Author’s response to reviews

Title: A Novel Combined Systemic Inflammation-Based Score Can Predict Survival of Intermediate-to-Advanced Hepatocellular Carcinoma Patients Undergoing Transarterial Chemoembolization

Authors:

Chang Liu (westchina_lc@foxmail.com)

Lei Li (85536819@qq.com)

Wu-sheng Lu (Icnolan@qq.com)

Hua Du (duhua3983@163.com)

Lu-nan Yan (yanlunan688@163.com)

Jia-yin Yang (13881899667@163.com)

Tian-fu Wen (tianfu1962@163.com)

Wu-ran Wei (jitamao55@163.com)

Li Jiang (jl339@126.com)

Wen-tao Wang (wwt02@163.com)

Ming-qing Xu (qlm66220@163.com)

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Author’s response to reviews:

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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: main-revised.docx).

Title: A Novel Combined Systemic Inflammation-Based Score Can Predict Survival of Intermediate-to-Advanced Hepatocellular Carcinoma Patients Undergoing Transarterial Chemoembolization
Author: Chang Liu; Lei Li; Wu-sheng Lu; Hua Du; Lu-nan Yan; Jia-yin Yang; Tian-fu Wen; Wu-ran Wei; Li Jiang; Wen-tao Wang; Ming-qing Xu

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All authors included in this research have declared that no competing interests exist.

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

Reviewer reports:

Nicola Personeni (Reviewer 1): This paper illustrates the prognostic impact of a combined dNLR-PNI score in HCC patients undergoing TACE. The paper is well written but results reported by the Authors do not appear convincing with respect to the usefulness of such score.

Major comments:

1) Authors state that the dNLR has a similar prognostic impact compared to the NLR and indeed it can be used when the lymphocyte count is not available. However, in the current study, the lymphocyte count was available and it was used to calculate the PNI. So, given the availability of the lymphocyte count, why did the Authors choose the dNLR instead of the NLR?

Response: Firstly, we should give our great thanks to you for your work.

We have to admit that your suggestion is reasonable, the combination of NLR and PNI is more convenient to calculate as lymphocyte count is not involved in both of them. In fact, we have explored the combination of NLR and PNI in another study and the result was satisfied. So in current study, we wanted to make an attempt to discuss the possibility and meaning of dNLR combined with PNI regardless of the lymphocyte, and the result showed its value.

On the other hand, the result of multivariate analysis showed the HR of dNLR-PNI was the best, and the survival analysis cure showed its ability of strafition patients outcomes with advanced HCC. So in our opinion, the exploration of dNLR-PNI in the setting of HCC patients received TACE is meaningful and worth our try.

Maybe it is the tiny meaning of this exploration, at least let other doctors and researchers know this combination of dNLR-PNI is of use, but limited in a way.
2) Line 69-70: the prognostic role of PNI should be discussed in the frame of patients undergoing TACE. Actually, evidences do not seem to be straightforward in this setting (for instance, see He and Lin, Plos 2017)

Response: We have searched the database, and there was few research investigated the value in patients received lipiodol-based conventional transarterial chemoembolization (cTACE). Besides the article reviewer suggested above, there is another research demonstrating the lower PNI was associated with unsatisfactory overall survival (Prognostic Nutritional Index Is Associated with Survival in Patients with Unresectable Hepatocellular Carcinoma Treated with Radioembolization. Samer Tohme, Alexis P. Chidi. Journal of vascular and interventional radiology. Volume 28, Issue 3).

However, both of them are not discussed in the frame of patients undergoing cTACE, instead of cTACE combined with humantype-5 adenovirus H101 or radioembolization.

So we would follow your suggestion and modify the sentence in the text to declare the background more clearly (line 69-71).

3) Line 187: According to this subchapter, Authors should report the discriminatory performances of the staging systems and inflammation scores. However, they only reported the performance of the inflammatory scores. The reader should be made aware of the performance of the staging system (BCLC) which is, moreover, reported to be an independent prognostic factor. These discriminatory performances need to be appropriately compared with the inflammation scores.

Response: Thanks for your suggestion. The BCLC staging system was added and we modified the subchapter (line 189-190), figure 3 and table 4 accordingly.

4) Line 192: the combined dNLR-PNI score had a superior discriminative capacity compared with the dNLR and PNI separately. This sentence is not supported by results on Table 4. Indeed the 95% CI of the respective AUROC are broadly overlapping and superiority of a certain score over another one cannot be claimed.

Response: Thanks for your suggestion, we have modified the expression more precisely in the context. Line 192-194.

5) Overall the AUROC values suggest a very modest discriminative efficacy of the different scores.

Response: We admit that the discriminative efficacy was limited of each score. However, we should also admit that there was an improvement of combination of dNLR and PNI indeed, although not dramatically. And both the multivariate analysis and survival analysis were showed
satisfactory result. So the AUROC was only one aspect of the research, was part of the whole research, the conclusion of the research was reached under a comprehensive consideration.

6) Among the limitations of this study is the lack of a training and validation set. This limitation need to be underscored.

Response: Thank you for your suggestion, we would clarify this information in the limitation part (line 286-287).

Minor comments:

1) Line 224: "predictive value" is not appropriate and has to be rephrased into prognostic value.

Response: Thanks, we would modify the sentence (line 224).

Toshiya Kamiyama (Reviewer 2): Major criticism

1. The author determined the cutoff value of the dNLR and PNI from ROC curve according to OS. What time did you decide on survival?

Response: Firstly, we should give our great thanks to you for your work. We adopted the date of death or the last follow-up date of the patients.

2. The patients were treated by only TACE? Were there the additional therapies after TACE refractory?

Response: Besides the TACE and anti-virus therapy for patients with HBV-infection, no other anti-treatments were administrated to patients in our center.

Sorafenib was recommended to patients for the treatment of TACE-refractory advanced hepatocellular carcinoma, however few patients could afford it by their own as its very high price in China. And some patients and their relatives might choose some Chinese patent medicine to help kill the cancer cells. In our opinion, the Chinese patent medicine would help them relieve symptom rather than control disease.

3. The author should describe clearly about the advantage of combination of dNLR and PLR in discussion.
Response: In the discussion part line 252-273, the advantage of dNLR-PNI was discussed as following summarized. 1) cheap and easily available; 2) with better discrimination and prognostic abilities; 3) related the tumor clinicopathological features such as tumor size, vascular invasion and liver function; 4) reflected the best survival outcome.

We followed your suggestion and modify the sentence in the discussion part line 268-271.

4. Figure 2 is not clear.

Response: The resolution of figure-2 is 600 dpi and fulfill the criteria of guideline of the submission. We would re-upload figure-2.

Thank you again for publishing our manuscript in the journal of BMC Cancer

Sincerely yours,

Wu-sheng Lu

Department of Liver Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China.
Phone: +86-28-85422867
Fax: +86-28-85422469
Email: westchina_otc@qq.com