Author's response to reviews

Title: Type and etiology of liver cirrhosis are not related to the presence of hepatic encephalopathy or health-related quality of life: a cross-sectional study

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Author's response to reviews:

Dear Dr Bucceri,

Thank you for giving us the opportunity of submitting a revised version of our manuscript entitled “Etiology of liver cirrhosis does not influence the severity of hepatic encephalopathy: a cross-sectional study” (MS: 1089327607214200). We would also like to thank the reviewers for a thorough review of our manuscript. We feel that by following their suggestions we have been able to considerably improve our paper. Changes made in the revised form of the manuscript are underlined. Our point-to-point responses to the questions raised by the referees are as follows:

Reviewer 1

1. The study title has been changed and the word “severity” has been replaced by the word “presence”. Please also see response to point 1 of reviewer 2.

2. The phrase “There are scarce and conflicting data on whether type or etiology of liver cirrhosis could be related to hepatic encephalopathy in patients with cirrhosis” has been added to the Background section of the Abstract.

3. The sentence “Diabetes mellitus…. hepatic encephalopathy” has been eliminated from the Background of the Abstract in the revised form of the manuscript.

4. The places of the two sentences of the Conclusions of the Abstract have been reversed in the revised form of the manuscript. The word “influence” has been replaced with “related to” and “associated with “, please see point 3 of reviewer 2.

5. “Sort” has been replaced by “short” in the 1st sentence of the subsection “Assessment of health-related quality of life” in the Patients and Methods in the revised form of the manuscript.

6. The word “more” has been replaced by the word “less” in the revised form of the manuscript (subsection “Hepatic encephalopathy in alcoholic cirrhosis vs.
cirrhosis due to hepatitis C vs. cholestatic cirrhosis” of the Results).

7. It has been recognized, in recent years, that non-alcoholic steatohepatitis (NASH) might be the underlying condition behind a significant proportion of patients diagnosed with cryptogenic cirrhosis. However, it is difficult to be certain that NASH has been the cause of cirrhosis in the cases it had not been diagnosed prior to cirrhosis development and it is also difficult to exclude an alcoholic etiology in these patients. Thus, patients with cryptogenic cirrhosis (negative extensive investigation regarding possible etiology and no NASH diagnosis prior to cirrhosis development) were excluded. This is further explained in the 1st paragraph of the Patients and Methods in the revised form of the manuscript.

Reviewer 2

1. They title of the study has been changed. Please also see response to point 3 (referee 2) as well as to point 1 of reviewer 1.

2. Diabetes mellitus has recently been reported to be associated to hepatic encephalopathy and neuropsychiatric measurements in patients with cirrhosis (references 5 and 6 of the revised version of the manuscript). On the other hand the prevalence of diabetes mellitus has been shown to differ between patients with hepatocellular cirrhosis (alcoholic or hepatitis C cirrhosis) and cholestatic cirrhosis (reference 7) (which is verified by the results of the current study). Thus, we feel that when investigating the presence of hepatic encephalopathy in hepatocellular vs. cholestatic liver cirrhosis diabetes is an important factor that should be taken into consideration. We have mentioned diabetes mellitus in the Introduction as it was specifically sought in this study. However, we do agree with the reviewer that this could be clarified in the Introduction and therefore we have rearranged the second paragraph in the revised version of the manuscript.

3. The point is well-taken. Since this was a cross-sectional study we can only explore the correlation and not any cause-effect mechanisms between the measured variables. This limitation is discussed in the last paragraph of the Discussion. To clarify this in the revised version of the paper, when defining objectives (last paragraph of the Introduction) the words “effect” and “impact” have been replaced with the word “relation”. Also in the first sentence of the first paragraph of the Discussion the word “effect” has been replaced by the word “relation”. The title has also been changed (please see response to point 1).

4. Several parameters were defined in the current study (age, gender, diabetes mellitus, portal hypertension, severity of liver cirrhosis, etc). Data on these variables are presented in table 1, 2, and 3. It is clear that for example cirrhosis severity or parameters of portal hypertension would be related to hepatic encephalopathy. However, we felt that these factors could not account for the lack of significant differences between the different types of liver cirrhosis as they did not differ significantly in patients with hepatocellular vs. cholestatic disease. These two groups differed only in the presence of diabetes mellitus and therefore
this was analyzed further by comparing patients with and without diabetes mellitus. Patients with alcoholic liver cirrhosis were significantly older and had ascites more commonly than patients with cirrhosis due to hepatitis C or cholestatic disease. However, they did not differ significantly in severity of liver cirrhosis expressed as the MELD or the Child-Pugh score nor did they differ significantly in the prevalence of hepatic encephalopathy from the other groups and thus no further analyses were performed.

5. Unfortunately no power estimation was done before the study was initiated as we intended (and to our knowledge managed) to invite all patients with cholestatic cirrhosis under our care to participate. We appreciate the fact that the 3rd reviewer considers this to be a large study but in the revised version of the manuscript we acknowledge the fact that a type-II error cannot be excluded and that a larger multicenter study might be necessary to fully delineate the role of type/etiology of liver cirrhosis in hepatic encephalopathy. To our knowledge ours is the largest study aiming to determine whether there is any difference in the presence of encephalopathy between patients with cholestatic and hepatocellular cirrhosis. The only two previous studies on this issue had included 123 (reference 3 of the manuscript) and 49 (reference 4 of the manuscript) patients compared to 156 in the current investigation. Also, our results are in accordance with those of a larger study (n= 280, reference 14) regarding the fact that alcoholic cirrhosis is not related to a greater degree of cognitive impairment compared to non-alcoholic cirrhosis.

6. Comparing patients with hepatocellular vs. cholestatic cirrhosis was one of the main aims of the current study particularly in view of the fact that they differ in the proportion of patients with diabetes mellitus (as explained in the 2nd paragraph of the Introduction of the revised version of the manuscript). To clarify this the title of the paper has been changed, the second paragraph of the Introduction has been modified (see also response to point 2), and this has been more clearly mentioned when the objectives of the study are defined in the last paragraph of the Introduction of the revised form of the manuscript. The course of data analysis is further explained in the statistics section of the Patients and Methods of the revised version of the manuscript.

Reviewer 3

1. “More common” has been replaced by “less common”, please also see response to point 6 of reviewer 1.

2. The typographical error in the first sentence of the Conclusion has been corrected.

Yours truly,

Evangelos Kalaitzakis MD, PhD