Author's response to reviews

Title: Clinical and prognostic significance of preoperative plasma hyperfibrinogenemia in gallbladder cancer following surgical resection

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Thank you for considering our work. Your suggestions are helpful and make our research more comprehensive. Some changes and explanations were made to answer the following questions. We hope our revision will meet your requirements.

1. The section of “Diagnostic performance of preoperative plasma fibrinogen levels for tumor staging in GBC patients” and Table 3 are misleading. It is not “diagnosis”. It simply means that “preoperative plasma fibrinogen level significantly correlated with tumor staging” and almost same result of Table 2. Therefore, the authors should delete Table 3 and that section. Preoperative tumor staging must be done by TMN factors from imaging study. Plasma fibrinogen level is just only supporting information in clinical practice because plasma fibrinogen level is easily affected by infection or general condition (such as liver function) as they documented in discussion.

We have removed Table 3 and changed the related conclusion accordingly. Since the preoperative tumor staging of gallbladder cancer can hardly achieved by imaging study alone, we suggest plasma fibrinogen level is a valuable index that can easily get before surgery. It may not predict the precise tumor stage accord with postoperative TMN stage, but it can help surgeons to make initial judgment whether the tumor is on its early/advanced stage alone with all the other index.
2. Their result firmly suggested that preoperative plasma fibrinogen level is the one of the prognostic factor of GBC. However, other factors such as TNM stage, nodal metastasis and margin status is also prognostic factors as they shown in Table 6. The sentence of conclusion “we advocate the use of preoperative plasma fibrinogen levels in new GBC patients to predict tumor progression and outcome” is misleading. As mentioned above, plasma fibrinogen level is just only supporting information. I believe that the cases with high plasma fibrinogen levels but early stage without metastasis and R0 resection will follow favorable clinical course and that the cases with low plasma fibrinogen levels but advanced stage with metastasis will follow poor outcome.

The conclusion “Preoperative plasma fibrinogen level is the one of the prognostic factor of GBC” is confirmed by strictly statistical analysis. In our last table, all the independently prognostic associated variables were listed in the order of their Hazard Ratio(HR). The HR of fibrinogen is statistically significant and ranked third after TNM stage and Lymph node metastasis. Thus the ability of preoperative plasma hyperfibrinogenemia to predict tumor progression and outcome does not contradict the same function of TNM stage, nodal metastasis and margin status. They only have the difference of significance.

To eliminate the misleading we changed the conclusion:

"Based on our findings, we suggest the use of preoperative plasma fibrinogen levels in new GBC patients to evaluate tumor progression and outcome. Furthermore, we conclude that fibrinogen enhances cell migration and invasion in vitro. However, our study was limited due to its retrospective design and the small number of patients included. Thus, further studies on larger numbers of patients, including prospective studies, are required to confirm the results of this study."