergoing colorectal cancer resection: Development and validation of a predictive nomogram for survival” reports a clinical study that collects 295 elderly CRC patients’ information to build a nomogram and predict the overall survival of elderly CRC patients (> 80 years). The authors determined eight patient factors for nomogram construction and followed machine learning requirements (60% of data for model construction and 40% of data for validation). Then the model was further validated using the concordance index, area under the receiver operating characteristic curve and calibration plots. The manuscript is well written and easy for understanding. The below lists several suggestions the authors may need to consider.

1. The first sentence in the introduction section, “The world’s population is aging at a faster rate”, is this true? Does this sentence express the meaning accurately?

Response: Thank you for pointing this out. We have revised this sentence to express the meaning accurately.

“The world’s population is rapidly aging, with currently over 84 million people aged 75 and above^[1]. Population aging will impact cancer control, as around 50% of all cancers affect the older population^[2].”

2. The last sentence in the first paragraph of the introduction section, the reference is lacking.

Response: Thank you for pointing this out. We have added the reference.

3. In the materials and methods section, “Data from the American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP)”, is there a website that can be accessed for validation or a reference?

Response: Thank you for your comments. The American College of Surgeons - National Surgical Quality Improvement Program (ACS-NSQIP) is a comprehensive database of surgical outcomes that provides a scientifically rigorous tool for measuring and comparing the quality of surgical care. The data collected includes patient characteristics, preoperative risk factors, intraoperative variables, and postoperative outcomes. Since 2017, Singapore General Hospital, the largest public healthcare institution in Singapore, has become a participating site of NSQIP. NSQIP data is not publicly accessible. It is a confidential, proprietary database that contains patient information gathered from participating hospitals and is used to track and evaluate the outcomes of surgical procedures. Access to NSQIP data is restricted to authorized users who have signed a confidentiality agreement. You

may access the NSQIP website at <https://www.facs.org/quality-programs/acs-nsqip> for reference purposes.

4. The conclusion section can be improved, to summarize and present the full story of the work.

Response: Thank you for your comments. The conclusion section has been edited as below.

“In summary, colorectal surgery in elderly CRC patients is associated with a lower likelihood of survival. We used data from ACS-NSQIP to construct and validate an original nomogram for the postoperative survival of elderly CRC patients over 80 years. By accurately predicting 1- and 3-year survival probabilities, our novel nomogram, which incorporated age, CCI, BMI, serum albumin level, distant metastasis, emergency surgery, postoperative pneumonia, and postoperative myocardial infarction, may facilitate preoperative clinical decisions for patients, caregivers, and clinicians.”

5. The quality of figures can be improved.

Response: Thank you for your comments. We have uploaded the original figures with a higher resolution.