Dear Editors and Reviewers,

We appreciate the reviewers for their careful review and insightful comments regarding our manuscript entitled "**An inflammation-related nomogram for predicting survival of patients with unresectable hepatocellular carcinoma received conversion therapy**" **(Manuscript NO.: 84230, Observational Study)**. We are pleased to revised our manuscript into the format of a Letter to the Editor. All the comments were very helpful in improving our manuscript, and we have addressed them in detail in the enclosed revised manuscript. In the point-to-point response document, our responses were presented in blue text.

REVIEWER COMMENTS
Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: The authors developed a prognostic nomogram based on ALB, BUN, GPR, PLR, MVI and tumour number for patients with unresectable HCC after conversion therapy, and compared with six conventional staging systems. Some questions see attachement.

Manuscript NO 84230, titled An inflammation-related nomogram for predicting survival of patients with unresectable hepatocellular carcinoma received conversion therapy.

The authors developed a prognostic nomogram based on ALB, BUN, GPR, PLR, MVI and tumour number for patients with unresectable HCC after conversion therapy, and compared with six conventional staging systems. Some questions as follows.
We are very grateful to the editor for the overall favourable evaluation and for the constructive criticism.

1. Meanwhile, active conversion strategies to increase the volume of future liver remnant and planning for patients who cannot achieve R0 resection are worth greater consideration.
We are sorry for the unclear description in our manuscript and grateful to the review for raising this concern. In the updated version of the manuscript, we added the explanation of the abbreviation for R0 resection according to the reviewer's comment in "TACE procedure and hepatic resection" section. The revised text read as follows:
"Curative resection was defined as complete remove of all tumor nodules with no residual tumor margin (R0 resection) confirmed by pathological examination."

2. Recently, numerous previous studies have indicated that preoperative inflammatory biomarkers can be capable of predicting HCC prognosis after HR.
We acknowledge and appreciate the reviewer's suggestion here. We agree that providing a more detailed introduction to inflammation-related markers and their role would enhance the coherence of the paper. We amended the text, which now reads as follows:

"Recently, numerous previous studies have indicated that preoperative inflammatory biomarkers can be capable of predicting HCC prognosis after HR [9, 10]. A previous study by Wang et al. evaluated the prognostic value of preoperative inflammation-related markers and demonstrated a high efficacy in predicting survival after surgical resection of HCC [9]. They also concluded that neutrophil to lymphocyte ratio (NLR) and gamma-glutamyl transpeptidase (GGT) to platelet ratio (GPR) were two inflammation-related markers associated with prognosis independently. However, it is unclear whether preoperative inflammatory biomarkers have a high efficacy in predicting the OS of unresectable HCC patients following conversion therapy."

3. The exclusion criteria, patient with infection should be excluded for Inflammation biomarkers. There is no description.

Great point. Patients with current or recent system infection disease were added to the exclusion criteria, as requested.

4. **TACE procedure and hepatic resection**

Thank you for your insightful advice. We significantly expanded the treatment details according to your comment as follows:

"Hepatic resection was performed under general anesthesia via an L-shaped laparotomy or bilateral subcostal incision with a midline extension. Intraoperative ultrasound (US) was routinely performed to evaluate the tumor burden, liver remnant, and the resection margin. Curative resection was defined as complete remove of all tumor nodules with no residual tumor margin (R0 resection) confirmed by pathological examination."

5. Tumour radiologic features showed that tumour number, satellite lesions, the largest tumour diameter, complete tumour capsule and MVI were observed in 110 (73.3%), 36 (24%) and 68 (45.3%) patients, respectively.

We are very sorry for the unclear statement we made here. We have modified relevant descriptions in the manuscript as you suggested.

Before

"Tumour radiologic features showed that tumour number, satellite lesions, the largest tumour diameter, complete tumour capsule and MVI were observed in 110 (73.3%), 36 (24%) and 68 (45.3%) patients , respectively."

After

"More than half of the patients (n=96, 64.0%) were with solitary tumour. Tumour radiologic features showed that well-defined tumour capsule, satellite nodules, and MVI were observed in 110 (73.3%), 36 (24.0%) and 68 (45.3%) patients, respectively."

6. The present study combined liver function factors, tumour burden and inflammation biomarkers (six significantly independent predictors: ALB, BUN, MVI, tumour number, GPR and PLR) to establish a more comprehensive model and construct a nomogram CT model that could accurately predict the prognosis for patients with unresectable HCC after conversion therapy.

Thank you for bringing this up. We have modified relevant descriptions in the manuscript as you suggested, as follows:

"The present study combined liver and renal function factors, tumour burden and inflammation biomarkers (six significantly independent predictors: ALB, BUN, MVI, tumour number, GPR and PLR) to establish a more comprehensive model and construct a nomogram CT model that could accurately predict the prognosis for patients with unresectable HCC after conversion therapy."

7. Considering that the inflammatory factors of the tumour microenvironment play an imperative role in HCC therapies, it is helpful to guide clinicians to carry out follow-up regimens and postoperative therapy for patients with a high or low risk of tumour recurrence after CT modelling.

Thank you for your valuable comment. As we mention in the introduction section that HCC is one of the most classic inflammation-linked tumours and hepatitis B virus infection (HBV) is one of the most common causes. It is well known that HBV have been associated with the development of progressive fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Luckily, in addition to therapies targeting inflammatory factors, there are several drugs and measures that can help supress HBV DNA replication, the HBV-induced inflammatory and support liver health.

Anti-viral drugs, such as Tenofovir disoproxil fumarate (TDF) and entecavir (ETV), are recommended as the first-line choices regarding the treatment of chronic HBV and have been proved benefit for the prognosis of chronic HBV-related liver cirrhosis patients as well as protection of liver function. Besides, ursodeoxycholic acid (UDCA), which has been shown to have hepatoprotective effects by reducing inflammation and oxidative stress in the liver. Additionally, silymarin (also known as milk thistle extract) has been used as a traditional remedy for liver disease and has been shown to have antioxidant and anti-inflammatory effects.

Other measures that can help support liver health include maintaining a healthy weight, avoiding alcohol and tobacco, and getting regular exercise. A diet rich in fruits, vegetables, whole grains, and lean proteins may also be beneficial for supporting liver function.

8. Preoperative renal dysfunction with high levels of BUN may lead to the development of major complications such as intractable ascites and spontaneous bacterial peritonitis (SBP).

Thank you for providing this important point. We have discussed this in the discussion section (lines 472-479), as follows:

"Preoperative renal dysfunction with high levels of BUN may lead to the development of major complications such as intractable ascites and spontaneous bacterial peritonitis (SBP). In clinical practice, serum creatinine concentration is generally used to assess kidney function in patients with liver diseases, which is also a major prognostic factor of cirrhosis included in the Model for End-Stage Liver Disease (MELD). However, several reports have shown that BUN levels have greater prognostic accuracy than serum creatinine concentrations."

In the present study, we also found that BUN was independently prognostic for OS in patients with HCC after conversion therapy and high BUN levels were related to worse liver function stage and poor OS outcomes. Hope this could answer your concern.

9. Second, statistical power may be limited because several routine clinical variables could not be measured in our study. For instance, performance score, body mass index, injected drugs and their dosages during TACE, and postoperative treatments were not homogenous across patients in the training and validation cohorts.

We thank the reviewer for the comment. We acknowledge that our research has several limitations due to the retrospective nature of our study. Larger multicentre prospective studies were required to further strength our result. We have modified our description in this part to the following:

"Second, statistical power may be limited because several routine clinical variables were not included in our study. For instance, performance score, body mass index, injected drugs and their dosages during TACE, and postoperative treatments were not homogenous across patients in the training and validation cohorts due to the retrospective nature of our study. Larger and multicentre prospective cohorts were required to further strengthen our results. Hence, we will conduct further investigation that incorporates more complete clinicopathological information, treatment details, and postoperative treatment modalities to improve the predictive performance of our model."

10. The work is meaningful for individualized management in HCC patients following conversion therapy. The prognostic nomogram is online for free use. Revise or explain above questions before acceptance.

Thank you for your very positive comments! We are very honored to be recognized and affirmed by you. Your valuable suggestions really promote the quality of our research. We appreciate your careful review very much!

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This study develops an inflammation-related nomogram to perform the survival prognosis of patients with unresectable HCC post-conversion therapy. Overall, the study was well-performed, and the data are presented well. Some minor suggestions are provided by the authors. Short title includes too many words. Rephrase the conclusion sentence in the abstract. The letters in Figure 5, Figure 6B-D, and Figure 7 are too small.

We appreciate and respect the reviewer's comments. Both short title and conclusion sentence in the abstract have been rephrase. We revised the sentence to:

"Short title: nomogram for conversion therapy

Conclusions: The nomogram achieved optimal individualized prognostication of OS in HCC patients who received conversion therapy, which could be a useful clinical tool to help guide postoperative personalized interventions and prognosis judgement."

We agree that in the previous version of the figures, the font size was too small and difficult to read. We now increased the font size in all Figures pointed by the reviewer.