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
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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 6th Feb. 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 highlighted).

Thank you.

Yours sincerely,

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Comments from Reviewer 1:

<Reviewer 1’s comment>

The manuscript improved a lot after revision. There is one thing for the authors to clarify:

In the logistic regression, what does it mean by the OR? Were the outcome variables binary? How did the authors cut the continuous variables like physical functioning, etc.? (Tables 5 and 6). We also need the authors' interpretation of the ORs obtained in the two Tables. This part is new in the revision. We may need a statistician's comments.

<Our response>

Univariate and multivariate logistic regressions were newly added as suggested by the Statistician Reviewer in last revision. Logistic regressions, instead of t-tests, were employed to assess the correlations between continuous QOL variables and categorical liver function variables e.g. Child’s class, presence of ascites etc. Odds ratio in logistic regressions refers to the ratio of the odds of having abnormal liver function against having normal liver function in patients with higher QOL score compared to lower QOL score. As an example, in multivariate logistic regression results for Child’s B/C in Table 6: the OR for QLQ-C30 ‘physical functioning’ was 0.987, this means for every 1 score increase (better score) in ‘physical functioning’, there was 1.3% reduction in chance of the patients to be in Child’s B or C class; whereas the OR for QLQ-HCC18 ‘abdominal swelling’ was 1.012, this means for every 1 score increase (worse score) in ‘abdominal swelling’, there was 1.2% increase in chance of the patients to be in Child’s B or C class. If odds ratio is less than 1, the chance of the patients belonging to poorer liver function group is lower; if odds ratio is more than 1, the chance of the patients
belonging to poorer liver function group is higher. Additional explanations of the odds ratios were added in the Methods sections.

Please refer to the Methods section, page 11, lines 1-3; and Tables 5 to 6.

We did not dichotomize any QOL variable; therefore all QOL variables remained continuous data. We did dichotomized categorical liver function parameters into normal versus abnormal liver function groups for logistic regression analyses as described above, e.g. Child’s A being the normal liver function group versus Child’s B&C being the abnormal liver function group.

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

Comments from Reviewer 3 (Statistical Reviewer):

< Reviewer 3’s comment>

The authors have collected quality of life (QoL), demographic, clinical and laboratory data to examine the relationships between these variables. This is a straightforward design that should allow the study objective to be addressed.

A large number of correlation coefficients are conducted along with regression analyses. In general, these statistics are appropriate, although the authors need to address some of the assumptions and decisions they make (as noted below). Also, it is possible for the authors to conduct biserial correlations rather than univariate logistic regressions, but one is not more correct than the other, so it is a matter of personal preference.

REQUESTED REVISIONS:

It would be useful to know if all of the data was collected for the same time period. In particular, it could be the case that the laboratory data represents results of samples that were taken some time before quality of life data was collected, so they might not represent patient data at the same points in time.

<Our response>

Every patient had QOL assessment and blood tests to collect laboratory data on the same day upon entering the study. We have clarified this point in the Methods section.

Please refer to the Methods section, page 9, line 18 and page 10, lines 3-4.
In the statistical analysis section the authors state that QoL variables that had p values less than 0.0001 in univariate logistic regressions were included in multivariate logistic regression. Yet, no justification is provided for choosing variables based on this p value. Choosing variables based on a p value alone is generally a poor idea, especially when many statistical tests are being conducted, as there is the potential to inflate the Type I error rate. Therefore, selecting variables based on a justified effect size would be more appropriate.

<Our response>

Thank you for pointing this out. We realized that the statistical description for the multivariate logistic regression was mis-conveyed and we apologize for the confusion created.

The following is the actual regression that was performed: factors with p-value less than 0.05 were entered into multivariate logistic regression model with stepwise selection.

Since this was the first exploratory analysis of correlations between QOL and liver function, there was no prior information to guide how large the effect size would be meaningful; we did not select variables based on effect size. We had, however, reported the measures of effect size (the odds ratios) and 95% confidence intervals to provide estimates of the magnitude of the effect and to quantify the uncertainty around these estimates.

Please refer to the Methods section, page 10, line 16 to page 11 line 4; page 11 lines 6-7; and Tables 5 to 6.

<Reviewer 3’s comment>

The authors indicate that they transformed liver function variables to meet the assumption of normality but for which test? It seems that these transformed variables were used in Spearman's rho and logistic regression tests, so why did the authors assume that normality was required? Also, if transformations were deemed appropriate for liver function variables, why were they not also conducted for the QoL variables?

<Our response>

We agree with the Reviewer that Spearman’s correlation does not require normally distributed variables for analyses. In our initial submission we performed Pearson’s correlation analyses between continuous QOL factors and continuous liver function variables, thus we performed natural logarithm for the liver function data for transformation into normal distribution. In last revision, another Reviewer commented Spearman’s correlation analysis would be more appropriate since not all QOL factors were normally distributed. We therefore reanalyzed the existing continuous liver function and QOL variables using Spearman’s correlation. Therefore this statement of the requirement of normality has now become obsolete and has been deleted from the Methods section.
All the logistic regression analyses involved only categorical liver function variables. These variables were dichotomized into normal liver function groups (e.g. Child’s A) and abnormal liver function groups (e.g. Child’s B&C) as a clinical distinction before correlation analyses with QOL variables were carried out.

Please refer to the Methods section, page 10, lines 11-16; and page 11, lines 4-6.

<Reviewer 3’s comment>
Correlation values greater than an absolute value of 0.3 were determined to be clinically important. This decision requires further justification, especially as it affects the interpretation of findings.

<Our response>
In last revision, another Reviewer pointed out that with large sample size even very weak correlations were found to have significant p-values, and such weak correlations might not be meaningful. In response to that and to facilitate results interpretation, we had set a minimal threshold in correlation coefficient of ≥0.3 to be qualified for potentially meaningful correlation. This threshold of 0.3 appeared to be an agreed minimum degree of correlation to be considered potentially meaningful by various reported literatures. We therefore have adopted this approach and have now supplemented the relevant references to justify this.

Please refer to the Methods section, page 11, line 8; and References no 34-37.

<Reviewer 3’s comment>
There is no need to report statistics (such as correlation coefficients and p values) to 4 decimal places - 2 decimal places is sufficient and you should not go beyond 3 decimal places.

<Our response>
The results have now been transformed according to the suggestion; they are now within 2 to 3 decimal places.

Please refer to the Results section, page 13, line 7; the Discussion section, page 17, line 11; and Tables 4 to 6.

<Reviewer 3’s comment>
The results of the correlation analyses are presented in detail in the text. This is unnecessary as the information is also presented in tables. Rather, a concise summary could be presented in the text.
<Our response>

We have rewritten the Results section into a concise summary as suggested.

Please refer to the Results section, page 12, line 12 to page 16, line 8.