

Dear editors and reviewers:

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

Title: Application of preoperative artificial neural network(preope-ANN) based on blood biomarkers and clinicopathological parameters for predicting long-term survival of patients with gastric cancer

Review 1 (Number ID: 02537403)

Conclusion: Accept (High priority)

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Reviewer's comments to authors:

The TNM staging system of AJCC is the most important prognostic factor for gastric cancer, serving as the main instrument for clinicians to choose the therapeutic management. However, pTNM staging needs information from the histopathological results of the resection specimen, which prevents the management from guiding the preoperative treatment plan. Hence, accurate preoperative tumor evaluation providing an individualized treatment for these patients is crucial for improving the prognosis. However, the clinical TNM staging (cTNM) system based on the imaging examination does not achieve the ideal preoperative accuracy for the prediction of the outcome. Literature data show that the inflammation and nutrition indexes are significant to the survival of cancer patients. The artificial neural network (ANN) model is a new computational model developed by simulating the function of human brain

that can create a nonlinear statistical model to analyze complex biological systems. This research combined the preoperative blood biomarkers (the inflammatory and nutritional indicators) and preoperative tumor characteristics to establish an ANN model in order to create a preoperative prediction system with the same accuracy of postoperative TNM staging. The results show that the accuracy of the preope-ANN model in predicting the 3-year survival rate is 91.7%; the accuracy and the fitting degree of the preope-ANN model were better than those of cTNM staging, and the preope-ANN could achieve the same prediction effect as pTNM staging. Moreover, the preope-ANN model can provide an even more detailed prediction for each patient than the TNM staging system and can be used to predict the long-term survival of patients before surgery and to choose the optimal individualized treatment according to the prognosis. Therefore, in patients with poor prognosis information before surgery, the prognosis may be improved by adopting neoadjuvant chemo-radiation. I read this paper with great interest. I was impressed by the complexity of this work and I consider that clinical implementation of this model may represent a step forward in the management of gastric cancer patients, and can be considered as part of preoperative risk stratification to guide the personalized treatment of patients. For the near future, the challenge is to create a web version of this model that can be dynamically adjusted for the input of different information.

The authors' answer:

Thank you to the reviewers for their meaningful comments. Thank you very much for your efforts.

Review 2 (Number ID: 03769068)

Conclusion: Accept (High priority)

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Reviewer's comments to authors:

The manuscript 'Application of preoperative artificial neural network(preoperative ANN) based on blood biomarkers and clinicopathological parameters for predicting long-term survival of patients with gastric cancer" submitted by Que et al. is an excellent job that evaluates the use of preoperative artificial neural network for predicting the long-term survival of patients with gastric cancer. However, the text formatting is inappropriate to World Journal of Gastroenterology standards. Please, correct the paper formatting.

The authors' answer:

We are sorry that our format does not meet the requirements of the magazine. We have revised the manuscript in accordance with the requirements of the World Journal of Gastroenterology standards.

Review 3 (Number ID: 02572357)

Conclusion: Accept (General priority)

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Reviewer's comments to authors:

In results is written that the male to female ratio was 2.84 : 1, but reading the manuscript we see that there were 484 men and 1376 women. #Table 1 has a typo at the top #In the results is written that "in the training set, the univariate logistics regression (Table 2) shows that CEA, CA199, AFP, NLR, PLR, AGR, PNI, , tumor location, tumor size, cT stage and cN stage were significant factors in the 3-year OS of the patients (all $p < 0.05$)". Then all the variables that the authors chose to include were significant? If it is so, do the authors not think that it is uncommon? Should this not deserve a commentary?

The authors' answer:

With regard to the inconsistent sex ratio mentioned in the comments, We are very sorry that we made a clerical error in the manuscript. In this study, the number of male patients was 1376, the number of female patients was 484, and the ratio of male to female was 2.84:1. We have made changes and will mark some of the changes red.

We have corrected the spelling errors in Table 1, changed the title of the error "All papapatient" into "All patient" and marked them in red fonts.

After our recalculation, the logistics univariate analysis of these variables (CEA, CA199, AFP, NLR, PLR, AGR, PNI, tumor location, tumor size, cT stage and cN stage) showed that all the P value was less than 0.05, and there was obvious statistical significance. This is similar to what has been reported in previous studies, previous studies have shown CEA, CA199, AFP, (1) NLR, PLR, AGR, PNI, (2-7) tumor location, tumor size, cT stage and cN stage (8) are good prognostic factors for gastric cancer patients.

Reference

1. Kodera Y, Yamamura Y, Torii A, Uesaka K, Hirai T, Yasui K, et al. The prognostic value of preoperative serum levels of CEA and CA19-9 in patients with gastric cancer. *Am J Gastroenterol*. 1996;91(1):49-53.
2. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001;357(9255):539-45.
3. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860-7.
4. Deng Q, He B, Liu X, Yue J, Ying H, Pan Y, et al. Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. *J Transl Med*. 2015;13:66.
5. Hirahara N, Tajima Y, Fujii Y, Yamamoto T, Hyakudomi R, Taniura T, et al. Preoperative Prognostic Nutritional Index Predicts Long-term Outcome in Gastric Cancer: A Propensity Score-matched Analysis. *Anticancer Res*. 2018;38(8):4735-46.
6. Liu X, Wu Z, Lin E, Li W, Chen Y, Sun X, et al. Systemic prognostic score

and nomogram based on inflammatory, nutritional and tumor markers predict cancer-specific survival in stage II-III gastric cancer patients with adjuvant chemotherapy. Clin Nutr. 2019;38(4):1853-60.

7. Pan QX, Su ZJ, Zhang JH, Wang CR, Ke SY. A comparison of the prognostic value of preoperative inflammation-based scores and TNM stage in patients with gastric cancer. Onco Targets Ther. 2015;8:1375-85.

8. Park SR, Kim MJ, Ryu KW, Lee JH, Lee JS, Nam BH, et al. Prognostic value of preoperative clinical staging assessed by computed tomography in resectable gastric cancer patients: a viewpoint in the era of preoperative treatment. Ann Surg. 2010;251(3):428-35.

Thank you very much.

Yours sincerely,

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