

Dear editors and reviewers:

Thank you for your comments concerning our manuscript entitled “ Prognostic significance of systemic immune-inflammation index in patients with intrahepatic cholangiocarcinoma undergoing hepatic resection”. 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 according to the comments. The revision has been marked with red signs in the revised paper. The main corrections in the paper and the responses to the reviewer’s comments are as following:

Reviewer: This manuscript is retrospective study regarding prognostic significance of systemic immune-inflammatory index for the intrahepatic cholangiocarcinoma. This concept was based on the inflammation make worse prognosis. The formula and the method for calculation of the optimal cutoff value ($SII = 450$) that the authors used is to be described, even though that was shown in previous reports. Additionally the definition of SII is amenable to be described, general concept and the specific formula for this study to understand the meaning. In table 1 & 2, the factors and values are so complex, need to be simplified. For example, BCLC stage is used for HCC generally, not for cholangiocarcinoma. Decimal is to be unified, ex) 5.1, not 5.13. The values in table 2, the meaning of the value in the parenthesis is different among the factors. For example 57.89 (9.53) of the age, what is the 9.53? The values in each factors may be different, which is to be differentiated. The survival curve in subgroup analysis are too many. Too many factors included, so too complex. The most important several figures give stronger impact. Authors mentioned that high SII group were associated with significant decreased frequencies of solitary tumor and node invasion. Reviewer has question whether it is the cause or effect. Putting interpretation of the meaning of this is amenable.

Response:

Thank you for your precious comments. We have revised our manuscript and tables according to your advice. The formula and the method for calculation of the optimal cutoff values for SII were addressed in the “Method” section and marked in red. We have deleted several parameters in tables, including BCLC, Child-Pugh grade, ascites, liver capsule invasion and cirrhosis. In addition, we have addressed the meaning of the value in the parenthesis is different among the factors in the table legends for each table. Several tables were showed in Supplementary files (Tables of validation cohort). The subgroup analyses were also simplified in the revised manuscript.

We demonstrated that tumors in high SII group were associated with significantly decreased frequencies of solitary tumor and increased incidence of node invasion. We have revised the sentences. We considered multiple tumors and node invasion as causes for elevated SII. Given SII was calculated by $\text{neutrophil} \times \text{platelet} / \text{lymphocyte}$, the factors relative to inflammation or immune systems might impact the value of SII. The host immune systems were suppressed in patients with multiple tumors or node invasion, thus, resulting poor prognosis. We performed the correlation analysis between SII and these factors to show their association. The elevated SII was a signal of tumor progression, which represented poor clinical outcomes.