

RESPONSES TO THE REVIEWERS' COMMENTS

Title: “Nomograms for the pre- and postoperative prediction of long-term survival among proximal gastric cancer patients: A large-scale, single-center retrospective study”

We are extremely grateful to the editor and the anonymous reviewer for their valuable comments and suggestions, which have helped improve the quality of the manuscript. We studied the reviewers' comments and made corresponding modifications and corrections, which we hope will be met with approval. We revised the manuscript according to your kind advice and the referee's detailed suggestions. Our descriptions of the revisions are provided below.

Review 1

Conclusion: Minor revision

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Comments:

This is an original article entitled “Nomograms for pre- and postoperative prediction of long-term survival for proximal gastric cancer patients: A large-scale, single-center retrospective study” by Chen et al., that analyses retrospective data of patients with proximal gastric cancer in order to develop nomograms as possible predictors of survival. Gastric cancer is extremely inhomogeneous in his clinical presentation due to different stage, features of primary tumor nodal involvement, histological type and patients' characteristics. Long survivors could be better selected to receive more aggressive therapies according to models that allow a better stratification of the patients with a better prognosis. Therefore, the topic is of interest and such a studies are necessary, as the current evidence is still debatable.

However, some adjustments are needed:

Introduction: - the aim of the study should be clearly defined and be the same in

abstract and text. Differences could confuse the reader. To “...explore the postoperative prognosis of upper stomach carcinoma and the related preoperative and postoperative factors...” is not a well-defined objective. Maybe the authors mean that the aim of the study was to develop preoperative and postoperative nomogram prediction models for long-term survival based on retrospectively analysed data regarding patients with proximal gastric cancer, after prior investigation of preoperative and postoperative prognostic factors. Please change.

The authors' answer:

We thank the reviewer for these suggestions and revised the corresponding sections as follows: “...explore the postoperative prognosis of upper stomach carcinoma and the related preoperative and postoperative factors...” was changed to “the aim of this study was to develop preoperative and postoperative nomogram prediction models for long-term survival based on retrospectively analyzed data from patients with proximal gastric cancer based on a prior investigation of the preoperative and postoperative prognostic factors.” The changes are marked in red.

Materials and methods: - proximal gastric cancer and upper third gastric cancer are used to define the same tumor site? Then please call it proximal gastric cancer as in the title and in the selection criteria section defined it correctly, i.e. “...primary adenocarcinoma in the proximal part (upper third) of the stomach...” instead of “...primary adenocarcinoma in the upper third of the stomach..-“. - “The preoperative size, location, T stage (with or without the presence of serosal invasion) and N stage (with or without LN metastasis) of the neoplasm were assessed in all the patients via upper digestive endoscopy with a biopsy, chest X-ray, total abdominal ultrasound, and abdominopelvic CT scan.” was written twice and is redundant. Please correct it in text.

The authors' answer:

According to the reviewer's suggestion, we revised "upper" to "proximal" and deleted the redundant part in the corresponding section of the manuscript.

In sections "The diagnostic standard for preoperative T and N staging" and "Follow-up" the same information is repeated as above. These two paragraphs could be summarized in one i.e "diagnosis and follow up". Please cancel redundant text above.

The authors' answer:

Based on your comments, we removed the redundant description and combined "The diagnostic standard for preoperative T and N staging" and "Follow-up" into "Diagnosis and follow up".

Factors analyzed in training and validation model should be mention in the "Statistical analysis" section. The appear suddenly only in the "Results".

The authors' answer:

Based on your comment, we added "The optimal threshold levels of preoperative blood CEA and CA19-9 for the prediction of prognosis, which were acquired using the log-rank test with the X-tile Software, were 4 ng/mL and 33.35 ng/mL, respectively" to the "Statistical analysis" section of the manuscript and delete this description from the original "Results" section.

Results: - Please do not use expression such as "closely related to OS". Instead significantly or not significantly or trend could better report the results. - **Results** are very confusing and complicated. I suggest to divide this section in two principal paragraphs: training and validation and for each of them to report pre- and post-

operative model/factors.

The authors' answer:

Based on your suggestion, we changed "closely related to OS" to "can significantly affect the OS (P all <0.05)" and rearranged the order of the results according to your comments.

Discussion: - Limits of the study are correctly reported at the end of the discussion. It could be useful if the authors add also a paragraph including points of strength and the importance of their findings.

The authors' answer:

Based on your suggestion, we added the following description at the end: "However, this study is the first to provide both preoperative and postoperative prognostic models for patients with proximal GC. Clinical surgeons can use this model to accurately assess the prognostic risk in such patients before surgery, and the postoperative model could help patients in terms of individualized treatment and follow-up guidance."

Review 2

Conclusion: Accept (General priority)

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

The authors showed the possibility of using nomograms to predict long-term results of patient treatment with proximal gastric cancer. They showed the possibility of using in the prognostic model not only postoperative, but also preoperative characteristics of the

tumor and patients. In addition, the authors noted the role of blood transfusion and postoperative complications as factors affecting the prognosis of gastric cancer. The presented data are scientifically substantiated and statistically confirmed. The results obtained are of interest to practical oncologists and may be useful for assessing the prognosis of the disease and individualizing the treatment of patients.

Minor bugs are easily fixed. In the Abstract, the phrase: "The data were split 75/25", needs to be clarified. It is needed to fix the phrase "methods or predicting" in the Abstract. In the Introduction, it is necessary to verify the correctness of the expression: "The performance of such nomogram-based models ion performance is superior to that of the traditional staging system."

The authors' answer:

According to your comment, we revised the text "Between January 2007 and June 2013, we prospectively collected and retrospectively analyzed the medical records of 746 patients with proximal GC. The data were split 75/25, with one group used for model development and the other group used for validation testing" to "Between January 2007 and June 2013, we prospectively collected and retrospectively analyzed the medical records of 746 patients with proximal GC, who were divided into the training set (n=560, 75%) and validation set (n=186, 25%)". There was a clerical error in the original sentence "The performance of such nomogram-based models ion performance is superior to that of the traditional staging system", and we modify this sentence as follows: "The performance of such nomogram-based models is superior to that of the traditional staging system ".

Review 3

Conclusion: Rejection

Scientific Quality: Grade D (Fair)

Language Quality: Grade D (Rejection)

This is a single centre study from China involving a retrospective review of prospectively collected clinical data. The authors have sought to develop a prognostic nomogram for patients with proximal gastric cancer undergoing radical surgery. Tumours were restricted to the proximal third of stomach and all patients underwent radical total gastrectomy. Overall, the methodology employed to develop a prognostic nomogram is sound. The investigators have included a large number of patients overall (n=746) and divided the subjects into development set and testing set. The developed nomogram appears to work reasonable accurately (approx. 75%). However:

1. How did the authors choose the variables to include in the nomogram? It would appear that many variables were analysed and those with a 'P value' were selected to be included. For example, why were tumour markers CEA and CA19-9 included. These are poor markers of disease activity and tumour biology. The authors have ignored completely well-established prognostic indicators, such as markers of systemic inflammation (eg CRP or neutrophil/lymphocyte ratio).

The authors' answer:

According to references ^{1,2}, our nomogram includes the variables with a P-value less than 0.05 in the Cox multivariate analysis, which were independent prognostic factors affecting survival. We added these description to the **Results** section. The CEA and CA19-9 data in the cohort in our study were complete, but data regarding preoperative systemic markers, such as CRP, were incomplete. Consequently, we aim to further analyze the prognostic factors affecting survival through multi-center data with preoperative inflammatory markers and establish a more powerful application of the new nomogram. We added this discussion to the limitations section in the manuscript.

References

1. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *Journal of Clinical Oncology*. 2008;26(8):1364-70.
2. Gondo OT, Riu HM, Gondo T, Hamada R. [Nomogram as predictive model in clinical practice]. *Gan to Kagaku Ryoho*. 2009;36(6):901-6.

There is no description on adjuvant treatment. How many patients received neo/adjuvant systemic therapy? Did receipt of systemic therapy alter the performance of the nomogram?

The authors' answer:

In Table 1, we supplemented the data with information regarding patient neoadjuvant and postoperative adjuvant chemotherapy, and the single and multivariate analyses of the neoadjuvant and postoperative adjuvant chemotherapy data in the training set was added to Table 3. We added these results to the corresponding parts of the manuscript. Our results showed that neoadjuvant chemotherapy was significant in the univariate analysis, but no significant difference was observed based on adjuvant chemotherapy. Further multivariate analysis showed that neoadjuvant chemotherapy was not a significant factor for OS. The results of the new supplement did not change the existing nomogram results.

3. What about control for surgical radicality? Surely some resections were more 'radical' than others. Did the lymph node ratio positivity have a bearing on prognosis?

The authors' answer:

All patients with proximal gastrectomy in this study underwent D2 lymph node dissection. We added this information to the Methods section. We added the relationship between the lymph node positive rate (LNR) and survival in Table 3. The results showed that LNR was not a significant factor in the Cox analysis ($P=0.053$).

4. The authors acknowledge the presence of weight loss as a poor prognostic indicator. However, they attribute this wholly to poor nutrition. There is no acknowledgement of the syndrome of cancer cachexia, which is well established as a poor prognostic indicator.

The authors' answer:

Thank you for this comment. Weight loss was a poor prognostic indicator because its occurrence could not only be due to malnutrition but also may be affected by cancer cachexia syndrome. Patients with cachexia often have obvious weight loss. A previous study¹ reported that patients with cachexia syndrome often have a poor prognosis, and we added this information to the **Discussion** section.

References

1. Ockenga J , Valentini L . Review article: anorexia and cachexia in gastrointestinal cancer[J]. Alimentary pharmacology & therapeutics, 2005, 22(7):583-594.

5. I am still unsure how the authors plan to use the nomogram. Are they proposing the 'poor' prognostic patients are offered alternative treatments? If so, I would suggest that 75% accuracy is not good enough for this.

The authors' answer:

This study aims to establish a nomogram providing guidance for the identification and prediction of patients with proximal GC before and after surgery. Preoperative predictive models can provide a simple and effective predictive tool to differentiate

preoperative high mortality and low mortality risk groups of proximal gastric cancer patients. Targeted and relevant more active and effective surgery is of great significance for improving the prognosis of patients with proximal GC. The postoperative nomogram could help patients in terms of individualized treatment and follow-up guidance.

6. The whole manuscript is too long and rambling - especially the discussion which is repetitive.

The authors' answer:

Based on your comments, we removed the duplicate discussion.

For the editor of WJCC

In order to ensure the English quality of the manuscript, we send the manuscript to AJE company to improve the quality of language.and the modified part were marked with red color.