Author’s response to reviews

Title: Predictive value of gamma-glutamyl transpeptidase to lymphocyte count ratio in hepatocellular carcinoma patients with microvascular invasion

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Author’s response to reviews:

Dear editor and reviewers:

Thank you very much for providing us an opportunity to revise our manuscript (BCAN-D-19-03722). The comments from editor and reviewers are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. In this revision, we have addressed all the concerns in detail and provided further explanation of the comments. My responses to the comments are described as follows. We hope that our revised manuscript is now suitable for your requirement.

Sincerely
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Review report
Manuscript ID number:
BCAN-D-19-03722
Title of paper:
Predictive value of gamma-glutamyl transpeptidase to lymphocyte count ratio in hepatocellular carcinoma patients with microvascular invasion

The point-by-point response to the reviewer's comments is as follows.

Reviewer #1:

1. Response to comment: The manuscript requires significant attention to improve grammar and the readability.
Response: Thank you for the correction of the article; the grammar and the readability have been improved for this article, further polishing by AJE company is accomplished and the serial number for the polishing proving is: FFA6-FDCB-C2E2-76D5-1EA1.

Reviewer #2:

1. Response to comment: The overall language of the manuscript is inadequate and causes difficulty to comprehend science. There are many spelling and grammar mistakes in the main body of the manuscript. I think taking help from a language editing service to improve the quality of English would be helpful. Particularly, the introduction and discussion section need to organized coherently and proofread thoroughly.
Response: Thank you for your correction. We have carefully checked and verified this article, and the alterations are marked in red. Further polishing by AJE company is accomplished and the serial number for the polishing proving is: FFA6-FDCB-C2E2-76D5-1EA1.

2. Response to comment: Authors should cite more references when stating a key scientific fact in the text for example introduction paragraph 1 line 14" liver cancer is a major public health problem facing the world. In addition to this, the references are missing and/or incorrectly cited in the manuscript.
Response: Thanks for your comment. We have carefully checked and proofread this article, and corresponding improvements are done.

3. Response to comment: How GLR estimation is a better biomarker for prediction of HCC with MVI than other known markers (if known any) needs to explain in more detail.

Response: The diagnosis of MVI in liver cancer patients depends on postoperative pathological examination, while the imageological and hematological examination’s value are not well documented yet. For example, a rough tumor edge [1] reported by imageological examination and the elevated serum AFP level [2], are independent predictors of MVI in liver cancer. Relatively speaking, GLR estimation is a favorable biomarker with high sensitivity and specificity for prediction of HCC with MVI, and it has the advantages of non-invasive and low-cost. Certainly, large-scale and prospective studies are in need to verified the general applicability of GLR.

4. Response to comment: Progression-free survival (PFS) and overall survival (OS) are not clearly defined and make the data interpretation difficult. The authors should clearly describe the difference between PFS and OS in the text.
Response: Yes, we did.

5. Response to comment: The sample size used in this study is fairly small and includes much fewer females in the MVI group. The authors should explain this limitation to the experiment. Additionally, did the authors calculate the cut-off GLR value for the non-MVI group? I think this is key information missing from the data analysis.
Response: Your suggestion is well appreciated! This study has some limitations indeed in terms of sample selection, that the small samples are collected from a single clinical institution and include much fewer women, which bears some relation to the higher incidence of HCC in men than in women in Asian countries. In the following studies, the sample size will be expanded; larger-scale and multicenter studies will be carried out either. On the determination of cut-off GLR value, this study mainly selects HCC with MVI as the variable objects, while the non-MVI HCC patients consist of the negative group in the binary classification variables.

6. Response to comment: The figure legends for all three figures are poorly written which needs to be more descriptive. Legends should include the details for the type of analysis performed, statistical details, etc. The detailed figure legends help readers to understand the experimental approach and data interpretation clearly.
Response: Yes, we did.

Reviewer #3:

1. Response to comment: Need more speculation on the mechanism of gamma-glutamyl transpeptidase to lymphocyte count ratio selection and its functional consequences.
Response: Your suggestion is well regarded! This study is a part of the clinical researches at present; in the following studies, we intend to investigate the mechanism and feasibility of gamma-glutamyl transpeptidase to lymphocyte count ratio in clinical practice, laying the foundation for GLR’s underlying application value for diagnosis and treatment of HCC.

2. Response to comment: What is the inclusion and exclusion criteria of the patients?
Response: We have added this part to the text. Based on the inclusion and exclusion criteria, a total of 230 patients with liver cancer who underwent radical resection entered the study. Patients were excluded if they had: (1) patients whose pathological diagnosis was not liver cancer (HCC), such as cholangiocarcinoma (CCC); (2) patients who died during the perioperative period; (3) patients with incomplete data or lost contact during the follow-up period; (4) infectious disease, immune system disease, blood system disease, or use of drugs that affect blood within one month; (5) patients...
underwent arterial chemoembolization before surgery or Radiofrequency ablation; (6) HIV positive patients.

3. Response to comment: How does author count the total lymphocyte count?
Response: Routinely, the blood routine test and biochemical indexes are required before surgical treatment. And the lymphocyte count is collected from the data of blood routine test report from the clinical laboratory.

4. Response to comment: How Gamma-glutamyl transpeptidase (GGT) levels were detected in HCC patients.
Response: Routinely, the blood routine test and biochemical indexes are requested before hepatic surgery. And the Gamma-glutamyl transpeptidase (GGT) is collected from the data of biochemical indexes test reported from the clinical laboratory.

5. Response to comment: How Gamma-glutamyl transpeptidase (GGT) correlates with disease progression and metastasis in HCC patients?
Response: At present, elevated serum levels of GGT are markers of oxidative stress according to many researches. The rise of GGT suggests poor prognosis for patients with liver cancer, and it may promote the malignant progression, invasive potency and other biological behaviors of cancer [3-5]. Other studies reveals that GGT is one of the inflammatory factors [6, 7], and plays a crucial role in tumorigenesis, invasion and metastasis.


6. Response to comment: Does total lymphocyte count include (B and T) cells? How B cells affect the disease progression in HCC patients?
Response: Lymphocyte count includes B and T cells. At present, the regulatory B (Breg) cells has been identified to regulate immune response by various means; the expansion of B cells can promote tumor immune escape, and the sub-type of PD-1hi B cells can inhibit tumor-specific T cell immunity [8, 9].


7. Response to comment: Discussion is written very vigorously and need to cite the relevant literature. Response: Thanks for your correction. Related articles have been cited in the article.

8. Response to comment: Entire manuscript entails a lot of English grammar as well as phrase construction. Response: Thank you for your correction. We have carefully checked and verified this article, and the alterations are marked in red. Further polishing by AJE company is accomplished and the serial number for the polishing proving is: FFA6-FDCB-C2E2-76D5-1EA1.

Reviewer #4:

1. Response to comment: In introduction please correct the sentence 'Liver cancer is a major public health problem facing the world' Response: Thank you for your point, and the sentence has been changed into 'Liver cancer is a significant public health problem facing the world'.

2. Response to comment: In result section (Clinicopathological parameters of HCC patients), authors have just shown the correlation, but they are concluding that 'These results suggest that inflammatory factors, such as NEUT, WBC, Globulin and AST, increase the risk of MVI in patients with HCC, and GLR acts as an inflammatory factor'. For this conclusion they have not shown any data. Authors should perform experiments showing how NEUT, WBC, Globulin and AST increase the risk of MVI in patients. Response: Inflammation is regarded as one of the characteristics of almost all cancers [10], which is a crucial factor in the tumor pathogenesis and plays an important role in tumorigenesis, invasion and metastasis [11]. Other common inflammatory factors like NEUT and AST are well known to people; in other studies, GLR has been listed as one of the inflammatory related factors [12]. Thank you for your correction, and corresponding corrections have been made in the article.


3. Response to comment: Please correct this line in the discussion section: 'This is consistent with the research results that anti-inflammatory therapy can effectively prevent the early stage of tumor occurrence and malignant transformation.12'. Is 12 a reference?
Response: Thank you for your correction. We have changed the part mentioned, and related articles have been cited.

4. Response to comment: In the result section: All the headings are just statements. It will be great if conclusions are added (heading) in the each section of the result. That can be very helpful for the reader to understand.
Response: We have added the conclusion to the result.

5. Response to comment: In conclusion section: Please change the line 'we fully believe'. It looks nonscientific.
Response: Thanks for your correction. The statement is inappropriate and nonscientific, and corresponding corrections have been done in the article.

6. Response to comment: Figure 2 and 3 are not high-resolution images. Please replace with better quality images.
Response: We have enlarged Figure 2 and Figure 3.

7. Response to comment: This study shows interesting results. I suggest authors to correlate their findings with publicly available databases.
Response: It is a good suggestion. And we will correlate some of the findings with publicly available databases when appropriate, and offer possible help to other researchers.