Author’s response to reviews

Title: Sorafenib versus Transarterial Chemoembolization for Advanced-Stage Hepatocellular Carcinoma: A Cost-Effectiveness Analysis

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Point-to-point Response to Reviewers’ Comments

Technical Comments:

Editor Comments:

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Reply: Thanks for your kindly reminder. We have also viewed the reports in the peer review system as you recommended, and revised the manuscript according to these comments.
Reviewer reports:

Jagpreet Chhatwal, Ph.D. (Reviewer 1):

1. In table 4 or in a separate table or even in the text, i.e. base case analysis section, provide all absolute values by 3 strategies. This is essential for model transparency.

Reply: Thanks for your constructive suggestions. We have provided the absolute values by these 3 strategies in a separate table in the revised manuscript (Table 4). Please check the revision. Thank you.

Rudolf Stauber (Reviewer 2):

Chen et al analyzed cost-effectiveness of treating advanced HCC with sorafenib (full-dose vs. dose-adjusted) vs. TACE based on a systematic review of 27 articles.

They conclude that full-dose sorafenib is cost-effective in advanced HCC under accepted thresholds of WTP. While this study provides some valuable insights in the costs of sorafenib and TACE treatment within the USA and China, I feel that the conclusions are not well supported by the data presented.

Several issues require further attention:

1. What are accepted thresholds of WTP?

Reply: Thanks for your valuable comment. As many other high-quality studies have stated, there is no empiric evidence to support the choice of a particular threshold of WTP [1-3]. Thus, as these high-quality studies on cost-effectiveness analysis did, we have adopted the commonly cited threshold of $50,000/QALY for the USA[1,2, 4], and the threshold value proposed by the WHO guidelines of cost-effectiveness analysis for China (3 times per capita GDP of China) [3,5]. We are terribly sorry not to have provided the references regarding the choice of our accepted thresholds of WTP in the original manuscript. In this revision, please see the added references in the Methods section (page 13, line 10-12).
References


2. Since medical charging systems are different throughout the world, the data presented in this study for USA and China cannot be easily extrapolated to other parts of the world.

Reply: Thanks for your critical comments. As you pointed out, it is true that the data presented in this study for USA and China cannot be easily extrapolated to other parts of the world, and it has been listed as one of the limitations of our study in the Discussion section in the original manuscript (page 19, line 17-26). Due to the different medical charging systems and paucity of data on cost estimates for each health state in different countries, it restricted us to make comparisons among more countries. Thus, we have considered the uncertainties of costs in sensitivity analyses by inputting a wide range of cost values (50%-200% of base-case value). In a sense, our model could be applied in those countries with efficacy and cost data falling within the ranges we have set.
Despite these, we know that it is still not easy to extrapolate our data for USA and China to other parts of the world. We respectfully would like to convey that this manuscript is the preliminary attempt to compare the cost-effectiveness of sorafenib and TACE for advanced-stage HCC in these two countries. Surely, it requires future high-quality studies from many other countries to confirm.

3. Characteristics of the patients remain largely unclear. As stated on page 7, adult patients with advanced HCC (vascular invasion/extrahepatic spread in symptomatic patients with Child-A/B stage) were studied in a Markov model. Information on the BCLC stage is lacking. Advanced stage (BCLC-C stage) may be due to either vascular invasion, extrahepatic spread or symptoms (ECOG PST 1-2), what were the individual proportions of these features in (i) TACE and (ii) sorafenib treated patients?

Reply: We are terribly sorry not to have provided detailed information on the BCLC stage for targeted populations. In the revised manuscript, we have added to supplement this part of information (Methods section, page 7, line 2-6). However, we are terribly sorry we cannot provide the data about the individual proportions of these features in TACE and sorafenib treated patients because the data input into our model were extracted from different literatures and the relevant proportions of these features in TACE and sorafenib treated patients were varied in different literatures. And this is the limitation of this type of research.

4. As correctly pointed out on page 6, there are no RCTs comparing efficacy of TACE and sorafenib in advanced HCC. Comparison of their efficacy based on retrospective data are of limited value due to selection bias.

Reply: Thanks for your kindly critiques. We respectfully agreed that the comparison of efficacy between TACE and sorafenib based on retrospective data was with selected bias. Thus, we have added to list it as one of the limitations of our study in the Discussion section (page 20, line 9-10). As we know, multicenter RCTs may be the best solution to compare TACE with sorafenib in advanced HCC. However, such large trials are difficult to conduct due to the difficulties of patient enrollment and treatment allocations. The Markov model would be a good solution for this issue. As you concern, we agree that it is the best to use markov model when efficacy data about these two treatments are sufficient and high-qualified. However, due to the current situation that no RCT was conducted in this respect, we have tried our best to obtain the data in our model with comprehensive literature review or to get them from a large HCC database.
5. Abbreviations should be explained when first mentioned in the manuscript (e.g. WTP = willing to pay, explained first on page 13 instead of page 12).

Reply: Thanks for your comments. It has been corrected as you suggested (Methods section, page 12, paragraph 2, line 9).

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (BMC_WRITING_RESOURCES_URL http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

Reply: Thanks. It is our pleasure to know that improvements to the English language within your manuscript have not been requested.

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Declarations

- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions

Reply: Thanks. We have formatted our manuscript according to the journal’s requirements.