

Answer to Reviewer 1's Comments

We would like to thank you for providing invaluable advices regarding our manuscript. We hope we will be able to address your comments properly. Changes appear underlined in the text.

Reviewer 2438768:

Comments for ESPS Manuscript NO 25172 This prospective study investigated the prognostic significance of IGFBP-3 in patients with cirrhosis. This is an interesting study; and this manuscript could provide useful information to readers. There are no major and few minor concerns. Regarding the latter, the format of this manuscript should be revised according to WJG's requirement.

R. As requested, the format was revised.

In addition, the language need to be improved, for example, on page 16, 2nd paragraph, under Discussion, line 12: Change 'supporting its investigation as a...' to 'supporting its utility as a...'.

R. English was revised as suggested and the mentioned sentence was modified.

Reviewer 53746:

The authors investigated the prognostic significance of IGFBP-3 in patients with cirrhosis. They examined IGF beta in two cohorts of patients (compensated and decompensated). They found that lower IGFBP-3 was associated with worse prognosis in both group of patients. Minor comments:

1. It would be interesting to know, if the levels of IGFBP-3 did differ between patients with different aetiology of cirrhosis?

R. There was no impact of etiology of liver cirrhosis on IGFBP-3 levels in both outpatients and hospitalized subjects. This information was included in the results section.

2. The author should explain, how they get the IGFBP-3 cutoff of 0.86 mcg/mL?

R. The best cutoffs of IGFBP-3 for predicting mortality, in both cohorts, were chosen based on the receiver operating characteristics (ROC) curves. This information was clarified in the methods section (Statistical Analysis subsection).

3. Did the IGFBP-3 levels have any prognostic role in the prediction of variceal bleeding?

R. When IGFBP-3 levels of the 27 patients who developed variceal bleeding during follow-up were compared to those who did not, no differences were observed (1.74 mcg/mL vs. 1.69 mcg/mL, $P = 0.478$). This information was included in the results section, subsection "IGFBP-3 in outpatients with stable cirrhosis".

4. Do the author have any idea, what is the relationship between IGFBP-3 levels and the degree of portal hypertension?

R. Unfortunately, we don't have data on HVP measurement. In addition, in our review, we failed to find any study that addressed this issue. However, based on IGFBP-3 biological behavior in patients with cirrhosis, an inverse relationship between these two parameters might be expected.

Reviewer 5986:

1. This study has the aim to investigate the usefulness of serum IGFBP level in clinical practice to assess prognosis in liver cirrhosis. For patients in the stable cirrhosis group, IGFBP level correlates with long term prognosis (25 months), for patients with acute decompensation, it correlates with short term prognosis (80days). This difference should be pointed out more clearly in order to avoid inappropriate use.

R. We modified the conclusions to emphasize this point.

2. Major points: For short term prognosis, a comparison with the MELD score is missing in the paper: MELD is the most widely used, best validated short term prognostic score, and it is not possible to avoid a comparison with it.

R. As suggested, MELD score was analyzed in detail along with Child-Pugh C and ACLF.

3. An important variable that has not been considered is if the disease causing liver cirrhosis is still active or not (e.g., if HCV has been eradicated). This variable is known to be associated to prognosis.

R. We do agree that prognosis in liver cirrhosis can be influenced by several factors, including the status of underlying cause of cirrhosis. However, from a practical point-of-view, it is not possible to control all the variables eventually related to disease activity for all causes of liver cirrhosis. Studies aimed at investigating prognostic tools in cirrhosis usually focused more at the consequences of liver cirrhosis in terms of synthetic dysfunction or indirect markers of hemodynamics changes of cirrhosis. This is the case of the mentioned MELD score. In clinical practice, a good prognostic marker should work appropriately regardless of the cause of cirrhosis. Although it would be of interest to evaluate the impact of the disease status (active or not), the consequence of an active disease is worsening of liver function and that is the focus of the biomarker studied in this paper. We included a sentence addressing this issue in the "limitations paragraph" of the discussion section.

4. The inclusion criteria for the stable disease group must be extended: e.g., patients with extrahepatic active cancer must be excluded.

R. Exclusion criteria for both groups also included: pregnancy; previously known severe extrahepatic diseases (e.g., chronic renal failure requiring hemodialysis, severe heart disease; severe chronic pulmonary disease; and also active extrahepatic cancer). This information was not previously included in the text because no patient with these characteristics was screened for inclusion. It was included now.

5. The majority of the patients in the stable disease group have a history of decompensation, some of them were CHILD B/C. Such patients are not considered as having stable disease.

R. This definition was considered based on several previous studies that used similar characterization. Stable patients were all outpatients without any sign of acute deterioration of their condition. They could be compensated or decompensated. The list below show some recent studies that used the exactly same definition for stable cirrhosis:

Dig Liver Dis. 2015 Dec;47(12):1047-51

Scand J Gastroenterol. 2015 Mar;50(3):347-54

Aliment Pharmacol Ther. 2014 Sep;40(6):705-15

Liver Int. 2015 Mar;35(3):724-34

Hepatology. 2014 Apr;59(4):1514-21

Liver Int. 2014 Jan;34(1):49-57

J Hepatol. 2011 Sep;55(3):574-81

6. The cut-off levels are different according to the group of patients: this makes its use in clinical practice difficult.

R. We agree that a single cut-off would be more practical. However, other prognostic markers such as MELD score and Child-Pugh also had different cut-offs for different clinical context. It is highly unlikely that a biomarker for prognosis in liver cirrhosis show similar performance for stable and acute decompensated patients at the same cut-off. We believe that the separation of stable cirrhosis from acute decompensated patients is a strength of our study exactly because we were able to identify adequate cut-offs for each clinical scenario.

7. Minor points: The first sentence of the Introduction section, which refers to a review on liver cirrhosis published 2008, has to be updated. Cirrhosis is not considered as always irreversible any more.

R. The reference was updated and the sentence changed as suggested.

8. The definition of active alcohol consumption used in the paper was from a trial in a different context (ref #14). It would be better to use a different definition.

R. The assessment of alcohol consumption in clinical studies is very controversial and it is difficult to balance practice and effectiveness in data collection. In this study, we used the thresholds recommended by a panel of experts from the AASLD in the paper "ENDPOINTS AND CLINICAL TRIAL DESIGN FOR NONALCOHOLIC STEATOHEPATITIS" (Hepatology. 2011 Jul;54(1):344-53). The trial was cited because it was the original study in which this definition was included. We changed the citation to the AASLD consensus paper.

9. The diagnostic criteria used to diagnose liver cirrhosis have to be specified.

R. The diagnosis of cirrhosis was established either histologically (when available) or by combination of clinical, imaging and laboratory findings in patients with evidence of portal hypertension. This information was included in the methods section. This criteria is the same of several previous studies.

10. Only propranolol is considered: no patient on carvedilol or nadolol?

R. None of our patients were on carvedilol or nadolol. Propranolol is supplied without any cost by the Brazilian public healthcare system, so it is unusual to see patients taking other beta-blockers in public practice.

11. Why only data on propranolol and PPI therapy were collected, and no data on other medications?

R. For both stable and acute decompensated cohorts data about all medications were collected. We choose to include only propranolol and PPI in the analysis because their potential role in the outcomes of liver cirrhosis.

12. The quality of the English language used should be improved.

R. English was revised as suggested.

Reviewer 71220:

I had the opportunity to review a paper "Circulating insulin-like growth factor-binding protein 3 as prognostic biomarker in liver cirrhosis", and I found very interesting. There is no problem to publish the manuscript.

R. Thank you very much.