

## Answering reviewers

### Reviewer #1:

1: line 89: MELD score includes INR, bilirubin, creatinine and dialysis in last 2 weeks, not etiology;

Response1: I have modified the MELD score, see line 94.

2: line 267: "varicose vein" - probably it is a mistake during english editing, I suppose you referred to oesophageal varice;

Response2: I have changed "variose vein" to "oesophageal variety", see line 261.

3: In titles of Fig 4b, 4c, 4d, 6b, 7b, 7c, 8b you should specify subgroups. In this way you improve the readability of figures;

Response3: I have added a description to the figure caption, see Fig 4b, 4c, 4d, 6b, 8b.

4: One of the most interesting result of your meta-analysis is the reduction of "complications rate". You should specify in M&M the cirrhosis-related complications (eg. ascites, jaundice, encephalopathy, gastrointestinal bleedings). If feasible, a meta-analysis for each complication could define the actual utility of BCAA in preventing the above-mentioned complications, causing an increase in morbidity and mortality in cirrhotic patients. This implementation could give a wider appeal of your work in the hepatology community;

Response4: Because the included studies did not perform separate statistics for complications, it is unfortunate that the study was temporarily not powered for analysis of single complications.

5: In the meta-analysis, BCAA supplementation was not correlated with a reduction of serum bilirubin (Fig 7a). I don't understand how a smaller sample size (Fig 7b - studies with <50 patients) or a shorter treatment period (Fig 7c - studies with patients treated for <1 month) could justify a statistical significance in the subgroup analysis you made. Additionally, these are analysis on only 2 studies. It seems a statistical stretch; if not, this decision need to be justified;

Response5: After discussion, it is considered that the subgroup analysis for bilirubin is not rigorous. Therefore, figures 7b and 7C and the corresponding subgroup analysis have been deleted.

6: In the subgroup analysis for ALT (Fig 6b) you excluded the study of Etsushi Kawamura et al. that have a majority of patients with a viral etiology. The pool of antiviral drugs available in 2009 could not permit to achieve a well-controlled viremia and consequentially persistent high serum AST/ALT levels. This is a possible bias that could justify the reason why the lack of

statistical significance in the meta-analysis (Fig. 6a). This should be specified in the "discussion";

Response6: I have explained this in the ALT subgroup analysis, see lines 228-231.

7: Concerning the "amelioration on liver function", I agree that BCAA supplementation surely has a role in reducing morbidity and mortality in cirrhotic patients and probably a role in improving residual liver function (with a consequential reduction of complications), but following these data is not possible to define an actual effect on liver function. Unfortunately, you do not have data on reduction in Child-Pugh and/or MELD score that are objective parameters for evaluation. You correlate an increase in serum albumin (probably due to an amino acids supplementation in patients that are frequently malnourished) and an uncertain reduction in serum bilirubin, but no data are reported on INR, creatinine, regression of ascites, resolution of encephalopathy. AST and ALT that, as you said, are influenced by several concomitant conditions are not utilized in hepatology for the evaluation of residual liver function. So, as a meta-analysis, is not possible to define a correlation between BCAA and liver function.

Response7: We agree with you but unfortunately included studies did not adequately report data on INR, creatinine, resolution of ascites, remission of encephalopathy. After our meta-analysis, AST and ALT would be decreased after BCAA treatment, but since AST and ALT are indeed affected by many concomitant diseases, as a meta-analysis, it is not possible to determine the correlation between branched chain amino acids and liver function. Now, it is hoped that there will be more studies to explore this in the future, and I have corrected the notes in the discussion section, see lines 298-301.

## **Reviewer #2:**

1: Please use abbreviations when you defined them. Please check the last sentence of your abstract.

Response1: I have changed some definitions in the last sentence of the abstract to abbreviations, see line 63.

2: Please define liver cirrhosis when it appeared for the first time in the Introduction section.

Response2: I already defined it at the time when cirrhosis first appeared in the introduction section, see line 81.

3: Some language editing is needed. For example, "research " is a mass noun (non-count noun). Please revise the sentence in lines 81-82. Another example, if the abbreviation of Branched-chain amino acids is defined as BCAA, then BCAA should be a plural form (lines 104-105). In fact, you should use

BCAAs as there are three amino acids.

Response3: I have re performed full text language editing.

4: In the discussion section, please elaborate why there is a rise of glucose.

Response4: I already detailed in the discussion section why glucose rises, see lines 308-316.

**Company editor-in-chief:**

1: Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

Response: I have already supplemented and refined the highlights of the latest cutting-edge research findings, thereby further refining the content of the manuscript.