Author’s response to reviews

Title: Young Age Increases the Risk for 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

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The authors would like to thank Reviewer 1 and 2 for their comments and suggestions of our study. We would like 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.

Finally, please note that all the line numbers refer to those in the updated Manuscript with changes marked.

Reviewer #1

1. Reviewer comment:

   Overall:
   - Grammar/language is awkward at points throughout the manuscript. This should be reviewed prior to publication.

   Author response:
   We thank the reviewer for taking time to read the manuscript and their approval of our study. The grammar/language of this manuscript has been reviewed and improved by American Journal Experts.

2. Reviewer comment:

   Abstract:
   - "colon cancer with mucosal invasion" is an odd statement; by definition T1 cancers invade the submucosa. Another term should be used to describe Tis to T2 as described in the manuscript.

   Author response:
   We have modified the description in the abstract of the revised manuscript. It was described as T1 to T2.
3. Reviewer comment:

Introduction

- Page 7, Line 12-20; "positive outcomes" appears to be misused here.

- The last paragraph should be revised. The detailed information regarding SEER should be moved to the methods section. The last sentence of the last paragraph is also confusing; I assume the authors are referring to the current study as the "recent study?"

Author response:

We appreciated this comment. "positive outcomes" in Page 11, Line 10 is modified to "positive survival".

The last paragraph of Introduction has been revised. The detailed information of SEER is moved to the methods section. The last sentence of last paragraph should be "In recent study", we modified this misunderstanding.

4. Reviewer comment:

Methods

- The abstract suggests that patients with Tis were included while the results section does not demonstrate any such patients. Please specify.

Author response:

The abstract was corrected. Only patients with T1-T2 were included in our study.

5. Reviewer comment:

Discussion

- NCCN guidelines recommend evaluation of 12 lymph nodes for colon cancer resections in general; not just for early stage (reference 17). This should be clarified.
Author response:

Agree and appreciate for this suggestion.

We checked the newly published NCCN guidelines (Colon Cancer, V1.2019) and updated the Reference 17 in the manuscript. The number of lymph nodes evaluation (12) in colon cancer patients is revised according to the newly updated NCCN guidelines.

6. Reviewer comment:

Page 15; "regional resection" should be clarified. "Aggressive regional resection" should also be clarified.

Author response:

We have add the clarification in the revised manuscript (Page20, Line7-14)

7. Reviewer comment:

Page 15; the suggestion that adjuvant chemoradiation might be an appropriate strategy for young patients with early stage colon cancers is not supported by the data. Post-resection, TNM stage is known through pathologic evaluation. Adjuvant chemotherapy certainly has a role in the treatment of stage III colon cancer and select stage II cases though adjuvant radiation is generally reserved for cases with positive margins, if at all.

Author response:

Agreed and thanks for this comment. We revised the last paragraph of Discussion section and discuss more details for multidisiplinary therapeutic strategies, including adjuvant chemotherapy.

8. Reviewer comment:

Conclusions

- The data do not necessarily support aggressive screening for young patients. While screening guidelines are certainly open for debate, this study does not relate to that debate. All patients
studied here have documented colon cancer. It is difficult to make statements about screening without analyses that involve rates of disease in a population.

- The statement that younger patients should be considered for more aggressive treatment strategies has merit. Specifically, with the broader adoption of EMR/ESD, these data suggest that younger patients would be at greater risk of lymph node positivity T-stage for T-stage relative to older patients. The hazards associated with EMR/ESD for younger patients should be more explicitly stated as I believe this is a powerful finding of your work.

Author response:
We appreciated this comment. According to this comment and suggestion, we revised the conclusion section of this manuscript and focus more on the potential hazards related to EMR/ESD.

9.Reviewer comment:
Table 1
- Two decimal places is an unnecessary degree of precision for the percentage column. Consider revising.
- P-values should be included in this table
- the data for left vs. right sided LN positivity should be included

Author response:
We have modified the percentage in the revised table. And the P value was added in the revised table.
In the SEER database, the tumor location of some patients was lack. So we did not add the number in the table as it was calculated using a subset of the database

10.Reviewer comment:
Table 2
- the reference group should be specified.
- Tumor location (left vs. right) appeared to be associated with lymph node positivity per the text yet it did not make it to the final model. Please explain.

Author response:

The reference group of age, race, size, mucinous, grade and depth of invasion was <40 years old, white, <10 mm, non-mucin, well differentiated and T1, respectively.

As question above, in the SEER database, the tumor location of some patients was lack. So we did not add the number in the table as it was calculated using a subset of the database.

11.Reviewer comment:

Figure 2A
- contains minor typos

Author response:

We have correct the typos of Figure 2A. Thanks.

12.Reviewer comment:

Figure 3
- Would benefit from more explanation in the text and/or caption.

Author response:

The explanation was in the figure legand.

Reviewer #2

Reviewer comment:
ON page 9 Line 29 - 40 there are some spelling errors. Otherwise I have no further suggestions.

Author response :

We appreciated this suggestion and his/her approval of our manuscript. The grammar/language of this manuscript has been reviewed and improved by American Journal Experts.

Reviewer #3

1.Reviewer comment :
For multivariate modeling, what variables were initially included in the analysis?
What method was used for model selection or variable selection?

Author response :

The linear regression method was used the model selection. Factors with significant differences in the univariate analysis were selected in the multivariate analysis.

2.Reviewer comment :
The Harrell’s concordance index (C-index) was below 0.70, which suggests that the models were not sufficiently fit. How did the authors interpret them?

Author response :

Thanks for this comment. 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. And we think this is one of our model’s limitation and need to improve with more data support.
3. Reviewer comment:

Table 1 The demographic and clinicopathological characteristics of patients. The appropriate statistical methods are needed to provide the P-values for the tests.

Author response:

We have added the P value in the revised table.

4. Reviewer comment:

For Table 2 The risk factors of predicted lymph node metastasis, it seems that here age was used as a continuous variable. However, in the text, authors claimed that age was compared at different range. Also we do not know what reference level of age was used for the comparison here?

Author response:

Age was compared at different range in the text and nomogram model.

5. Reviewer comment:

Figure 1, readers need to know the p-values for age comparison.

Author response:

We have add the p value in the revised figure.

6. Reviewer comment:

Figure 4 only had two legends, why have four lines?
Author response:

We didn’t have figure 4 in our manuscript. In figure 3, the dot line is the 95% confidence interval.