

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Development and Validation of a Prediction Model for Microvascular Invasion in Hepatocellular Carcinoma" (53430). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewers' comments are flowing:

Responds to the reviewer's comments:

1. Response to comment (Reviewer #1): (This is an excellent retrospective study that searched for a prediction model for microvascular invasion (MVI) in HCC. Since MIV is usually found after the surgical resection and the presence of MIV is associated with recurrence and metastasis, their approach to find the risk factors presurgery is of significant value for the treating physicians/surgeons. In their retrospective analysis, the authors identified 4 risk factors independently associated with MVI pre-surgery. Fortunately the factors are all easily available items, tumor size, tumor number, neutrophil count and AFP. Authors admitted that the results are derived from one institution. However, the numbers of patients they analyzed is a fairly large number of cases. Thus, their findings may have application for the time being while further studies may confirm their findings.)

Response: Thank you very much for your careful review and constructive suggestions. As the reviewer suggested that all these findings may have application for the time being, and we will continue to expand the sample size to further verify and evaluate the accuracy and practicability of the model. Thanks again for your evaluation and affirmation of our research.

2. Response to comment (Reviewer #2): (In the table 4, the interpretation of significance regarding the result, predicted probability in particular, will be helpful for readers. )

Response: Thank you very much for your careful review and constructive suggestions. Considering the reviewer's suggestion, we added a note below Table 4 “ Predicted probability referred to the optimal cut-off value for MVI prediction based on the maximum Youden index ”.

3. Response to comment (Reviewer #2): (As authors mentioned that the neutrophil is significant factor unexpectedly, reviewer also have question about this. Elevation of neutrophil is acute inflammatory marker, this is fluctuating. Interpretation regarding this is required.)

Response: We agree with the reviewer's comments. As the reviewer mentioned that elevation of neutrophil is acute inflammatory marker. Neutrophil count is fluctuating and affected by many factors. This is also the focus of our attention. Therefore, we have explained the following in the paragraph on study limitations:

“ the neutrophil count was considered an important predictor in our study. As a common inflammatory marker in peripheral blood, rises in neutrophil levels usually occur due to infections or injuries. However, "antiviral treatment", "infection" and "trauma" were set as the only three control conditions in our model. In fact, the neutrophil count can also fluctuate under the influence of various factors, such as time, eating, exercise, pain, and emotion. How to avoid or correct the effects of these factors on neutrophils is a challenge.”

Other changes:

We added information about supportive foundations “ Supported by the National Natural Science Foundation of China, No. 81672100; the Key Laboratory for

Laboratory Medicine of Jiangsu Province of China, No. ZDXKB2016005.”

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. All these changes have been marked in red in revised paper. We appreciate for Editor/Reviewers’ warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Shiyang Pan & Lin Wang

Corresponding author:

Shiyang Pan, MD, PhD