ANSWERING REVIEWERS

July 27, 2014
Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12312-edited.doc).

Title: Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: A meta-analysis

Author: Jian-Jun Yang, Zhi-Gao Hu, Wu-Xiang Shi, Te Deng, Song-Qing He, Sheng-Guang Yuan

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

2 Revision has been made according to the suggestions of the reviewer
  (1) Comment: The paper needs improvement in writing and editing.
Response: we checked the manuscript carefully and corrected some mistakes; the manuscript also has been edited by a professional English language editing company.
  (2) Comment: The authors should substitute reference 12 by a more specific one.
Response: we changed the reference 12 as suggested, see reference list.
  (3) Comment: There have been a new so-called derived NLR published by Procter et al., which has been already validated in pancreatic cancer. The authors have to cite in their discussion section shortly these two papers: Br J Cancer. 2012 Aug 7; 107(4):695-9; PLoS One. 2013 Nov 4; 8(11):e78225
Response: we cited these two papers in the discussion section and discussed as follows: Interestingly, a large cohort study reported a newly derived NLR (dNLR) constructed as the neutrophil count to (white cell count-neutrophil count) had a similar prognostic value as the NLR in various cancer types. The prognostic role of dNLR was also verified in pancreatic cancer. Future studies and clinical practice should pay more attention to this universally available dNLR.

  (4) Comment: In "Study selection" the authors stated that additional information was asked in the articles with doubts. Please clarify what kind of information was asked as well as in which articles
Response: In "Study selection", we supposed that we asked the authors to supply additional information if there were doubts about the original articles. After checked all the selected articles, we found all kinds of the data we needed are available, therefore, no additional information were asked from the original authors.
  (5) Comment: Most patients with pancreatic cancer, especially in unresectable one, die from pancreatic cancer. Therefore, it is somewhat unclear whether cancer-specific survival, rather than overall survival, analysis was clinically relevant.
Response: As we known, the prognosis of pancreatic cancer is particularly poor, most patients lose

opportunities of radical surgery after diagnosis, overall survival and cancer specific survival are almost the same in pancreatic cancer, therefore most of the studies evaluated overall survival rather than cancer specifical survival.

(6) Comment: Countries shown in Table 1 appeared incorrect

Response: the reviewer is right; we carefully checked the table 1 and corrected it.

(7) Comment: In Figure 2, it is unclear which analysis indicated the association of NLR and which factor e.g. CA199 etc. Please add CA199, CRP etc. in each plot.

Response: Based on the reviewer's suggestion, we add CA199, CRP etc. in each plot of figure 2.

(8) Comment: In the description of the selection of the studies, the authors started from 66 studies and they report the arguments why at the end they did the meta-analysis in 11 groups. They clearly define the exclusion-criteria of 46 studies, but there are 10 studies which they don't comment why they were not included in the meta-analysis. This should be explained.

Response: In the previous version, we made a mistake; it should be "55 studies were excluded". We corrected it in this current version.

(9) Statistics must be presented in conventional way, with the entire p value

Response: We presented statistics in conventional way with entire p value in current version.

(10) Comment: additional details on treatment performed in the individual studies must be provided.

Response: We added additional details on treatment performed in the individual studies to "***Selection and characteristics of studies"*** as below:

Three studies evaluated the NLR for outcomes of patients who had undergone surgery, chemotherapy, radiotherapy or the combination of these treatments (grouped as the mixed treatment group); four studies that evaluated NLR for palliative chemotherapy outcomes were classified as the chemotherapy group; and one study that evaluated the NLR for outcomes of patients who had undergone surgical resection was defined as the surgical resection group.

(11) Comment: Albumin correlation with NLR should be described in detail taking into account the possible effect of inflammation on serum protein.

Response: Yes, we described in the discussion section as: "A low albumin level, as an independent prognostic marker, has been demonstrated in renal cell carcinoma; the serum albumin level is modulated by systemic inflammation and the prognostic role of serum albumin combined with CRP has been reported in various cancers. In our meta-analysis, we showed that a high NLR is associated with low albumin, which also indicated that NLR is a potential indicator of the prognosis."

(12) Apart the prognostic role, the authors should describe the potential of NLR as a predictive factor, as described on lung cancer, in order to provide a whole scenario of NLR investigation

Response: Additionally, NLR might potentially and extensively be used as a novel predictive factor in pancreatic cancer; however, our selected studies that evaluated the prognostic role of NLR were all retrospective analysis. Additional large cohorts of prospective studies are needed to confirm the NLR as a potential predictor of the prognosis in pancreatic cancer."

3 References and typesetting were corrected.

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

Sincerely yours,

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