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Dear Editor,

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Title: Inflammation-based scores predict survival for patients with HBV–related hepatocellular carcinoma

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Name of Journal: *World Journal of Gastroenterology*

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We are very grateful to you for reviewing our manuscript and reconsidering it in your journal. We greatly value the comments from your reviewers and found them to be very helpful in improving our work and the overall manuscript. The manuscript has been updated based on your reviewer's comments, and in doing so, the paper is improved.

We have answered the comments in a point-by-point fashion as follows below, and resubmit our revised paper to your journal as a new manuscript.

Thank you for your kind help and time in dealing with this and we look forward to hearing from you.

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) Referee #1 (Comments to the Author): The authors made an intersting and useful study to improve the estimation of the prognosis in patients with HBV–related hepatocellular carcinoma after transarterial chemoembolization. The methodology, statistical analysis and results are made well. This a single center experience with some particularities regarding the patients, but the idea of combination between an inflammation-based prognostic score (GPS) and a staging system (CLIP score) can be tested in other future studies, too. There are some grammatical mistakes (from abstract to discussion) that should be corrected. In my opinion, the article is useful and deserves to be published.

Answer:
Thank you so much for your valuable comments. The grammatical mistakes (from abstract to discussion) had been corrected carefully.

(2) Referee #2 (Comments to the Author):The authors compared six inflammation scores, TNM stage, CLIP score and BCLC stage as a prognostic factor for HBV related HCC patients treated by TACE. They concluded that GPS is superior to other inflammation scores and advocated a combined score of GPS and CLIP as a strong predictor of survival. The univariate analyses for survival were performed by log-rank test. Table 2 demonstrated the p values for univariate analysis. Log-rank test is usually compared two groups for survival. There were a lot of continuous variables such as WBC, and CRP. If they divided patients into two groups by setting a cut off value from a continuous variable and compared the two groups using log-rank test, the cut off value should be described in the table. If they compared each variable as continuous variable, the statistical method should be described in detail. The comparison of the AUC between inflammation scores and staging systems should give statistical differences of AUC between the scores. Otherwise, they could not conclude the superiority of GPS to other inflammation scores. From the survival curves for GPS scores, there were no differences between GPS1 and GPS2. The differences of survival were just determined by GPS0 and others. They compared CLIP and combined CLIP and GPS by AUC analysis as a predictor of survival. However, the strength of predictor of survival should be compared by hazard ratio of survival by cox proportional hazard model. The statistical method of this study is not appropriate. Therefore, the manuscript should be reconsidered especially in statistical analysis.

Answer:
Thank you very much for your important suggestions.
We are sorry for our mistake to mix the baseline clinicopahtological characteristics with univariate and multivariate analysis in Table 2, which lead to the statistics confusion. To make it clear, we listed the patients' baseline clinicopahtological characteristics (Table 2), and univariate and multivariate analysis results (Table 3) respectively in our revised manuscript.
Secondly, we compared the prognostic power of GPS, mGPS, PI, NLR, PNI, PLR in different time-points by ROC analysis. According to the 95%CI, they were overlapped each other which indicated that the p values should be >0.05. But according to Table 4 and Figure 2, the GPS consistently had a higher AUC value at different time-points in comparison with other inflammation-based prognostic scores. So we chose the GPS as the optimal inflammation score to combine with clinical stage.
Thirdly, there were no differences between GPS1 and GPS2, and the differences of survival were just determined by GPS0 and others. The reason might be due to the small sample size; since there were only 24 patients with GPS2 were included in present study.
Fourthly, the strength of combined scores of survival had been compared by hazard ratio of survival by cox proportional hazard model. The HR for combined scores is 1.724 (95% CI 1.347–2.285, P<0.001). We have added this result in page 13, paragraph 2.

(3) Referee #3 (Comments to the Author): Dongsheng Zhou et al reported that the superior prognostic ability of GPS compared to other inflammation scores for patient with unresectable HBV-related HCC undergoing TACE; the author suggest that the combined use of GPS and CLIP can improve the prognostic power for OS. The work is clearly written and well conducted; the findings are however limited to HBV-HCC patients. Comments 1) The author should explain why only HBV-HCC patients have been considered. 2) There is a clear imbalance between male/female in the study: is there a specific reason for this? Can this aspect somehow influence the results? 3) Are there any

relation between the age of the subjects and the outcome of the study? The ages of the subject are rather scattered can this affect the results?

Answer:
Thank you very much for you important comments. There are three questions and our answers are: 1) In China, HBV infection is the most common etiology for HCC, more than 95% of HCC are HBV-related. So we only recruited the HBV-HCC patients in present study. We had added this statement in page 13, paragraph 3. 2) As reported by literatures, in high-incidence regions such as China the ratios for male/female were varied from 5.1 to 8.7. In present study the ratio for male/female was 7.96. 3) Up to date, there is no report showing the relationship between age and OS for patients with HCC undergoing TACE. But we believed that it would be a good question to be answered in our future study.

(4) Referee #4 (Comments to the Author): For Authors: Hepatocellular carcinoma (HCC) is one of the most common solid tumors worldwide, and the third leading cause of cancer-related deaths. Only 10-30% of HCCs are amenable to curative treatments including surgical resection, liver transplantation and local ablation, while transarterial chemoembolization (TACE) is considered to be the standard care for unresectable and unablatable HCCs, and shows survival benefit in selected patients. Therefore, it is important to select patients who would most likely benefit from TACE. There is increasing interest in the role of systemic inflammation as a predictor of outcome in HCC, and several imflammation scores were suggested to be useful as a predictor of outcome in HCC. However, which inflammation scores is more suitable for predicting outcome in patients with HBV-related HCC undergoing TACE has not been fully elucidated. The manuscript by Zhou D. et al. described the validation of the prognostic value of inflammation-based prognostic scores including the GPS, mGPS, NLR, PLR, PI, and PNI for patients with HBV-related HCC undergoing TACE, and also the validation of the combination of staging system and inflammation score to improve the prognostic power. They demonstrated that the GPS is superior to the other inflammation-based prognostic scores, and the combination of CLIP and GPS might improve the prognostic power. This paper is worth to be published in World Journal of Gastroenterology because it is innovative that the combination of CLIP and GPS might improve the prognostic power using ROC analyses. The authors need to describe about ROC and AUC analyses which they used in more detail. In ROC analysis, the association between continuous data and outcome is usually investigated. However, the authors analysed the relation between several scores which are not continuous variables (GPS, mGPS, PI, combination score of the GPS and CLIP score) and outcome using ROC method. Also, there are some descriptions which the authors should add or correct. Major compulsory revisions: 1. The authors need to describe in more detail regarding ROC and AUC analyses which they used to investigate the validation of the prognostic value of inflammation-based scores. 2. In Table 1, the authors should describe why they selected 3, 150, and 45 as the cut-off value in NLR, PLR and PNI, respectively. Minor essential revisions: 1. In page 3, in Abstract, the authors should add the description about platelet-lymphocyte ratio (PLR) in Purpose. 2. In page 15, line 2 and in page 17, line 17, “The GPS” should be corrected to “the GPS”.

Answer:
Thank you so much for your valuable comments. Firstly, according to your suggestion,

we described ROC and AUC analyses in more detail in our revised manuscript. Secondly, the systemic inflammation scores (GPS, mGPS, NLR, PNI, PLR, PI) as predictors for HCC patients had been reported by many literatures. In present study, the universal cut-off values reported by literatures (3, 150, and 45 as the cut-off value for NLR, PLR and PNI, respectively) were utilized in present study. We had added this statement in Page 10, Paragraph 3.
Minor essential revisions: 1) We had re-wrote the aim instead of purpose to agree with the format of the *World Journal of Gastroenterology*. 2) We had corrected "The GPS" to "the GPS" already.

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

Sincerely yours,
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