

Responses to reviewers' comments on the manuscript "Prognostic Value of Circulating Tumor Cells Combined with Neutrophil-Lymphocyte Ratio in Patients with Hepatocellular Carcinoma" (Manuscript NO.: 88963, Observational Study)

We sincerely thank the editor and all reviewers for their valuable feedback that we have used to improve the quality of our manuscript. The reviewer comments are laid out below in italicized font and specific concerns have been numbered. Our response is given in normal font and changes/additions to the manuscript are given in the yellow text.

1. Reviewer #1:

● *I read this manuscript. It's interesting, but author have to rewrite the abstract. Overall, this manuscript has original findings.*

We think this is an excellent suggestion. We have re-written this part according to the Reviewer's suggestion and highlighted the original research findings.

**Background:** Circulating tumor cell (CTC) count and neutrophil-to-lymphocyte ratio (NLR) are both closely associated with the prognosis of hepatocellular carcinoma (HCC).

**Aim :** The present study aimed to investigate the prognostic value of combining these two indicators in HCC.

**Materials and Methods:** Clinical data were collected from patients with advanced HCC who received immune therapy combined with targeted therapy at the Department of Oncology, the Affiliated Hospital of Southwest Medical University, Sichuan, China, from 2021 to 2023. The optimal cutoff values for CTC programmed death-ligand 1 (PD-L1)(+)  $> 1$  or CTC PD-L1(+)  $\leq 1$  and NLR  $> 3.89$  or NLR  $\leq 3.89$  were evaluated using X-Tile software. Patients were categorized into three groups based on CTC PD-L1(+) counts and NLR: CTC-NLR (0), CTC-NLR (1), and CTC-NLR (2). The relationship between CTC-NLR and clinical variables as well as survival rates was assessed.

**Results:** Patients with high CTC PD-L1(+) expression or NLR at baseline had shorter median progression-free survival (mPFS) and median overall survival (mOS) than those with low levels of CTC PD-L1(+) or NLR ( $P < 0.001$ ). Meanwhile, patients in the CTC-NLR (2) group showed a significant decrease in mPFS and mOS. Cox regression analysis revealed that alpha-fetoprotein (AFP), CTC PD-L1(+), and CTC-NLR were independent predictors of OS. The time-dependent receiver operating characteristic (ROC) curve showed that the area under the curve (AUC) of CTC-NLR at 12 months (0.821) and 18 months (0.821) was superior to that of AFP and CTC PD-L1(+).

**Conclusions:** HCC patients with high CTC PD-L1(+) or NLR expression tend to exhibit poor prognosis, and a high baseline CTC-NLR score may indicate low survival. CTC-NLR may serve as an effective prognostic indicator for patients with advanced HCC receiving immunotherapy combined with targeted therapy.

2. Company editor-in-chief:

● *I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.*

We sincerely appreciate the valuable comments. We have checked the literature carefully and added more content about latest cutting-edge research results into the INTRODUCTION part in the revised manuscript. "In peripheral blood, CTCs can interact with inflammatory cells to

induce systemic inflammation, promote metastasis, and worsen prognosis<sup>[25,26]</sup>. Considering NLR based on CTCs can improve risk stratification and optimize management in cancer patients<sup>[27]</sup>."

We tried our best to improve the manuscript and made some changes marked in yellow in revised paper which will not influence the content and framework of the paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope the correction will meet with approval. Once again, thank you very much for your comments and suggestions.