

March 26, 2022

Re: Manuscript No.: 75311

Dear Prof. Peter Schemmer, FACS, MD, PhD

Thank you for the opportunity to submit a revised version of our manuscript entitled “*The impact of comorbid renal dysfunction in patients with hepatocellular carcinoma on long-term outcomes after curative resection*”. The authors would like to thank the editor and the reviewers for their time and invaluable comments. We have carefully addressed all the comments. The corresponding changes and refinements made in the revised paper are shown in tracked changes. We also provide point-by-point responses to the reviewers’ comments.

We have one request. We hope to add Yoichi M. Ito, the Chief of the Data Science Center, Promotion Unit, Institute of Health Science Innovation for Medical Care, Hokkaido University Hospital, because he reviewed the statistical methods in our manuscript was in detail.

We appreciate in advance for your re-reviewing of our paper. We hope our work is publishable and will be of great interest to the readers of *World Journal of Gastrointestinal Surgery*.

Sincerely,

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We appreciate for the thoughtful comments and suggestions from the reviewers. Our responses to the comments are as follows. We changed the manuscript accordingly.

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: The Authors have conducted a retrospective study to evaluate the impact of comorbid renal dysfunction, stratified by eGFR, and assessed the validity of hepatectomy for HCC patients with this condition. The study is interesting and well conducted, in a large population of patients. Results can have a relevance for clinical practice. I have only one major concern: patients were recruited over a long period of time, 18 years. Can this have somehow influenced the results, given the progresses of patients management over time?

#### Response to Reviewer #1

As the reviewer noted, the patients were recruited over a long period of time in this study, so perioperative management and treatment such as the use of some medicines or surgical devices have developed over time. However, our hepatectomy procedure with an ultrasonic scalpel, intermittent inflow occlusion (Pringle's maneuver), intraoperative ultrasonographic guidance has not changed much for decades, so these factors do not a significant influence on the results.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors enrolled HCC patients who underwent hepatectomy and categorized patients into two (RD,  $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ ; non-RD,  $60 \leq \text{eGFR}$ ) and three groups (severe CKD,  $\text{eGFR} < 30$ ; mild CKD,  $30 \leq \text{eGFR} < 60$ ; control,  $60 \leq \text{eGFR}$ ) according to renal function as defined by the eGFR, and the overall survival (OS) and recurrence-free survival (RFS) were compared among these groups with the log-rank test, and we also analyzed survival, and the concluded that the comorbid RD had a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy with appropriate perioperative management, and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection. The present manuscript is a very well written article, with a proper and well-designed methodology, however, the main drawback of the study is that the liver function of RD patients was quite better than that of non-RD patients because surgeons might consider and exclude RD patients who had liver dysfunction, and therefore,

the number of HCC patients with RD who underwent hepatectomy, was small. The discussion is concise, but is lacking a more extensive comparison of the results to other publications regarding this subject.

#### Response to Reviewer #2

We noted that “the liver function of the RD patients was better than that of the non-RD patients because physicians might exclude RD patients with severe liver function” (lines 382-383); this point is a limitation of this study. However, we did not exclude RD patients with liver dysfunction. Additionally, our criteria for hepatectomy were decided regardless of renal function. Moreover, we revealed that the comparison of OS and RFS rates between matched patients with and without RD showed no significant difference by using a propensity score matching model constructed with patients’ liver function, such as the levels of serum T-bil, AST, and ALT (Figure 3) or Child–Pugh grade A (Figure 4). In addition, we added and modified the sentence “On the other hand, Shirata et al. mentioned that liver resection for Child–Pugh A patients with RD is safe and has comparable oncological outcomes to those for non-RD patients, but the selection of liver resection candidates among Child–Pugh B patients with RD should be stricter<sup>[14]</sup>” in the Discussion section (lines 334-338).

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Only one study has reported the effects of preoperative RD defined by using the eGFR in patients with HCC, but little is known about the impact of preoperative RD on the long-term prognosis or postoperative complications, including acute kidney disease (AKI) and the initiation of hemodialysis in HCC patients who underwent hepatectomy. The manuscript fully and properly explains the research results and highlights the key points concisely, clearly and logically. Although comorbid RD has a negligible impact on the prognosis of HCC patients undergoing therapeutic hepatectomy and appropriate perioperative management, close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection. Although liver cancer patients with RD are rare, this study gives clear treatment recommendations.

#### Response to Reviewer #3

Thank you for your detailed review and invaluable comments.

Editorial office’s comments

(1) Science editor:

Response to Science editor

We provided point-by-point responses to the Science editor's comments as follows.

This retrospective study is to evaluate the impacts of comorbid renal dysfunction, stratified by eGFR, on curative hepatectomies for HCC patients. The manuscript is well-written and the perioperative management (especially for RD patients) was excellent according to the favorable surgical outcome and prognosis. However, there are some concerns need to be addressed. As the liver function, the proportion of curability A or B, and prognostic factors like vascular invasion and advanced fibrosis of the RD group was better than that of the non-RD group, there was an obvious selection bias in this retrospective study. Although the OS and RFS rates were similar in the RD and non-RD groups in the PSM model, the problem of small case number in severe CKD group (n=19) remained. As a result, the authors' statement "comorbid RD has a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy with appropriate perioperative management" seems only valid on mild RD patients owing to the small case number of the severe RD group. Please specify this issue in the "Discussion" and "Conclusion" sections.

As noted, although the OS and RFS rates were similar in the RD and non-RD groups in the PSM model, the problem of a small case number in the severe CKD group (n=19) remained. We added "and we could not entirely conclude that severe RD has a negligible impact on the prognosis of HCC patients" to the Discussion section (lines 386-388) and modified "Comorbid RD" to "Comorbid mild RD" in the Conclusions (lines 101 and 393).

The reference number (n=28 < 30) is suboptimal in this manuscript. Only five of cited references (5/28 = 18% < 50%) represent publications from the recent 5 years. Please cite more recent publications. The self-referencing rate is 7% (2/28) in this manuscript, a little higher than 3%.

We modified the references appropriately.

There are now 32 references; there are 16/32 recent publications; and the self-referencing rate is 3% (1/32).

The significant P values in Table 7 and Supplemental Table 1 should be uniformly manifested as  $P < 0.05$ ,  $P < 0.01$ ,  $P < 0.001$ , and  $P < 0.0001$ , just like those in other tables.

We made these revisions (Table 7 and Supplemental Table 1).

The language quality is grade B. Please visit the following website for the professional English language editing companies that we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

Our manuscript has been edited by American Journal Experts again, and we have provided the editing certification.

The ORCID number should be provided for every author.

We provide the ORCID number of every author.

As a retrospective study, the authors offered Institutional Review Board Approval Form and Signed Informed Consent Form.

We provide the Institutional Review Board Approval Form and Signed Informed Consent Form.

The Non-Native Speakers of English Editing Certificate contained a title “Renal dysfunction in HCC” different from that of this manuscript and therefore is invalid.

We modified the Non-Native Speakers of English Editing Certificate.

Conflict-of-Interest Disclosure Form, Copyright License Agreement, and Biostatistics Review Certificate are not provided.

We provide the Conflict-of-Interest Disclosure Form, Copyright License Agreement, and Biostatistics Review Certificate.

The statistical methods used in this manuscript should be reviewed by a biostatistician and the review certificate should be provided accordingly.

The statistical methods in this manuscript were reviewed by Yoichi M. Ito, the Chief of the Data Science Center, Hokkaido University Hospital, and we changed the manuscript as follows.

1. We deleted “followed Dunn’s multiple comparison test” (line 203 and the legends of Tables 2, 4, and 6).
2. We added “The eGFR values before and one month after hepatectomy in patients with severe CKD were compared by paired t test” (lines 203-204).
3. We added “This PSM model was constructed with patients’ age, etiology, and laboratory data, such as the levels of serum total bilirubin (T-bil), aspartate aminotransferase (AST), aspartate aminotransferase (ALT), and HbA1c” (lines 208-210).
4. We modified the JMP version from JMP “14” to “16” (line 213).
5. We added and modified “This PSM model was constructed with patients’ age, etiology, and laboratory data, such as the levels of serum T-bil, AST, ALT, and HbA1c, so a total of 110 pairs of matched HCC patients undergoing hepatectomy were selected in this model (Sup Table 1)” (lines 305-306).
6. We added and modified the hazard ratio scores (HR (95% CI)) in the univariate analysis in Table 7. (Table 7)

Finally, all the issues raised by the peer reviewers should be addressed.

We provided point-by-point responses to the issues raised by the peer reviewers.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Surgery, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. 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. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

[Response to Company editor-in-chief](#)

[We provided decomposable figures and required items.](#)