Author’s response to reviews

Title: Young Age Increases the Risk for of Lymph Node Metastasis in Patients with Early Colon Cancer

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Response to reviewers

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Manuscript title: Younger Age Increases Risk for Lymph Node Metastasis in Early Colon Cancer

Author: Xin Xie; Jianhao Yin; Zhangjian Zhou; Chengxue Dang; Hao Zhang; Yong Zhang

The authors would like to thank Editor, Reviewer 1 for their comments and suggestions of our study. We also want to thank Reviewer 3 for his/her professional comments for our nomogram predicting system and statistical analysis methods.

We have addressed all comments from all reviewers, the responses are listed below.
Please note that all the line numbers refer to those in the updated Manuscript with changes marked.

Editor Comments:

1. The list of authors appears to have been removed from the title page, please re-include the list of authors on the title page.

Authors’ response:

Thanks for the kindly reminder. The authors’ list was added on the title page.

2. Please remove the "Key Points" section from under the title page, this is not a standard section in BMC Cancer. Please integrate the information in this section in other parts of the manuscript.

Authors’ response:

We’ve removed the “Key Points” section from the title page.

3. Please change the headings in the Abstract, they should be: Background, Methods, Results, Conclusions.

Authors’ response:

The Abstract section and the headings have been revised.

4. Please confirm whether your study was submitted to and approved by your institutional ethics committee and include a statement to this effect in your Methods and Ethics approval and consent to participate sections. Please also ensure that the full name of your ethics committee is included in this statement. If the need for ethics approval was waived by an IRB or is deemed
unnecessary according to national regulations, please clearly state this, including the name of the IRB or a reference to the relevant legislation.

Authors’ response:

Our study was submitted to and approved by the Ethics Committee of the First Affiliated Hospital of Xi’an Jiaotong University. And we were given approval to access the SEER database by the SEER program.

5. Please confirm whether informed consent, written or verbal, was obtained from all participants and clearly state this in your Methods and Ethics approval and consent to participate sections. If verbal, please state the reason and whether the ethics committee approved this procedure. If the need for consent was waived by an IRB or is deemed unnecessary according to national regulations, please clearly state this, including the name of the IRB or a reference to the relevant legislation.

We are aware that this study used patient records, however, we still need a statement regarding patient consent.

Authors’ response:

This retrospective study is based on the open-accessed SEER database, and we’ve approved to get access and analyze the data from this database. So, there is no need for informed consent.

6. Please state in the Ethics approval and consent to participate section whether permissions were needed to access the data used in this study.

Authors’ response:

The statement of Ethics approval and the SEER database access approval were added in the Method section, Page13, Line 22.
7. Please note, the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared in the Funding section.

Authors’ response:

The funding body of our study was listed in the Funding section.

8. Please remove "Dr" from the Authors' Contributions, please just refer to the authors by their initials.

Authors’ response:

All the title of “Dr” has been removed from the Author’s Contributions section.

9. Please include a statement in the Authors' contributions section to the effect that all authors have read and approved the manuscript, and ensure that this is the case.

Authors’ response:

We added this statement of “Authors’ approval” to the Author’s Contribution section.

Reviewer reports:

Reviewer 1:

1. Overall:

- Awkward language constructions persist throughout the text. These must be further revised.

Example: Page 7, Line 3: Is younger age has effect on lymph node positivity in colon cancer T1 to T2?
This is not an appropriate English language construction. This should read: Does younger age have an effect on lymph node positivity in T1-2 colon cancer?

Authors’ response:

Thanks for this comment. We’ve checked our manuscript again and modified some grammar mistakes.

2. Abstract:

- There is still a reference to colon cancer with "mucosal invasion." Again, as previously noted, T1 colon cancer invades the submucosa. According to the AJCC 8th edition, mucosal invasion would describe patients with intramucosal carcinoma which are not a part of this study. This must be revised.

Authors’ response:

The authors would thank this comment. We have checked the 8th AJCC manual and mucosal invasion should also included Tis stage, such as high grade dysplasia (HGD). But for our study, we are focus on adenocarcinoma, there is no in-situ adenocarcinoma for colorectal carcinoma. If the tumor did not invade into the submucosa (T1), we think it should be HGD, not adenocarcinoma. So we excluded Tis stage for our study.

3. The author’s replied that: "Although the C-index is below 0.70, this nomogram prediction is still based on large group of patients (n=41490) and shows more accurate prediction than traditional AJCC TNM system, which means this nomogram model exhibits better clinical application potential."

Please clarify this statement. How is this more accurate than the AJCC TNM system? TNM uses the nodal status as a predictor. Your model attempts to predict nodal status. They are two totally different things and cannot be compared.

Authors’ response:

We apologize for this mistake. The nomogram prediction system in this study is to predict LN+ by different risk factors. We introduced the Harrell’s C-index and Decision curve analysis to
assess our models accuracy and clinical application potential. In this study, we didn’t compare our model with AJCC TNM staging system.

4. Introduction:

- This sentence needs to be revised as it does not communicate a clear idea: Although current screening guidelines do not recommend routine screening for young adults, several examinations, such as colonoscopy and faecal occult blood test, which are necessary for young adults with suspected CRC.

Authors’ response:

We have revised this sentence at Page 12, Line1-4.

5. Increasing numbers of positive lymph nodes is a negative prognostic sign, not a positive sign. This must be revised.

Authors’ response:

Thanks for this suggestion. We modified this sentence at Page 12, Line10-11.

6. "the involvement of an increased number of lymph nodes is associated with positive outcomes survival" 18,19

Authors’ response:

The authors thank the Reviewer’s suggestion. This sentence has been revised at Page 12, Line10-11.

7. Methods:

- the means of model selection are still not specified.
Authors’ response:

In our study, the nomogram model includes the patients who were clinicopathologically diagnosed with colon adenocarcinoma according to the “SEER RESEARCH DATA RECORD DESCRIPTION”.

8. Results:

- Page 14, Line 5: average age +/- presumably refers to standard deviation but this should be specified.

Authors’ response:

The expression of “average age +/-” has been revised at Page 15, Line 8-9.

9. - Page 15, line 15: it states that five factors entered the analysis but only four are listed; grade, depth of invasion, age, race.

Authors’ response:

We apologize to this mistake. In our nomogram prediction system, there are four risk factors: grade, depth of invasion, age and race, which are listed at Page 16, Line 20.

10. - This statement must be clarified. What exactly are the authors advocating in this circumstance? Complete mesocolic excision? This is a controversial statement that would need further supporting evidence.

Page 19, Line 14-15: "and regional lymph node 15 resection might not be sufficient to treat these patients"

Authors’ response:

We thank the Review 1 for this comment. We have revised this statement (Page 14, Line 18-19) and integrate this statement into next paragraph with more supporting references for further discussion (Page 21, Line 15-18).
11. The authors advocate: more aggressive regional 2 resections (extend colon resection and/or extend lymph nodes resection) and yet offer no evidence to support extended lymphadenectomy. This should be further supported if this claim is to remain.

Authors’ response:

We appreciate the Reviewer 1’s comment and suggestion. We have expended our discussion and add two more references (Ref.22 and 33) to support our statement (Page21, Line13–Page22, Line3).

12. What exactly does this refer to: “Regional resections.” Resections with inadequate lymph node retrieval?

Authors’ response:

The “Regional resections” in Page21, Line 21 refers to “resections with inadequate lymph node retrieval”. We specified this statement at Page 21, Line 22. Thanks for the Reviewer 1’s suggestion.

13. The specific clinical utility of the nomogram and the decision analysis curve should be discussed in further detail.

Authors’ response:

We thank the Reviewer 1’s comments. We expended the discussion and attached more references about the DCA curve and clinical utility at Page 20, Line 19–Page 21, Line 8.

14. Again, the reference category should be explicitly stated

Authors’ response: The additional explanation was added in the revised table.
Research Square (Reviewer 3): "STATISTICAL REVIEWER ASSESSMENT:

1. The study stated that ""The positive lymph node rates 7 for patients 20 to 39 years of age were significantly higher than in patients in the 8 reference group for early colon cancer."" However, for Table 1, we do not know which level of age group was used as reference group. Also since several age groups were defined, details of multiple age groups are needed. The reported general p-value is not sufficient.

Authors’ response:
We appreciate the Reviewer 3 for his/her comments and suggestions. We have modified Table1, and more statistical details were added.

2. For multiple regression analysis, we want to know the details of modeling process: which covariates were included and what methods were used for selecting variables and final model looks like. In Table 1, there are several significant demographic and clinicopathological characteristics of patients. These variables should be adjusted.

Authors’ response:
We have add some details in Table 1 in the revised version..Factors with significant differences and clinical importance were included in the model.

3. C-statistic = 0.633 is not large, which indicates that the predictive model is not good enough. A plot of observed probabilities against predictive proportion is needed to visualize the accuracy of the developed predictive model.

Authors’ response:
We’ve acknowledged that C-index with 0.633 is not sufficient enough. In Discussion section (Page21, Line1-3) and Limitation section (Page 22, Line 21-Page 23, Line1), we analyzed and discussed the result of C index and this (C-index=0.633) might be a clue for surgeons and digestive physicians and further studies are needed to modified the nomogram prediction model.