Peer Review File

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Reviewer A

< Major Points >

Comment 1: It well known that OS is substantially different between BCLC stages B and C. Thus, it would be inappropriate to mix up those patients and conduct survival analysis. Although the authors performed multivariable analyses, it still raises a concern. It would be better to exclude BCLC-B patients.

Reply: We thank the Reviewer for this comment. This is also a key point we were discussing at the initial stage of our study. As far as we are concerned, we wish to keep those BCLC-B patients in the present study for the following reasons. First, in addition to BCLC-C patients, more and more BCLC-B patients are undergoing combined therapy, and data about this population are necessary. According to one of our recent studies, approximately 50% of BCLC-B patients who had undergone TACE would eventually develop TACE refractoriness, and earlier use of sorafenib may provide more survival benefits. The study aims to find a suitable indication or contradiction for both stage B and C patients to start the combined treatment. Second, in addition to the overall survival of the whole patients, we conducted several analyses in the two stages, respectively, providing evidence that ALBI and PALBI were capable of identifying the candidates to survival benefits in both BCLC-B and BCLC-C rather than simply mixing them up (described on Page 13, Lines 15-Page 14, Lines 2).

Comment 2: The authors argued that both ALBI and PALBI showed larger AUROC compared to CP score. However, the authors need to provide P-values for the comparison of each AUROC to show statistical significance.

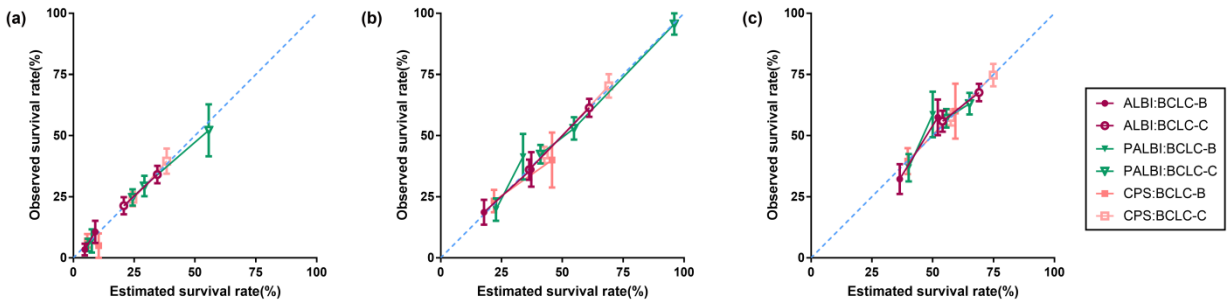
Reply: We thank the Reviewer for the helpful comment. In fact, we could hardly find any P-value that was statistically significant among the comparison, though the

AUROC of ALBI and PALBI were shown slightly better. We ascribe this to the large heterogeneity among patients classified as BCLC-B, and which would be even more considerable among BCLC-C patients, in which case a single index or criterion with a small number of parameters would not likely be effective enough. Even though, ALBI and PALBI demonstrated the ability to stratify survival in the Child-Pugh A population, which we take as advantages comparing to the classic Child-Pugh grade. Meanwhile, with regards to the effectiveness of the CP score A5 or A6, the ±1 point will be determined by one of two subjective parameters (hepatoencephalopathy and ascites), which might lower its accuracy to some extent. These have been discussed in the manuscript and help to interpret our results. Therefore, eventually, we still provided the AUROC results as the supporting information, although it did not reach statistical significance.

Comment 3: The authors reported that both ALBI and PALBI has better discrimination function than Child-Pugh score. It would be additionally necessary to provide and compare the calibration function of each scoring system.

Reply: We thank the Reviewer. We added the calibration curve of each scoring system in the revised manuscript as Figure 4 (see Page 13, Lines 10-12).

Changes in the text: The calibration function of each scoring system was validated by the calibration curves (Figure 4), showing satisfactory capacities of ALBI and PALBI grade as well.



Comment 4: The AUROCs of both ALBI and PALBI are not good enough although it

is slightly better than or comparable to Child-Pugh score.

Reply: We thank the Reviewer for this crucial point. As we declared in Point 2, ALBI and PALBI are considered more capable than CP score for patient stratification. ALBI and PALBI definitely do not appear to be a perfect criterion for screening candidates intended for the combined treatment. Nevertheless, their results can help select ideal candidates, maybe in a more comprehensive manner. We hope that the current study might inspire further studies from multiple centers to establish a thorough standard for TACE+sorafenib treatment.

< Minor Points >

1. Capitalization of Sorafenib is not required.

Reply: We thank the Reviewer. The capitalization has been revised throughout the manuscript.

Reviewer B

This is an interesting and well written paper. Only minor comments

Comment 1: Among the exclusion criteria "had any severe complications or concomitant conditions of other organs" Can be the authors more specific?

Reply: We thank the Reviewer for the comment. We added several specific conditions that were making a patient not suitable for enrollment (kidney dysfunction, central nervous system dysfunction, heart failure, respiratory failure, severe thrombocytopenia, or pancytopenia) (see Page 8, Lines 4-6).

Changes in the text: The patients should be excluded if they: 1) had another malignancy in addition to HCC; 2) had any severe complications or concomitant conditions of other organs, including but not limited to kidney dysfunction, central nervous system dysfunction, heart failure, respiratory failure, severe thrombocytopenia, or pancytopenia; 3) lack of records of laboratory tests to calculate pre-treatment ALBI or PALBI grade; 4) received other anti-tumor treatments prior to TACE with sorafenib.

Comment 2: The authors concluded that "Based on our study, patients with ALBI or PALBI grade 1 are the best candidates for TACE combined with Sorafenib treatment". However, I think that this should have an arm with only TACE for definite conclusions

Reply: We thank the Reviewer for a useful point. There are mainly two concerns about the point. On the one hand, we cited external data of TACE alone therapy from published studies in the discussions of our manuscript for comparison (see Page 15, Lines 7-10), in order to make us more persuasive. On the other hand, the main purpose of the present study was to sort out the patients who would possibly benefit from the combined therapy to meet the demand of present clinical application; thus, we have modified our text as follows: “patients with ALBI or PALBI grade 1 are the better candidates for TACE combined with sorafenib treatment compared to those with ALBI grade 2 or PALBI grade 2 or 3”. We revised the related sentence to make sure it is not misleading (see Page 16, Lines 20-Page 17, Lines 1).

Changes in the text: Based on our study, patients with ALBI or PALBI grade 1

are the better candidates for TACE combined with sorafenib treatment compared to those with ALBI grade 2 or PALBI grade 2 or 3.