Author’s response to reviews

Title: Liver function changes after transarterial chemoembolization in US hepatocellular carcinoma patients: The LiverT study

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Linda Gummlich, Editor
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Dear Dr Gummlich,

Thank you for the opportunity for submitting a revised, and hopefully significantly improved version of our manuscript (Reference number: BCAN-D-19-00018).

Please find below our point-by-point summary of author responses and subsequent amends made to the manuscript following resubmission. Our replies are reported in underlined text here below.

Reviewer reports:
Nicholas Fidelman (Reviewer 1): The authors have thoughtfully addressed the majority of the reviewers' comments.

Specific comments are included below.

1. Please specify whether values reported in Table 4 and Figure 1 were based on primary analysis.

Author Response: We had specified in the text of the results that data for figure 1 were based on the primary analysis (Page 8, line 193) and in the legend for Figure 1. Data used in Table 4 are the absolute values for each laboratory parameter that were used for all analyses in the study.

2. Data on TARE is limited to 78 patients and does not contribute to the overall message of the study. Please focus on patients who underwent TACE

Author Response: We have removed TARE data from the manuscript, including the introduction, methods, results, and discussion.

3. Patients with chronic liver disease and cirrhosis develop deterioration of liver function over time. A note should be made in the limitations section of Discussion that the study lacked a control group of patients (such as MELD-matched patients without HCC) who could have demonstrated prevalence of liver function deterioration over a 3 month time period without the concomitant effect of liver-directed therapy.

Author Response: We have added this point to the limitations section of the ‘Discussion’ (Page 13, lines 322–325).

Roman Kloeckner (Reviewer 2): Overall, all comments have been addressed. Although all issues are adequately discussed in the revised version now, the LiverT-study still lacks from a certain selection bias as described before. However, this cannot be changed now and is somewhat inherent to all kinds of retrospective data analysis. The most important issue regarding the choice of parameters (ALT and AST not optimal to assess liver function (deterioration)) has now been fully addressed by including/highlighting other, more appropriate parameters (e.g. Albumin and Bilirubin).

Author Response: We thank the reviewer for their comments and for acknowledging the changes that have been made to the manuscript.

Irene Bargellini (Reviewer 3): The paper has been carefully revised and has greatly improved, particularly with regards to the discussion section. Some minor revisions would be desirable.

Specific comments are included below.

1. I would suggest the authors to substitute the last sentence of the conclusions in the abstract ("Decisions about TACE treatments should consider the risk of chronic deterioration in liver function even after a single TACE"), with the last sentence reported in the conclusions of the manuscript ("the present findings highlight the need for the careful selection of patients for TACE is important to help optimize the benefit of the overall HCC treatment course").
Author Response: We have amended the conclusion of the abstract according to the change outlined above (Page 2, lines 47–49).

2. Although I understand the authors' point of view, I still believe that the TARE population should be deleted from the present study.

Author Response: We have removed TARE data from the manuscript, including the introduction, methods, results, and discussion.

3. Regarding Table S2: are the reported median times calculated from the date of TACE? If so, it has to be noted that the median time to the last value of the so-called "chronic period" is little more than one month after TACE (35 days approximately) and very close to the worst data of the acute period. If this is the case, it should be underlined that this time interval cannot be considered representative of "long-term" or "chronic" deterioration of liver function. Please clearly report these data in the results and add a comment on this point in the discussion. How many patients had laboratory values reported at 3 months? Would it be possible to provide separate data for these patients?

Author Response: Regarding the first point, the data in Table S2 is the median time from day 30 post-TACE, i.e. the start of the chronic period, as opposed to from baseline. We have amended the legend and column titles of the table to clarify this (Page 31, line 583): “The median intervals between day 30 after TACE to the worst value and the last value for the chronic period”. This means that a median time of 35 days corresponds to 65 days from baseline; therefore, we feel that this will be representative of the chronic period.

For the second point, all patients included in the analysis had to have laboratory values in all three time periods, within the respective range rather than at specific time points; therefore, for the chronic period, available values were taken within the defined chronic time range (30–90 days) and not always at month 3. We do not currently have individual patient data for the 3-month time point and because this may only be for a very small number of patients, and we do not feel that it would add to the current manuscript.

Yours sincerely,

Fabio Piscaglia