Author’s response to reviews

Title: The association of liver function and quality of life of patients with liver cancer

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Author’s response to reviews:

Dr Cecilia Devoto,
Editor-in-Chief
BMC Gastroenterology
BioMed Central

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Dear Dr Devoto,

Re:

Manuscript Title: The association of liver function and quality of life of patients with liver cancer

Category: Research Article

Submission number: BMGE-D-18-00262
Thank you for the email dated 18th Dec. We have revised the manuscript according to the suggestions. We would like to re-submit the revised manuscript to the Journal. Please find enclosed point-by-point responses to the comments, and two copies of the manuscript (including one copy in which the changes are marked).

Thank you.

Yours sincerely,

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Comments from Reviewer 1:

<Reviewer 1’s comment>

The authors of this manuscript assessed the association between the EORTC QLQ-C30 and HCC18 scores and liver function indices of 472 patients with newly diagnosed HCC. There are some questions to be answered:

1. The authors may describe the ways of detection and guidelines for treatment of HCC. Is there any screening program for high-risk groups?

<Our response>

While Japan has national screening program for HCC, in most parts of the world including Hong Kong, there is no structured population screening for HCC. Individual physicians, at their discretions, may offer opportunistic HCC screening to patients with chronic liver diseases by means of regular ultrasonography and serum alpha-feto protein level.

There are a number of guidelines available for the management of HCC; these include the Barcelona Clinic Liver Cancer staging classification and treatment approach for HCC (BCLC) (references 4-5), Asia-Pacific Association for the Study of the Liver guidelines on the management of HCC (APASL) (reference 6), European Association For The Study Of The Liver-European Organization For Research And Treatment Of Cancer clinical practice guidelines on management of HCC (EASL) (reference 7), American Association for the Study of Liver Diseases guidelines for the treatment of HCC (AASLD) (reference 8). Practices can vary
among different centres according to the availability of treatment modalities, local expertise, physician preferences and reimbursement schemes etc.

We have added descriptions of screening, detection, treatment guidelines and citations to the Background section, page 6, lines 5-18; and References 2-8.

<Reviewer 1’s comment>

2. How was the sample size determined? Is there any prior information?

<Our response>

To our knowledge, this is the first report evaluating the correlation between QOL and liver function in hepatocellular carcinoma patients, therefore no prior information was available to assist us to estimate the target Spearman’s rank correlation coefficient. Therefore in this study, we assumed Spearman’s rho to be ≥0.3 for sample size calculation; this figure is generally accepted to indicate potentially clinically important correlation. With two sided alpha-level of 0.05 and power of 0.9, the required sample size was 133 patients. We aimed to obtain C30 and HCC18 index-scores for all analyzed patients. This required all patients to have all QOL questions answered. For this reason complete-case analysis would be preferred in this study in order to calculate index-scores accurately. To minimize the impact of complete-case analysis, we set the final target sample size to be three times the original sample size (399 patients).

Please refer to the Methods section, page 11, lines 7-9 and 12-19.

<Reviewer 1’s comment>

3. The authors developed many indices for either C30 / HCC18 and liver biochemistry or other blood data.

a. The index scores of C30 / HCC18 came from a paper reference 21. Usually the two questionnaires are analyzed with separate domain scores. The reference developed index scores according to survival prediction. It is a little ambitious to develop such scores.

<Our response>

We developed C30 and HCC18 index-scores in an attempt to simplify the various domains and items scores in the EORTC QLQ-C30 and QLQ-HCC18 tools respectively for survival analyses in our earlier study in HCC patients. These two indices were assessed together with the original QLQ-C30 and QLQ-HCC18 domains and items; they were found to be significant prognostic factors for survival. We proposed to use these 2 respective index scores as they are easy to calculate and could be conducted in daily clinic setting. None-the-less, we acknowledge that they are by no means able to replace the domains and items within QLQ-C30 and QLQ-HCC18 that addressed QOL in HCC patients in greater depth.
In the current analysis, we aimed to assess the correlations between QOL and liver function in HCC patients. Without prior knowledge of the level of correlations with various QOL factors, we have included the available index-scores alongside the ‘standard’ QOL domains and items in the analyses in order to assess how well these could perform.

Findings from the current analyses support the fact that the 2 index-scores have potentially clinically important correlations with four continuous liver function variables. Please refer to the Discussion section, page 19, line 13 to page 20, line 5; and Reference 30.

<Reviewer 1’s comment>

3b. The index scores for liver function are even more ambitious. The ALBI and MELD are composite scores of biochemistry data. The Alb-ALP and ALP-PL are ratios of biochemistry or blood cell data. These are seldom used in studies assessing liver diseases. The authors may provide more basis for development of them.

<Our response>

Please refer to responses to questions 3a. In addition, since we do not have prior information on the relationship between QOL and liver function, we included a broad array of liver function variables that have been previously reported to be of various degrees of clinical values. Apart from analyzing the liver biochemistries (albumin, bilirubin, alkaline phosphatase, alanine transaminase, international normalized ratio) within the routine liver function blood test panel, we were interested to explore commonly used clinical liver function classification systems, e.g. Child’s, ALBI, MELD, as well as some not so commonly used parameters e.g. albumin-to-alkaline phosphatase ratio and alkaline phosphatase-to-platelet ratio. Moreover, most of these clinical factors, including albumin-to-alkaline phosphatase ratio (references 17, 18 and 25) and alkaline phosphatase-to-platelet ratio (reference 24), have been proven to be independent prognostic factors for survival in HCC studies. Interestingly, it turned out that albumin-to-alkaline phosphatase ratio had the highest number of potentially clinically important correlations with QOL among the continuous liver function variables tested.

Please refer to the Background section, page 7, lines 7-12; and page 8, lines 15-18. Please also refer to the Methods section, page 10, lines 5-7; the Results section, page 15, lines 8-15; Table 4; and References 15-25.

<Reviewer 1’s comment>

4. The correlation is assessed by Pearson or Spearman’s r rather than t-test or ANOVA. The statistical method in Table 4 sounds not appropriate. For those scores which are not normally distributed, Spearman may be better.

<Our response>
We thank the Reviewer for highlighting this issue. We acknowledge the QOL data in the study were not normally distributed, therefore we have reanalyzed the correlations between QOL and continuous liver function variables using Spearman’s rank correlation analysis. As a result, the Methods, Results, Discussion sections as well as Table 4 have been revised accordingly.

Please refer to the Methods section, page 11, lines 4-9; the Results section, page 12, line 12 to page 16 line 5; the Discussion section, page 19, lines 3 to page 20, line 3; and Table 4.

<Reviewer 1’s comment>

5. For correlation, significant results are easy to obtained once the sample size is large. The authors may comment this issue in Discussion.

<Our response>

We agree with the Reviewer that the large sample size of this study allowed even weak correlations between certain QOL factors and liver functions to be identified with statistically significant p-values. To address this issue, we defined those correlations with rho ≥0.3 or ≤-0.3 to be the ones that could be regarded as potentially clinically important. Based on this approach, a number of QOL factors showed significant correlations with ln(ALT level) and ln(ALP-to-platelet ratio), but the magnitudes of these Spearman’s rho were too weak and were thus considered not to be clinically important. On the other hand, a number of liver function variables, namely ln(albumin level), ln(bilirubin level), ln(ALP) and ln(albumin-to-ALP ratio), showed potentially clinically important correlations with QOL.

Please refer to the Methods section, page 11, lines 7-9; the Results section, page 12, line 12 to page 16, line 5; and the Discussion section, page 20, lines 6-15.

<Reviewer 1’s comment>

6. This is a cross-sectional study. Did the authors conduct any follow up? Both QOL and liver condition may change during treatment.

<Our response>

We did not conduct follow up reassessments of liver function and QOL. We agree that these data could be very valuable, since correlation analyses between QOL and liver function at later time-points may provide further information on the relationships between liver function and QOL. Future studies with longitudinal follow-up are warranted. We regarded this as a limitation of the current study and this has been discussed in Discussion section, page 20, lines 11-15.
7. The value of this study is also to be discussed. QOL and clinical or lab data are of different concepts and measurement constructs. What do the authors want to tell the readers?

<Our response>

QOL has gained increasing attention in HCC patient management; specifically, improving patients’ QOL has become an important goal to clinicians. Most phase III clinical trials in HCC patients reported QOL as one of the main study endpoints (references 34-38). QOL in HCC patients is known to be related to the tumor severity and treatment toxicity. The current study reported potentially clinically important correlations between QOL and liver function in HCC patients. The study findings highlight to clinicians the relevance of liver function in addition to tumor burden to QOL among HCC patients. Along with HCC tumor per se, liver functional impairment may be the result of other co-existing conditions including viral infections and biliary obstruction. Interventional treatments, by means of anti-viral drug administration and radiological or surgical biliary drainage respectively might improve liver function and have positive impact on QOL of HCC patients. We believe future trials are warranted to assess whether treatment to enhance liver function could improve QOL.

Please refer to the Discussion section, page 20, line 16 to page 21, line 7; and References 34-38.

Comments from Reviewer 3 (Statistical Reviewer):

<Reviewer 3’s comment>

The manuscript entitled “The association of liver function and quality of life of patients with liver cancer” presents correlation analyses between a few quality-of-life (QOL) parameters and a few liver functions in the patients having Hepatocellular carcinoma (HCC), a common type of liver cancer. The authors briefly describe the QOL parameters and the liver function parameters in tables. They also briefly describe the association studies done elsewhere and the importance of such relationship in the overall survival of the patients with HCC. After the study, the authors were able to observe some association/correlation between the QOL and liver functions. Strength of the manuscript is the large number of subjects in the study and weaknesses are the statistical analysis and English write-up. Appropriately revised manuscript can be interesting to some people working in the area of HCC.

REQUESTED REVISIONS:

1. The statistical analysis part of the manuscript is very weak. The authors have wrongly mentioned that T-test was used to assess the correlation. T test does not measure the correlation. T-test is used to assess the difference in mean scores between the two groups. The way it is presented in the manuscript, it looks like a few liver functions were dichotomized and the two sample T-test was used to assess the difference in the QOL scores between the two groups of liver functions. However, the rationale of such dichotomization should be presented. For
example, why child class was grouped as A vs B+C, ALBI grade was grouped as G1 vs G2+3 etc. Alternatively, the comparison of the QOL scores can be done for more than two groups using One-way ANOVA or Kruskall Wallis test.

<Our response>

We have performed univariate logistic regression to evaluate the correlations between continuous QOL variables and dichotomized liver function variables as suggested. The Methods and Results sections have been clarified accordingly.

Please refer to the Methods section page 10, lines 15-16, page 11, lines 1-2. Please also refer to the Results section, page 16, line 7 to page 18, line 16; and Table 5.

We dichotomized the categorical liver function variables by applying the principle of separating patients into those who had normal versus those who had abnormal liver function subgroups, so that the analyses would carry clinical meaning. For example, patients of Child’s class A (normal liver function group) were analyzed against patients of classes B and C (abnormal liver function group). Likewise, ALBI was dichotomized into grade 1 (normal) and grades 2 and 3 (abnormal); MELD was dichotomized into grade 1 (normal) and grades 2 and 3 (abnormal).

Please refer to the Methods section, page 10, lines 11-16; and Tables 5-6.

<Reviewer 3’s comment>

2. Next, a large number of pairwise comparisons were done and presented in the manuscript. However, no multiple testing adjustments are done. The type I error increases as number of comparisons increase and therefore appropriate adjustments are required before drawing any interpretations. There are several methods to do that e.g. Bonferroni method, Benzamini and Hochberg's FDR method etc. This will help in controlling false positives.

<Our response>

We have performed multivariate logistic regressions to adjust for baseline clinical variables. QOL remained significantly correlated with Child-Pugh class, ALBI grade and the presence of ascites. The Methods, Results and Discussion sections have been revised.

Please refer to the Methods section, page 10, line 16 to page 11, line 2. Please also refer to the Results section, page 16, line 7 to page 18, line 16; the Discussion section, page 19, lines 7-9; and Table 6.

<Reviewer 3’s comment>
3. The authors talk about overall survival (OS) but there is no analysis or discussion presented in the manuscript about any survival analysis. Perhaps, survival analysis is out of scope of this manuscript.

<Our response>

We apologize for the confusion in this report. Liver function variables and QOL are established independent prognostic markers for OS in HCC patients. The objective of this cross-sectional study was to look for potential correlations between QOL and liver function in treatment-naïve HCC patients. The description of overall survival in the Methods and Results sections were originally intended to show the robustness of the data but might have created ambiguity about the study design. As a result, we have amended this part in the manuscript to maintain focus and clarity of the manuscript.

Please refer to Methods section, page 10, line 2 and 8; and the Results section, page 12, line 10.

<Reviewer 3’s comment>

4. In the results section, authors have simply described the large number of correlations in words. It would be helpful to the readers if the authors present the selected important results in the form of figures and diagrams. For example, the comparison across the groups can be presented with boxplots, and comparison of the continuous variables with scatter plots with trend lines on them.

<Our response>

We thank the Reviewer for the suggestion. We have now generated representative scatter plots to provide graphical description of the results as suggested.

Please refer to Figures 1-4:

Figure 1 shows the scatter plot of HCC18 index-score against ln(albumin level)

Figure 2 shows the scatter plot of HCC18 index-score against ln(bilirubin level)

Figure 3a shows the scatter plot of C30 index-score against ln(alkaline phosphatase level)

Figure 3b shows the scatter plot of HCC18 index-score against ln(alkaline phosphatase level)

Figure 4a shows the scatter plot of C30 index-score against ln(albumin to alkaline phosphatase ratio)

Figure 4b shows the scatter plot of HCC18 index-score against ln(albumin to alkaline phosphatase ratio)
<Reviewer 3’s comment>

5. There are several grammatical errors throughout the manuscript. At some places, it is very hard to understand what the authors mean. Professional English language edit is required to improve the manuscript.

<Our response>

The language of the manuscript has been improved with grammatical corrections highlighted and areas within Background and Discussion have been rewritten to be easier to read.