**January 19, 2022**

**RE: Manuscript NO: 73311 "Prognostic factors of recurrent intrahepatic cholangiocarcinoma after hepatectomy: A retrospective study"**

**Dear Editors and Reviewers:**

Thank you very much for your time and energy in reviewing this manuscript. We are truly grateful to the editors and reviewers for such valuable and constructive comments and suggestions, which helped us significantly improve this manuscript. We have fully addressed all comments in a point-by-point manner. We appreciate your patience while we made all necessary revisions. The revised portions of the manuscript are marked with highlighting.

We are submitting a revised manuscript for your consideration. All authors have read and approved of the final revised version. Please refer to our point-to-point responses below. We hope that the revised manuscript is now suitable for publication in the *World Journal of Gastroenterology*.

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**Comments by the reviewers:**

**Reviewer #1**

**1. Response to comment: Although the topic is of interest and the article is well organized and well written, the information contributed to scientific and clinical communities is limited and lacking of novelty.**

Reply: Thank you very much for your evaluation. This article analyses the prognostic factors of recurrent intrahepatic cholangiocarcinoma (ICC) and the treatment of patients after recurrence. In the analysis of prognostic factors, preoperative and postrecurrence primary tumour indicators (CA19-9, CEA), tumour pathological characteristics, disease-free survival (DFS), lymph node dissection, adjuvant treatment, and treatment after recurrence were included, which are believed to have good reference value for the clinical diagnosis and treatment of recurrent ICC.

To address the comment on the proposed investigation scope, in which the reviewer indicated that "the authors may extend scope of the investigation to the other view, e.g., the underlying disease, other co-morbidities, other current medications which may affect the progression of disease", we have included additional prognostic factors: smoking status and alcohol consumption; the presence of hypertension, diabetes, or cholelithiasis; and anti-hepatitis virus treatment. It was exciting to find that alcohol consumption was an independent risk factor for relapse. This result has important guiding significance for patients. We have added the abovementioned content in the Table 1 and 2 (updated in the Abstract, Core tip, Results, Discussion, and Conclusion, marked with highlighting).

The current research status of ICC is as follows: 1. Most studies have focused on the factors associated with recurrence after hepatectomy, but there are few studies on the prognostic factors of recurrent ICC. 2. At present, most studies have explored the

efficacy of secondary hepatectomy in patients with recurrent ICC, but a multimodal therapy model is rarely involved. 3. Since recurrent ICC is a rare medical entity, although studies are conducted across multiple centres, the number of medical records is still small, and there are differences in the diagnosis and treatment across different centres. The innovative points of this paper are as follows: 1. It provides a detailed analysis of prognostic factors for patients with recurrent ICC. 2. Bioinformatics technology was integrated into the analysis, a Venn diagram was drawn to describe the recurrence site, and the recurrence mode of ICC was more clearly displayed. 3. In our opinion, it is most important that we explore the therapeutic effects of different treatment strategies for recurrent ICC and describe the application value of multimodal therapy for recurrent ICC, which has not been clarified in previous studies.

**2.Response to comment: The investigation on prognostic factors are limited for a few known factors and the positive results are found with those known non-modifiable factors (or few of modifiable factors). The authors may extend scope of the investigation to the other view, e.g., the underlying disease, other co-morbidities, other current medications which may affect the progression of disease.**

Reply: Thank you very much for your excellent suggestions. As you pointed out, this study actually incorporated fewer factors that can be modified. To better provide the information contributed to scientific and clinical communities, we have included additional prognostic factors: smoking status and alcohol consumption; the presence of hypertension, diabetes, or cholelithiasis; and anti-hepatitis virus treatment. Through

single-factor and multiple-factor analyses, the results showed that alcohol consumption was both a prognostic factor and an independent risk factor for recurrent ICC. These results are exciting. Reducing alcohol intake may be an important recommendation for patients with recurrent ICC. We have added the abovementioned content in the Table 1 and 2 (updated in the Abstract, Core tip, Results, Discussion, and Conclusion, marked with highlighting).

**minor points:**

**1.Check the definition of intrahepatic cholangiocarcinoma.**

Reply: Thank you very much for this comment. Intrahepatic cholangiocarcinoma (ICC) is a highly malignant tumour originating from intrahepatic bile duct epithelial cells[1]. We have updated the definition in the Introduction section marked with highlighting.

1 Kelley RK, Bridgewater J, Gores GJ, Zhu AX. Systemic therapies for intrahepatic cholangiocarcinoma. J Hepatol 2020; 72: 353-363 [PMID: 31954497 DOI: 10.1016/j.jhep.2019.10.009]

**2.Clarify when was the earliest time to follow up the patients after hepatectomy. Clarify how often the following up was done, this could affect the time of detecting recurrent tumor.**

Reply: Thank you very much for this important opinion. Because these points are not clearly stated in the paper, we apologize. As you pointed out, the frequency of following up will indeed affect the time to detect recurrent tumours. Due to the clinical characteristics of high recurrence and invasion of ICC, we consider the clinical working

time and the cost of patient review and ensure that the patients' conditions will not be affected ,and our centre started follow-up at 1 month after ICC hepatectomy, followed by every 3 months for the next 2 years and every 6 months after 2 years. This is essentially the same as the NCCN guidelines[2] .We have added the abovementioned content in the Materials and Methods section marked with highlighting.

2 Benson AB, D'Angelica MI, Abbott DE,etl Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network : JNCCN 2021; 19(5): 541-565 [PMID: 34030131 DOI: 10.6004/jnccn.2021.0022]

**3.Check 95% CI of HR in Table 2, at the row of treatment after recurrence.**

Reply: Thank you very much for your comments. This error has been corrected in the Table 2 marked with highlighting.

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**Reviewer #2**

**1.Response to comment: I'm not the English language wearer and can't assess fully the quality of language of the manuscript, but it is quite acceptable for me.**

Reply: Thank you very much for your positive evaluation and recognition of the value

of this study. Regarding the language quality of the manuscript, we have polished the language throughout the manuscript, carefully reviewed grammar, punctuation consistency, spelling and word selection, and obtained an editing certificate to ensure that the language quality of the manuscript meets the requirements of *World Journal of Gastroenterology*.

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**Science editor:**

**1.Response to comment:This is an interesting paper that supports better management of recurrent intrahepatic cholangiocarcinoma after hepatectomy. The article is well organized, but the information provided is limited and lacks novelty.**

Reply: We thank the science editor very much for these comments. The current research status of intrahepatic cholangiocarcinoma (ICC) is as follows: 1. Most studies have focused on the factors associated with recurrence after hepatectomy, but there are few studies on the prognostic factors of recurrent ICC. 2. At present, most studies have explored the efficacy of secondary hepatectomy in patients with recurrent ICC, but a multimodal therapy model is rarely involved. 3. Since recurrent ICC is a rare medical entity, although studies are conducted across multiple centres, the number of medical records is still small, and there are differences in the diagnosis and treatment across different centres. The innovative points of this paper are as follows: 1. It provides a detailed analysis of prognostic factors for patients with recurrent ICC. 2. Bioinformatics

technology was integrated into the analysis, a Venn diagram was drawn to describe the recurrence site, and the recurrence mode of ICC was more clearly displayed. 3 Based on the peer review, we included additional modifiable prognostic factors, which could provide important guidance for recurrent patients. 4. We believe that the most important thing is that we analysed the therapeutic effects of different treatment strategies for recurrent ICC and discussed the application value of multimodal therapy for recurrent ICC, which has not been explicitly discussed in previous studies.

**In addition to revised part, we added the Article Highlights section marked with highlighting.**

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**Company editor-in-chief:**

**Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden.**

Reply: We thank the editor-in-chief for these comments. A PowerPoint file of the figure and standard three-line tables have been provided as requested.

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All the above was our point-by-point reply. we had made all necessary modifications

and updating in the revised manuscript meanwhile. These valuable comments and suggestions really helped us to improve our manuscript a great deal. Hopefully, Editors and Reviewers can review our revised manuscript for further consideration of its acceptance to the journal of *World Journal of Gastroenterology.*

If you have any further questions or suggestions, we would be happy to address them and improve the manuscript further.

All the best to you and all your staff.

Yours sincerely,

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