Jin-Lei Wang
Company Editor-in-Chief
Editorial Office
World Journal of Clinical Oncology

Dear Dr. Wang

Thank you very much for your letter dated May 12, 2022, and for the careful review of our manuscript, which we have amended following the reviewers' suggestions. A copy of the revised manuscript with the changes highlighted in red font has been uploaded to the submission system. Also, please find below an itemized point-by-point response to the reviewers' comments.

We look forward to hearing from you about the status of this manuscript, which we hope is now acceptable for publication in the World Journal of Clinical Oncology. Please feel free to contact me if you require any additional information.

Sincerely,

Dr. Ajacio Brandão, PhD
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Dear Editor,
We are submitting our responses to reviewers' comments. Based on the comments, we have added Figures 3 and 4 as well as 10 new bibliographic references. We hope we have made all necessary changes. Please let us know if you have any questions.

Reviewer #1

- *Dear Review Editor: "Propensity-matched analysis of patients with intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma and hepatocellular carcinoma undergoing a liver transplant" I have three points that I would like to raise with the authors. Sincerely, To the authors: "Propensity-matched analysis of patients with intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma and hepatocellular carcinoma undergoing a liver transplant" My comments are as follows.*

1. Please analyze progression-free survival and overall survival using Kaplan-Meier analysis in patients with intrahepatic cholangiocarcinoma (ICC) or mixed hepatocellular-cholangiocarcinoma (HCC-CC) compared with patients with hepatocellular carcinoma (HCC).

Response: Following your suggestion, we analyzed progression-free survival and overall mortality using the Kaplan-Meier method in patients with intrahepatic cholangiocarcinoma (ICC) or mixed hepatocellular-cholangiocarcinoma (HCC-CC) compared with patients with hepatocellular carcinoma (HCC). We then added Figures 3 and 4, each with four Kaplan-Meier curves. In statistical analysis, we added the following sentence: "Progression-free survival and overall mortality rates were computed with the Kaplan-Meier method using Cox regression for comparison."

2. Please show the rationale whether HBV and HCV be present or not.

Response: Thank you for the comment. We aimed to demonstrate all etiologies of cirrhosis in this series. Tables 1 and 2 show the numbers of patients with ICC, HCC-CC, and HCC with HBV and HCV. If your question was not addressed, please let us know.

3. Please evaluate the hepatic reserve using Child-Pugh classification and the HCC stage using Barcelona Clinic Liver Cancer classification.

Response: We added the hepatic reserve using Child-Pugh classification to Tables 1 and 2. Unfortunately, we do not have information on the HCC stage using Barcelona Clinic Liver Cancer classification in our database.

4. I think the number of patients is relatively small to lead your conclusion. I hope that my comments will be useful in improving the article.

Response: Thank you for the comment. We agree with you that the number of patients is small, and we addressed that issue in the Discussion section. This is a limitation, but

even with limited cases we could demonstrated statistically significant differences between ICC and HCC prognoses.

Reviewer #2:

Brando et al. reviewed 475 patients with presumptive hepatocellular carcinoma (HCC) who underwent liver transplantation (LT) in their institute. All cases were preoperatively diagnosed with HCC but postoperative investigation revealed that 1.7% of the LT recipients had intrahepatic cholangiocarcinoma (CC) and 1.5% had mixed HCC and CC (HCC-CC). Then, they compared postoperative prognosis of CC or HCC-CC with that of HCC by the Cox regression analysis of propensity-matched subjects. They found that prognosis of CC was worse than that of HCC after LT but prognosis did not differ significantly between HCC-CC and HCC. This is an interesting and informative study for consideration of LT for intrahepatic CC, of which indication remains controversial. The greatest problem of this manuscript is small numbers of CC and HCC-CC cases, as the authors mentioned in the Discussion. However, this may be unavoidable, because LT for CC and HCC-CC was the result of preoperative misdiagnosis of HCC. In addition, I would like to make some comments.

1. There are some errors in the numbers in the text: (p.10, l.7) 76.2% should be 67.2%. (p.10, l.9) 65.2% should be 56.2%.

Response: Thank you for your careful reading. We have corrected any typos.

2. P values in Tables 1 and 2 should be thoroughly recalculated. I guess there may be quite a few errors. For example, P = 0.036 is described in Neoadjuvant therapy no, Pre-LT factors, of Table 1. However, according to my calculation, P value should be 0.1062 by chi-square test, 0.2513 by chi-square test with Yates' correction, and 0.176 by Fisher's exact test. Furthermore, analytical method of each P value had better be specified.

Response: We added a third variable indicating the number of patients who did not undergo any neoadjuvant therapy to Tables 1 and 2, in "Neoadjuvant therapy." Thus, the values found on Fischer exact test are clarified. The analytical method for each P-value has been added to the tables.

Reviewer #4:

This study showed a small proportion of misdiagnosis among patients who underwent LT with presumptive HCC and clinical outcomes among them. Because liver biopsy is not routinely recommended to detect ICC, and the diagnosis of HCC-CC is very difficult, patients with ICC or HCC-CC could be misdiagnosed as HCC and undergo unnecessary LT. However, recent studies suggested that LT might be considerable as therapeutic option for ICC and HCC-CC. Please discuss the need of an accurate diagnosis before LT and possible advantages of LT in detail.

Response: Thank you for the suggestion. We added the following sentence to the Conclusion section: "Improvement in the detection of these rare tumors in pretransplant evaluation is essential for the eventual adoption of LT as an effective treatment for these patients."

Reviewer #5:

The authors report a single centre experience of ICC in explanted livers propensely matched with HCC-ICC and HCC only. The conclusions are that ICC have worse outcomes than patients undergoing LT for HCC and outcomes did not differ significantly between patients with HCC-CC and patients with HCC. The findings are not novel and the retrospective methodology is subject to bias by definition; also the small number is a major limitation of this study. What lessons could be learned by this report? I would suggest to implement the part on pre-listing and follow up with some advice for transplant oncology, a new emerging indication.

Response: Thank you for the suggestion. We added the following paragraph: "Transplant oncology is a new concept encompassing multiple disciplines of transplantation medicine and oncology (transplant oncologists, hepatologists, gastroenterologists, transplant hepatobiliary surgeons, interventional radiologists, and immunologists) designed to push the envelope of the treatment and research of hepatobiliary cancers.[38,39] This field will certainly improve treatments and cure rates for patients with HCC, ICC, or HCC-CC, as well as other cancer types."

Science editor:

Dear Authors, once I familiarized with the Reviewer Reports, I feel that major rather than minor revisions should be required. Some aspects such as pre-listing and follow-up with advice for transplant oncology, errors in percentage values or addition of survival curves could be easily implemented. However, the amount of errors in values (including statistical significance) and the need to recalculate Table 1 and 2 has introduced the uncertainty whether your results are in fact valid. Please double-check the entire manuscript and provide strong justifications in the comprehensive response letter. Once revised, the paper could be reconsidered.

Response: We appreciate your comments. We have attempted to provide responses to all questions made by the reviewers and address their observations. We believe that the reported data are correct.