

January 6, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: rev_Comorbidity in cirrhosis_submitted.docx). Figure 1 is reprinted from our article published in Gastroenterology (Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. Gastroenterology 2013;146:147-156), and Table 2 is adapted from the same article. I have attached the permission to reuse as an 'image file'.

Title: Comorbidity in cirrhosis.

Author: Peter Jepsen

Name of Journal: World Journal of Gastroenterology

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The manuscript has been improved according to the suggestions by reviewers 02540656 and 02540666. Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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Reviewer 02540656:

1. *Indicate the departments and do not duplicate the hospital address.*

Reply: I apologize if I misread the instructions to authors. This has been corrected.

2. Abstract. "Here we review..., and we emphasize..." As there is only one author it should be changed to I...

Reply: This has been changed.

Reviewer 02540666:

The present manuscript has the potential to provide a good overview on the present knowledge on comorbidity in patients with cirrhosis. However the scope of the manuscript should be clearer. This can be achieved by substantial revision. The following comments are meant to serve as suggestions for revision. The manuscript may consist of the following paragraphs

1. *Introduction: A clear overall definition of comorbidity may be followed by something like "Comorbidities may increase mortality in patients with cirrhosis (cirrhotic patients) and are therefore clinically relevant/important. The presence of comorbidity may also be an important source of confounding and should be accounted for in epidemiological studies....."*

Reply: I am following your suggestion.

2. *... followed by a clear description of the difference between comorbidity and complications. The statement of cholangiocarcinoma must be substantiated.*

Reply: The problem is that there is no evidence to determine the causal relationship between cirrhosis and cholangiocarcinoma. Cholangiocarcinoma may be a consequence of cirrhosis, cholangiocarcinoma and cirrhosis may share risk factors, or both. However, I only wanted to exemplify the general problem of determining the causal relationship between cirrhosis and other diseases, so I have deleted the statements about cholangiocarcinoma.

3. *... followed by a clear statement regarding the scope of the manuscript.*

Reply: We have added a paragraph describing the aim of the review (page 3, bottom).

4. *The paragraph “prevalence of comorbidity” is merely a summary of results from the mentioned paper. May be left out or moved somewhere else.*

Reply: The information presented in this paragraph has been moved to the paragraph about the CirCom score.

5. *Comorbidity scoring systems: The first paragraph must be rephrased and line 3 (after diagnosis) => line 8(after second) may be left out. The description of the 3 mentioned scoring systems must be rephrased; A table with the 3 scoring systems and a list of the different diseases included in the score may provide a better overview for the reader. You may also include the adjusted HR for the different diseases.*

Reply: I have rephrased the first paragraph as suggested and included a Table listing the comorbidities included in the three scoring systems.

6. *The Charlson Comorbidity Index; leave out the 17 diseases (avoid “he or she”). The statements on the development or presence of the different diseases mentioned in the four reasons for the suboptimal use of the Charlson Index must be substantiated by references.*

Reply: I have left out the 17 diseases and the “he or she”, and I have added references supporting the reasons why the Charlson Index may be suboptimal among cirrhosis patients.

7. *CCI-OLT score; List the included diseases in a table.*

Reply: I have done as suggested.

8. *CirCom score; How much better is this score? You may mention the external validation of the score.*

Reply: As suggested, the comparison of CirCom vs. Charlson and the external validation are now described.

9. *Know the 3 current scoring systems is described. Which one should we use? and why?*

Reply: I have added a paragraph entitled “Which comorbidity scoring system should be preferred?” that answers these questions (page 7).

10. *Which comorbidities are important in cirrhosis? The author has described 3 scoring systems already to some extent validated in patients with cirrhosis. Why should the reader now consider single comorbidities in the context of cirrhosis? Explain. On what basis is the mentioned comorbidities selected? Elaborate. Since the paragraphs mainly discuss the performance of the Circom score the title for this*

section may be rephrased. Alternatively the performances of the other scoring systems may be discussed. The performance of the different scores may be depicted in a table including HR and the HR can be left out in the text. This will provide a better overview for the reader.

Reply: In the revised manuscript I specify that studies of individual comorbidities will teach us more about the pathophysiology of cirrhosis, and the choice of comorbid diseases is determined by the available evidence (page 7, bottom). Hazard ratios are now shown in Table 2.

11. *Diabetes: Why was diabetes with complications “below the limit”, what limit? Rephrase.*

Reply: I agree that the limit for inclusion into the CirCom score is not important here. I have consequently deleted it.

12. *Cardiovascular disease: The inclusion of CD is only mentioned for the CirCom score. It is included in all the scores. Line 7 (Apart..) to line 10 in this paragraph may be speculation. Must be substantiated or left out.*

Reply: I now also clarify that coronary disease is included in the CCI-OLT. I have also deleted lines 7 to 10 and replaced them with the statement that “...the reasons are unclear.”

13. *Lung disease: Are patients with lung disease more likely not to receive the recommended treatment with beta blockers? Evidence?*

Reply: There is no evidence that patients with lung disease actually receive less beta-blocker treatment, so I have deleted this speculation. Chronic obstructive lung disease is a contraindication to beta-blocker treatment, but I now cite evidence that ligation of varices is an acceptable alternative.

14. *The conclusion may include what we know so far about the area, what scoring system should be used in epidemiological studies and what is yet to be clarified?*

Reply: I have done as suggested and modified the conclusion to answer these questions.

15. *Abstract: Rephrase the first 3 lines. Avoid “he or she”. It is either “cirrhotic patient” or “patients with cirrhosis”.*

Reply: I have done as requested.

16. *The manuscript needs linguistic revision.*

Reply: The manuscript has been revised for language.