

Title: Survival benefit of younger gastric cancer patients in China than the US: a comparative study of survival, prediction model, and biological analysis

Dear Editor and Reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. A list of responses to all issues that the reviewers raised is provided below.

Reviewer 1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors compared clinicopathological characteristics, prognostic nomogram, and biological analysis in gastric cancer patients in China and the US. Such studies are of great importance, as they make it possible to establish new factors influencing the prognosis of the disease and note new approaches to the treatment of this formidable disease. The authors used one of the largest patient samples, which made it possible to construct prognostic nomograms for younger gastric cancer patients in China and the USA. The data obtained are undoubtedly of great interest for practical and fundamental oncology. At the same time, one cannot fail to note a number of significant, but quite correctable shortcomings of the submitted manuscript.

(1) Abstract Please edit the purpose of the study, noting that the comparison of the studied characteristics was performed in patients with gastric cancer.

Done as suggested.

We have revised the purpose section of the Abstract, and emphasized that the comparison was made in Chinese and American younger patients with gastric cancer.

(2) In the methods, it should be noted that the SEER database is a program of the National Cancer Institute USA. Unfortunately, the authors in the Abstract did not reflect the possible reasons for the observed differences in survival (e.g., differences in disease stage, tumor location, differentiation, linitis plastica) and factors that contributed to the improvement in the survival of patients with gastric cancer in China (e.g., early cancer screening and other). My opinion is that these data should be indicated in the Abstract, as they are of great importance.

Done as suggested.

In the conclusion of the Abstract, we have revised and added the possible reasons for the observed differences in survival. On the one hand, this survival disparity may be due to the difference in surgical methods between China and the US. On the other hand, the survival advantage of younger Chinese patients with gastric cancer may also be attributed to the improvement of the cancer screening and early detection programs in China. In Discussion, as highlighted by the reviewer, we analyzed the reasons for the survival disparity of younger patients between China and the US. Moreover, benefit from multivariate cox analysis, we might eliminate the impact of factors other than region on the survival of gastric cancer in younger adults, such as pTNM stage, tumor location, and differentiation.

(3) Statistical Analysis Without considering the distribution of variables, the use of the Student's t-test to compare continuous variables is highly questionable.

Done as suggested.

The statistical methods used in this article have been refined by statisticians. Comparisons were performed using the t-test for normally

distributed continuous variables or the Mann-Whitney U test for variables not normally distributed. We have re-comparisined continuous variables and corresponding results have been changed in tables and manuscript.

(4) Results The statement “Compare to the US, China group has a higher ratio of younger patients over periods” does not correspond to the data in Table 1. It is true only for the period from 2009 to 2013.

Done as suggested.

In Table 1, we revealed the proportion of younger gastric cancer patients in a certain period to all the periods in the 20 years, which does not correspond to the proportion of younger gastric cancer patients for all the patients (including younger and older patients). The statement “Compare to the US, China group has a higher ratio of younger patients over periods” is the display of the result of Figure1, which revealed the ratio of younger patients for all gastric cancer patients. We apologize for the misunderstanding caused by not explaining well.

(5) The interpretation of the results of Table 1 requires serious revision due to the inaccuracies identified in it (some percentages are calculated incorrectly, since a number of characteristics do not add up to 100%).

Done as suggested.

Such calculations are inappropriate, so we reanalyzed the data and made careful revisions in Table 1 with reference to the reviewer’s comments.

(6) It hardly makes sense to include in the prognostic nomogram the period in which patients received treatment.

Done as suggested.

The comments made by the reviewers are correct and more applicable to clinical practice. Following the reviewer’s suggestion, we constructed the nomogram model without period of diagnosis. Based on the results of multivariate Cox regression and features of clinical significance, we

constructed a prediction model for the prognosis of gastric cancer in Chinese youth, and the factors included were Linitis plastica, Surgery, ELN ≥ 15 , and pTNM stage. For the US group, the factors were as follows: race, diagnostic period, gender, location, differentiation, linitis plastica, signet ring cell, pTNM stage, surgery, and chemotherapy.

(7) In the same way, one must be careful when interpreting data on surgical treatment, since the authors combined into one group patients with known data (there was no operation, there was no lymphadenectomy – the latter is very doubtful) and patients in whom information about this was absent.

Done as suggested.

The comment made by the reviewers was of great importance. Following the reviewer's suggestion, we cleaned up our data and removed unknown data (involves Linitis plastica, signet ring cell carcinoma, surgery, lymph node dissection, and lymphadenectomy with at least 15 lymph nodes). Later, we reanalyzed the data and made corresponding modification based on the original chart results.

(8) Moreover, for example, in a univariate analysis, the presence of chemotherapy in patients with gastric cancer was associated with an unfavorable prognosis, while in a multivariate analysis, on the contrary, with an improvement in the prognosis of the disease.

Done as suggested.

Firstly, after we optimized the data according to the reviewer's suggestion, we still obtained the same results as before, which might be due to the relatively small sample size. We have carefully checked the data and results, and there are no errors. Secondly, we performed a collinearity test on the results, and there was no problem with the relationship between the included variables.

(9) The presentation of the ROC curves in the manuscript would greatly improve the demonstration of the proposed model. Supplementary Material – not loaded into the system.

Done as suggested.

As shown in Figure 4, we reconstructed and validated the survival prediction model for gastric cancer among young adults in China and the US. Later, the ROC curves for the training set and validation set were plotted and were shown as Supplementary Figure 1. From the results, the prognosis prediction models for both Chinese and the US younger gastric cancer patients showed great performance, with the AUC 0.848 in the training set and 0.786 validation set in China group, the AUC 0.864 in the training set and 0.842 validation set in the US group.

(10) Discussion Considering that the authors did not distinguish between cases where surgery and proper volume of lymph node dissection were not performed and cases where these data were unknown, the interpretation of differences in treatment tactics in the US and China should be very cautious.

Done as suggested.

Following the reviewer's suggestion, we optimized the data on linitis plastica, signet ring cell carcinoma, surgery and lymphadenectomy. Later, we further compared surgery, non-operation, lymph node dissection, no lymph node dissection, and the number of lymph node dissections between Chinese and American younger gastric cancer patients and their impact on prognosis. Our findings based on two cohorts are objective and interpretable.

(11) Tables In Table 1, for some characteristics, the percentage of cases does not add up to 100%. This applies, for example, to "Primary tumor location", "Differentiation" and many other characteristics. It is necessary to carefully recalculate the percentages in all groups" !!!
In addition, it is necessary to check the absolute values of the indicators. For example, in the USA, the number of patients with M1 is 1492, while the number of patients with stage IV gastric cancer is 1687.

Done as suggested.

We have reorganized the data and the number of patients with M1 stage has been corrected. Thank you again for your careful review.

(12) Indicate in the titles of the tables or in the notation which analysis (univariate or multivariate analysis) was used in tables 3 and 4.

Done as suggested.

Following your suggestion, the titles of the tables has been changed. Table 3 revealed the results of univariate Cox regression, and Table 4 showed the results of multivariate Cox regression.

(13) Figures The drawings are layered on each other and on the captions. Figure 3. If you want to show differences in survival between compared groups, it is more representative to use one vertical dashed line from one, three, or five years, and two horizontal dotted lines from its intersection with survival probability curves. In this case, you are showing exactly the differences in survival between groups.

Done as suggested.

Following your suggestion, the vertical dashed line from one, three, and five-years survival between China and the US group, as well as different races were added. As you expected, the survival differences between groups are showed exactly.

(14) Figure 3A is not mentioned in the text of the manuscript.

Done as suggested.

We have marked the location of Figure 3A in the revised manuscript. All tables and Figures are carefully checked to ensure that they were cited.

(15) Language The manuscript needs stylistic correction of the text. Just some examples: Wrong wording: "As described from our previous results [8],

younger patients with GC had aggressive behavior and dismal prognosis.”
Unnecessary repetition: “The histologically confirmed GC cases in China were selected through the China National Cancer Center Gastric Cancer Database (NCCGCDB). The NCCGCDB was a clinical gastric cancer database sourced from China National Cancer Center.” etc.

Done as suggested.

We have carefully revised the language, grammar and expression in the article. The article was then reviewed by the native English speakers with some minor changes, and the revised portion were marked in yellow in the paper.

Reviewer #2:

(1) Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Dear Authors, Congratulations on writing this article. The article will need few grammatical conditions, which may please be done

Done as suggested.

We have carefully revised our language, grammar and expression in the article, which was then reviewed by the native English speakers, and the revised portion were marked in yellow in our manuscript.