

Reply to Reviewer's comments

Dear Editors and Reviewers,

We appreciate your time spent on reviewing our manuscript. We accepted a transfer to the World Journal of Hepatology from the World Journal of Gastroenterology. We tried our best to address the issues raised by peer-reviewers. Please see the reply comments below for detail. This manuscript was drafted and edited with Native-English speaker co-authors. Regarding Figure 1, we created this image using statistical software, and this is an original image that we are not able to modify or enable edits. I created a separate figure a file with PowerPoint to enable modification of text portion so that editor can modify the text.

Step 4: Verify the accuracy of general information for your manuscript

We request a minor change to below indicated with bold.

Name of journal: World Journal of Hepatology

Manuscript NO.: 56048

Column: Retrospective Study

Title: Factors Associated with 5-Year Survival of Combined Hepatocellular and Cholangiocarcinoma

Authors: Tomoki Sempokuya, Eric A Wien, Robert J Pattison, Jihyun Ma and Linda L Wong

Corresponding author: Tomoki Sempokuya, MD, Doctor, Physician, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Nebraska Medical Center, 982000 Nebraska Medical Center, Omaha, NE 68198, United States. tsempoku@hawaii.edu

Received Date: 2020-04-15

First decision: 2020-06-04

Step 5: Peer-review report(s)

The authors must resolve all issues in the manuscript based on peer-review report(s) and make a point-to point response to the issues raised in the peer-review report(s) which listed below:

Our responses are in bold.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: In the following paper, the authors aim to identify potential factors HCC/CC-related that may correlate with 5-year survival. Although it is a retrospective study designed extracting data from SEER database, they focused the analysis on a rare entity (HCC/CC) for whom there are no prospective randomized trials. The manuscript is well written in English and clear to the reader. The manuscript deserves publication after minor revisions:

We appreciate the positive comments.

The authors should add in the discussion that it is not possible to retrieve from SEER data concerning laboratory exams that may have an impact on 5-year survival. I.E lab features used for CHILD Pugh score in HCC, or other parameters that may be novel candidate as prognostic factors for CC.

Thank you for your suggestion. We modified sentences located on page 13-14 to the followings:

Data from the SEER did not report the underlying chronic liver disease, laboratory studies to assess hepatic function, and calculate CHILD Pugh score or detailed information on tumor characteristics, which would be important in determining resectability and transplant candidacy and thus impact on 5-year survival.

Please cite in the references: Salati M, Caputo F, Cunningham D, et al. The A.L.A.N. score identifies prognostic classes in advanced biliary cancer patients receiving first-line chemotherapy. Eur J Cancer. 2019;117:84 - 90. doi:10.1016/j.ejca.2019.05.030

We appreciate your insight. We added a sentence on page 13 as following:

The A.L.A.N. score, which is calculated with baseline Actual neutrophil count, Lymphocytes-monocytes ratio, Albumin, and Neutrophil-lymphocytes ratio developed by a group in the U.K., may provide prognostic information for patients with advanced biliary cancer who received the first-line chemotherapy^[34].

- Moreover, authors should add in the discussion as limitation that it is not possible to know if patients who underwent surgery received a post operative treatment in particular in the case where the CC component is higher than HCC. Adjuvant treatment for CC is an hot topic in oncology and data from randomized trials are often conflicting. Please, cite in the reference: - Messina C, Merz V, Frisinghelli M, et al. Adjuvant chemotherapy in resected bile duct cancer: A systematic review and meta-analysis of randomized trials. Crit Rev Oncol Hematol. 2019;143:124 - 129. doi:10.1016/j.critrevonc.2019.09.002 Format:

We appreciate the comments. We added a sentence on page 14 as following:

Due to the nature of the SEER database, it is not possible to know if patients received adjuvant chemotherapy after surgical treatment, which may improve recurrence-free survival if combined HCC/CC has a higher CC component^[37].

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This manuscript has evaluated factors associated with 5-year survival of combined hepatocellular and cholangiocarcinoma. This paper is well written, and will be acceptable. However, it will require some revision before publication. 1, Why was the factors of background liver disease and/or liver function?

We appreciate your comments. As a reviewer 1 suggested, due to the nature of the SEER Database study, it is not possible to assess underlying liver disease or liver function. We clarified this based on reviewer 1's comments.

(1) Science Editor:

1 Scientific quality: The manuscript describes a retrospective study of the five-year survival of combined hepatocellular and cholangiocarcinoma. The topic is within the scope of the WJG. (1) Classification: Grade B and Grade C; (2) Summary of the Peer-Review Report: This manuscript has evaluated factors associated with 5-year survival of combined hepatocellular and cholangiocarcinoma. This paper is well written and clear to the reader. The authors should add in the discussion that it is not possible to retrieve from SEER data concerning laboratory exams that may have an impact on 5-year

survival. Moreover, authors need to discuss the limitation of this study. The questions raised by the reviewers should be answered; and

We added sentences for a clarification. Please see above for more detail.

(3) Format: There are 4 tables and 1 figure. A total of 36 references are cited, including 13 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A and Grade B. The manuscript is from the United States. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. This study used publicly available database without interaction with individual patients, therefore informed consent and the Institutional Review Board Approval Form were not required to conduct this study. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an invited manuscript. The study is without financial support. The topic has not previously been published in the WJG. The corresponding author has published 1 article in the BPG. 5 Issues raised: I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Our figure was an original figure created by statistical software. We attempted to modify the figure using PowerPoint, so that text portion is editable. Please review a figure file with PowerPoint format.

6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

(2) Editorial Office Director: I have checked the comments written by the science editor.

(3) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Hepatology.

We would like to thank editors and reviewer again for considering our manuscript for a potential publication. Please feel free to contact us if there is any issue with our manuscript.

Sincerely,

Tomoki Sempokuya, MD: Corresponding author

Dear Editor, We appreciate the comment. We understand the value of having underlying liver disease or liver function. Unfortunately, as a reviewer 1 suggested, due to the nature of the SEER Database study, it is not possible to assess underlying liver disease or liver function from available data from this database. Sincerely, Tomoki Sempokuya, MD