

July 12, 2021

BPG Editorial Office,  
World Journal of Clinical Cases

Thank you for your kind e-mail dated July 5, 2021. We are happy to receive your favorable opinions concerning our manuscript. As requested, we have revised our manuscript according to the reviewers' comments. The revised sentences are shown in RED in the revised manuscript.

**Replies to Reviewer #1 :**

Thank you for your constructive comments on improving our manuscript. In response to your concerns, we have revised the manuscript as follows:

1. The grouping of biliary tract cancer in this manuscript included a large group of diverse cancers (cholangiocarcinoma, gallbladder cancer, and cancer of papilla of Vater). These cancers are reported with having different etiologies, aggressive and progressive phenotypes, and therapeutic responses. The sensitivity analysis by sub-grouping of them may provide more sensitivity and reliability of the predictive factors (as they were shown in the current version that even specificity is high, but the sensitivity of each factor is particular low). The subgroup analysis for survival time and levels of these biomarker should be also provided.

We believe this comment is reasonable. According to the reviewer's comments, we re-examined the data for each biliary tract cancer (intrahepatic bile duct, extrahepatic bile duct, gallbladder, and ampullary cancers). The revised Table 4 shows the biomarkers and survival time, and Table 5 shows the sensitivity analysis. Sensitivity

analysis showed that the data of all biliary tract cancers and each biliary tract cancer are quite similar, and as per the reviewer's comment, while the specificity is high, the sensitivity is particularly low both in all biliary tract cancers and each biliary tract cancer. We have added these findings to the Results section.

2. It is not clear whether this paper suggests to use each biomarker individually or in combination. In Table 4, it shows the estimate of reduction rate for EL for each biomarker. However, the authors did not mention whether these factors were elevated in the same patients or different patients. What are the suggestions if all or just some of these makers were elevated? A discussion on this issue should be added.

We agree with your comment. As per your suggestion, we have added Table 6 which shows the data of estimated reduction rate of exploratory laparotomy of the combination of the biomarker results in the original Table 4. When the number of positive factors increased, the estimated reduction rate of the EL gradually increased. If all four factors were positive, the rate was 33.3%. Thus, a combination of biomarker results could be useful for predicting occult metastasis. We have added this issue to the Results and Discussion section.

3. The authors should clarify the meaning and the suggestion of using estimate of reduction rate in Table 4. How valid of these data should be given in details and references of the calculation should be given (or provide more rationale if this is originally proposed by this paper).

According to the suggestion, we have revised Table 4 (we changed original Table 4 to new Table 6). We believe that a combination of biomarker results could be useful

in predicting occult metastasis in biliary tract cancers. We have added the usefulness of the combination of these markers to the Conclusion.

4. There are some minor grammatical errors, especially the subject-verb form agreement. Please carefully check throughout the manuscript.

Our original paper has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing papers (Editage). However, as suggested by the reviewer, the revised paper has been thoroughly re-checked for language and grammatical errors. We have attached a copy of the language editing certificate.