

Peer Review File

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Reviewer A

A retrospective study of the SEER database to construct a survival nomogram for elderly patients with stage 2/3 colorectal cancer.

Overall well written with sound statistics and good presentation of information. These are my comments:

Introduction:

1. line 60/61: "TNM staging has certain shortcomings, and has a limited role in providing clinicians with treatment decisions." This line should be removed / rephrased. Many of us still base our clinical recommendations on the clinical TNM staging.

Reply 1: Thank you for your comment, we have rewritten the sentence. It is now stated as follows "However, there is growing evidence that the introduction of other observational indicators based on the TNM staging system performs better than using the TNM staging system alone to predict the patient's prognosis."

Changes in the text: We have modified our text as advised (see Page 5-6, line 72-75).

Discussion and conclusion:

The authors mention that this nomogram identifies high risk patients to adopt more aggressive treatment strategies. Can the authors elaborate more on this?

Reply 2: Thank you for your comment, this is a very meaningful question. Based on the prediction nomogram we constructed, the risk score of each patient can be calculated. To address your concerns, we have revised our manuscript in the discussion section as follows: "Among all factors, factors such as surgery, extent of intraoperative lymph node dissection, and chemotherapy are changeable. For some patients with high-risk scores, clinicians can actively adopt surgical treatment, chemotherapy or comprehensive treatment to reduce the risk score and ultimately extend the patient's survival time. For patients who have been treated aggressively but still have a high-risk score, monitoring can be strengthened, postoperative management can be enhanced, and even immunotherapy can be considered to improve the patient's prognosis (PMID: 36672193)."

Changes in the text: We have added some discussion to the discussion section (see Page 14, line 267-273).

How would the treatment decision for surgery and or adjuvant therapy differ between a high risk patient and a low risk patient? Currently most of us base our treatment decisions based on the clinical TNM staging.

Reply 3: Thank you for your comment. Yes, clinical treatment decisions are still largely based

on clinical TNM staging. Similar to comment 2, based on our constructed nomogram, the risk scores of patients under the conditions of whether or not to take surgery, chemotherapy, and the extent of intraoperative lymph node clearance can be calculated to compare the difference in patient survival to decide the treatment. The main goal of this paper is to predict patient survival, and the risk stratification demonstrates that the model is well constructed and can accurately differentiate between populations and predict patient prognosis.

Changes in the text: We have revised our manuscript in the discussion section (see Page 14, line 267-273).

And what how would the treatment decision change if this is a non-elderly patient?

Reply 4: Thank you for your comment, the question you raised is very meaningful. In this article, we mainly focus on elderly patients, the treatment decisions for non-elderly patients need to be further explored. We think that the question you raised is a very important topic, which is very interesting and we hope to explore the topic carefully in our next studies, thank you again for your valuable comments.

Changes in the text: None.

Reviewer B

The manuscript is well written. My concerns are as follows:

- There have been many CRC nomograms published to date, including several that incorporate CEA (eg. Zhang, Zy., Gao, W., Luo, Qf. et al. A nomogram improves AJCC stages for colorectal cancers by introducing CEA, modified lymph node ratio and negative lymph node count. Sci Rep 6, 39028 (2016). <https://doi.org/10.1038/srep39028>). It is unclear how this nomogram is superior to others or that it addresses a subset of patients not captured in other models.

Reply 1: Thank you for your comment. Yes, many nomograms on CRC have been published to accurately identify patients with tumors, improve treatment regimens, predicting patient prognosis, and so on. However, a nomogram specifically for elderly patients (a special group) has not yet been constructed, especially for phase II-III clinical patients.

We have descriptions of this in the manuscript, see:

page 5, line 66-67: “For traditional stage II-III CRC patients, the standard treatment is radical resection and adjuvant chemoradiotherapy”

page 5, line 67-70: Older persons are a special category, “elderly colorectal cancer patients are a special category because they are older, in poorer health, have more underlying diseases and do not tolerate surgery and adjuvant chemoradiotherapy as well as younger colorectal cancer patients”

page 5, line 61-64: “With the aging of the population, colorectal surgeons will have to deal with older patients in the future than they do today. It is estimated that in 2023, elderly patients (age ≥ 65 years) will account for approximately 56% of new CRC patients in the United State”

To address your concerns, we have revised our manuscript in the discussion section as follows: “Zhen-yu Zhang et al. (PMID: 27941905) constructed a well-performing prognosis nomogram of CRC patients (3-years AUC: 0.781) based on information such as modified lymph node ratio and CEA level, indicating that it is feasible to predict the survival of CRC patients based on CEA level. The nomogram of this study is the first nomogram of elderly (age> 65 years) CRC patients, and the overall performance is good. Aik Yong Chok et al. (PMID: 37342856) constructed a prognostic nomogram of CRC patients over the age of 80. Although the model performance is acceptable, its credibility is reduced due to the small sample size (n=295).”

Changes in the text: We have revised our manuscript in the discussion section (see Page 13, lines 235-241).

- the gold standard for constructing nomograms is a process of k-fold cross validation. It seems the authors have done only one iteration of training of the model. Perhaps a justification for this chosen method is required.

Reply 2: Thank you for your comment, simple cross validation was used in the study, which is convenient and suitable for large sample sizes. Based on your comments, we internally validated the model again using k-fold cross validation (k=10), and the results showed that the model accuracy was good (mean AUC=0.7412).

Changes in the text: Method: We have revised our manuscript in the Methods and Results section (see Page 7, lines 116-117 and page 10, lines 180-181).

- The practical utility of the nomogram would be greatly enhanced by creating an online calculator for clinicians to use while managing patients.

Reply 3: Thank you for your comment, it is very meaningful. Based on your comments, we have created an online dynamic survival calculator based on our model for nomogram applications. (Get the URL https://dynnomleb.shinyapps.io/JGO_ElderlyCRC_StageII-III/) (Note: If you encounter any errors, please click Quit and then click Reload, the program will work.)

Changes in the text: We have revised our manuscript and Figure 3, and added an online dynamic survival calculator based on our nomogram as advised.

See page 10, lines 173-175; page 25-26, lines 432-438.