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Title: Validation and Evaluation of Clinical Prediction Systems for First and Repeated Trans-arterial Chemoembolization in Unresectable Hepatocellular Carcinoma: A Chinese Multicenter Retrospective Study

Dec. 7 2019

Dear editors:

The authors thank the reviewers for their valuable comments and suggestions, which have improved our manuscript furtherly. Please find our point-by-point responses to their comments in the following document.

Reviewer 1 (03724558) report:

Comments 1: In the abstract, you wrote that the study was conducted from January 2009 to December 2015 and then in the manuscript, you wrote that the study was conducted from January 2010 to May 2016.

Response: Thank you for the suggestion. We feel so sorry for the mistake in the abstract

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and have revised it highlighted (page 8).

Comments 2: Follow up of patients, you wrote that Contrast enhanced CT or MRI was done every 8 weeks. This is against International guidelines. Is it special for your locality guidelines and this may harm your patients (Contrast nephropathy)?

Response: Thank you for the suggestion. According to the present EASL guidelines, TACE re-treatment in aggressive schedule (every 2 months) is not recommended, but should be depended on radiological response. In this study protocol, patients were suggested to have radiologic evaluation during week fourth and eighth after treatment and every eight weeks thereafter, which was consistent with our previous multicenter studies about TACE treatment or its combination with sorafenib (Ann Oncol 2013; 24:1786-92; Int J Cancer 2016; 139:928-37; J Hepatology 2019;70:893-903). However, in clinical practice, the intensity of follow up depended on individuals' baseline characteristics (Including kidney function) and responses to the last treatment, i.e., on demand. Thus, not all patients strictly stuck to this imaging follow-up schedule. Moreover, no contrast-induced nephropathy was observed in the current cohort. We have added this in the revised manuscript (Page 14).

Comments 3: In page 17, You wrote that as shown in table 3 and it must be as shown in

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table 4.

Response: Thank you for the suggestion. We feel so sorry for the mistake in the manuscript and have revised it highlighted (Page 18).

Comments 4: According to your results, for first TACE 553 patients are not candidates for TACE Would you recommend change in guidelines in the future for those non candidates for TACE.

Response: Thank you for the suggestion. mHAP3 had taken both liver function and tumor burden into its Prognostic Index (PI), which might lead to much accuracy of mHAP3 in patient-selection beyond other scores. Our results are based on the developed scores and need an assessment in wider population for next step. Furthermore, the outcome of non-candidates receiving first TACE in our study should be compared to the those of other treatments in similar baseline patients within cohorts in future studies. Also, more scores will be published in the future, and their prognostic abilities need further assessment. Therefore, our conclusion may be changed by impact of the new ones. In summary, the recommendation of change in guidelines ought to be proposed, but should be based on the results of corresponding studies in the future.

Comments 5: What about recommendations for this study, would you recommend

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Larger number of patients to validate these results?

Response: Thank you for the suggestion. We will further assess our conclusion among a wider population for the next step study. Also, any format of external validation is welcome and recommended. We have clarified it in the discussion part (Page 23).

Reviewer 2 (03867417) report:

Comments 1: The article is well-written and a pleasure to read and the authors should be commended for this. The main thing I would like to see improved is the addition of the treatment lines at progression before inferring on the overall survival effect.

Response: Thank you very much for the consideration and suggestion. Once patients entered advanced stage according to the specialized assessment, they would receive the recommended treatment according to the national guidelines including systemic therapies and best support care (BSC). Then, follow-up was continuously conducted by local investigators until happen of terminal event or loss of follow-up. We have added this part in the revised manuscript (Page 14).

Comments 2: Minor comments: Define abbreviations at the first occurrence in the text

Response: Thank you for the suggestion. We have checked all the abbreviations used in our article and added the definition missed by carelessness.

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Comments 3: Summarize briefly the 6&12 criteria in the introduction

Response: Thank you for the suggestion. We have added this part of summarization in the introduction (Page 12).

Reviewer 3 (03502576) report:

Comments 1: The article talked about the validation of and Evaluation of Clinical Prediction Systems for First and Repeated Trans-arterial Chemoembolization in Unresectable Hepatocellular Carcinoma: A Chinese Multicenter Retrospective Study. This study found that the 6&12 (Six-and-twelve) criteria were closely correlated with radiological response, mHAP3 (modified Hepatoma Arterial-embolization Prognostic version 3) predicted overall survival (OS) best, and ABCR (standing for alpha-fetoprotein, BCLC, Child-Pugh and Response) was a reliable predictive system for the post repeated TACE survival (PTRS). And the sequential combination of them performed well in outcome prediction. The methods and conclusion are appropriate. It will help the doctor to make decision in different case and perform personal treatment.

Response: Thank you very much for the consideration of this article.

Comments 2: However, the conclusion needs to be further assessed in a multicenter

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prospective study.

Response: Thank you for the suggestion. We will further assess our conclusion among a wider population for the next step study. Also, any format of external validation is welcome and recommended. We have clarified it in the discussion part (Page 23).