Author's response to reviews

Title: Efficacy and safety of oral branched-chain amino acid supplementation in patients undergoing interventions for hepatocellular carcinoma: a meta-analysis

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Author's response to reviews:

Dear Dr. Matam Vijay-kumar:

On behalf of my co-authors, we thank you for giving us an opportunity to revise our manuscript. We appreciate the positive comments and constructive suggestions regarding our manuscript entitled “Efficacy and safety of oral branched-chain amino acid supplementation in patients undergoing interventions for hepatocellular carcinoma: a meta-analysis”. (ID: 1171407798167109). These comments provide valuable insight for revising and improving our paper, as well as guidance to our research.

The main corrections in the paper and the responses to the reviewers' comments are detailed below. Please see our point by point responses.

First, we have included the ‘Acknowledgements’ section at the end of the manuscript, before the reference list. We also highlight all changes made when revising the manuscript with colored text.

Reviewer #1:
Comment:

Abstract and discussion too elaborate; would benefit from being shortened.

Response: We have followed your advice and shortened the Abstract and Discussion sections by removing non-critical statements, rephrasing passages for brevity and including Supplemental Table S4 to summarize some of the information.

Reviewer #2:

Comment 1: More discussions on the rationale why BCAA given to HCC patients, the nutritional deficiencies that aggravate/worsen HCC, how does BCAA supplementation overcome such problem and 'malnutrition' as a risk factor during HCC therapy.

Response: We have made appropriate adjustments in the 'Discussion' section. In the first paragraph, we more explicitly discussed the relationship between BCAAs and HCC. Because liver function is impaired in most HCC patients, many patients suffer from decreased biosynthesis and secretion of albumin in hepatocytes, which commonly leads to the occurrence of hypoproteinemia, the manifestation of malnutrition. Hypoproteinemia or complications of hypoalbuminemia, such as ascites and edema, can increase the risk of discontinuing anti-cancer therapy and adversely affecting the therapeutic effects of anti-cancer treatments. BCAAs can significantly improve the BCAA/AAA ratio and further increase the biosynthesis and secretion of albumin, decreasing the rate of therapy interruption due to hypoproteinemia.

Comment 2: It is not clear whether these other anti-HCC treatment present a possible confounding variable.

Response: This concern can be resolved by performing subgroup analyses for the different anti-cancer therapies. However, because of the restriction on the number of documents for each interesting outcome, we cannot do a subgroup analysis, and thus it is difficult to determine whether this factor presents a confounding variable, which may be a limitation of our article.
Comment 3: More discussions on the association of BCAA metabolism with insulin resistance, obesity and other metabolic disorders and how metabolic abnormalities in HCC patients could potential influence efficacy of BCAA.

Response: Because insulin resistance was reported to be an HCC risk factor, and BCAAs suppress the incidence of hepatocarcinogenesis, we think it is appropriate to discuss them together with HCC recurrence. The detailed content is in the third paragraph of the ‘Discussion’ section.

Comment 4: An additional Table that summarizes the results in the articles reviewed (eg: study by et al, BCAA treatment reduce mortality and ___ but not ___; duration of study; side effects observed).

Response: Thank you for this pertinent suggestion. According to your proposal, we have constructed this table, named ‘Supplemental Table S4’. This supplemental table allows a simpler and more intuitive draft because it replaces text which expresses similar meaning.

Comment 5: The discussion regarding BCAA effects on different class of Child-Pugh patients is very interesting. It would be more impactful if this Child-Pugh factor is included in the meta-analysis (in other words, should be in the Result section).

Response: We have included this part in the ‘Results’ section, under the ‘Mortality’ subsection and included corresponding context in the ‘Discussion’ section (in the second paragraph). Additionally, we changed the previous ‘Table S4’ to ‘Table 2’ and put it at the end of manuscript immediately after ‘Table 1’.

These changes will not influence the content and framework of the paper. We appreciate the Editors/Reviewers’ comments and believe that our corrections will meet with your approval.

Again, thank you for your comments and suggestions. We look forward to
hearing from you. If you have any further questions, please do not hesitate to contact me at the address below.

Thank you and best regards.

Yours sincerely,

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