

ANSWERING REVIEWERS

December 24, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 6910-Revised.doc).

Title: Inflammation-related factors predicting prognosis of gastric cancer

Author: Wen-Jun Chang, Yan Du, Xin Zhao, Li-Ye Ma, Guang-Wen Cao

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6910

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated. We also had native English speakers professionally edited the manuscript.

2 Revision has been made according to the suggestions of the reviewer

1) Reviewer 02438143

The authors made a complete review on inflammation-related prognostic factors of gastric cancer in this manuscript. There is a difference between the overall 5-year survival rates of USA GC patients and Japanese or Korean GC patients. Expression patterns of those inflammatory prognostic factors in GC tissues should be analyzed and discussed comparatively.

Answer: During the past decades, there has been a large amount of speculations considering the differences of the outcomes of gastric cancer (GC) patients between different countries. The associations between GC survival and ethnics haven't been clearly established and remain controversial. As early as in 1985, Bako G. *et al.* (Bako G. *et al.* Factors influencing the survival of patients with cancer of the stomach. Clin Invest Med 1985; 8: 22-8) mentioned that ethnicity may be associated with GC outcome. Since then, many hypotheses have been proposed to explain these differences, including differences of proximal versus distal cancer incidences, environmental exposures, dominant pathological types, percentage of early GC patients at first diagnosis, surgical factors, and neoadjuvant/adjuvant treatment protocols. However, many unmeasured covariates and/or confounders make it difficult to directly compare GC survival between

different populations. Recently, a study (Strong VE, *et al.* Comparison of disease-specific survival in the United States and Korea after resection for early-stage node-negative gastric carcinoma. *Journal of Surgical Oncology* 2013; 107:634-640) found that the survival did not differ significantly between Korean and the US GC patients when comparing the patients at similar stages (node-negative and without treatment). To address the issue raised by this reviewer, we added paragraphs of discussion in the manuscript (Page 5, Line 8-17 & Page 17, Paragraph 2, Line 6-8), and also provided the country origins of the GC patients in this revised version of Table 1 and Table 2. However, it is difficult at the current stage to have a comprehensive comparison of the molecular expression patterns of different populations.

Typos: P5, L2 from bottom, “non-sterioidal”; P6, L10, “have to shown”? Explanations of abbreviations should be added when it first appeared. (eg, CCL)

Answer: We corrected “non-sterioidal” to “non-steroidal” (Page 6, Line 3), and “have to shown” to “have been shown” (Page 6, Line 15). We checked all abbreviations used and added them during the first appearance.

Reviewed by 02445881

Dear Sirs, In this manuscript the authors have made an attempt to review the literature regarding the correlation of inflammation-related factors and the ability to predict the prognosis of gastric cancer. This is an interesting manuscript with a very good structure and summary of data. Considering the importance of this field it would be good if the authors could revise the utility of a predictive model which combined some of the factors into a clinically usable model. Nevertheless, the manuscript is pertinent and is in conditions to be accepted for publication.

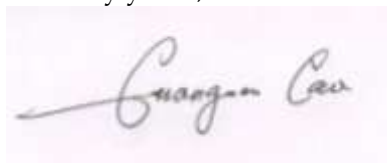
Answer: We quite agree with this reviewer. Previous studies have already investigated some simple combinations, such as Foxp3⁺/CD4⁺ and Foxp3⁺/CD8⁺ ratios, Th1/Th2 ratio

in relation with GC outcome. While with the advancement of systems biology and vast amount of -omics data, it is of great importance to incorporate these data with clinical and pathological variables to more accurately predict cancer outcomes. Studies have already looked at combining gene expression data with clinicopathological data to better predict HCC (Villanueva A, *et al.* Combining clinical, pathology, and gene expression data to predict recurrence of hepatocellular carcinoma. *Gastroenterology* 2011; 140: 1501-12.e2) and CRC (Chang W, *et al.* Gene expression profiling-derived immunohistochemistry signature with high prognostic value in colorectal carcinoma. *Gut* 2013 Oct 30. doi: 10.1136/gutjnl-2013-305475.) prognosis. However, we conducted a comprehensive literature search, and only found a couple of papers (Peng CW, *et al.* Combined features based on MT1-MMP expression, CD11b+ immunocytes density and LNR predict clinical outcomes of gastric cancer. *J Transl Med* 2013; 11:153 & Pasini FS, Zilberstein B, Snitcovsky I, Roela RA, Mangone FR, Ribeiro U Jr, Nonogaki S, Brito GC, Callegari GD, Cecconello I, Alves VA, Eluf-Neto J, Chammas R, Federico MH. A gene expression profile related to immune dampening in the tumor microenvironment is associated with poor prognosis in gastric adenocarcinoma. *J Gastroenterol.* 2013; [PMID:24217965]) that discussed combining inflammation related factors to predict GC outcome. This is a promising field of research and we added some discussions in this revised manuscript (Page 17, paragraph 2, Line 8-14), although we were not able to give an exhaustive investigation in the current review.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Guangwen Cao', is written on a light pink rectangular background.

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