

ANSWERING REVIEWERS

December 28, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15223-edited.doc).

Title: Ascites and Alfa-Fetoprotein improve prognostic performance of BCLC for hepatocellular carcinoma

Author: Asmaa Gomaa, Alzhraa AlKhatib, Wael Abdel-Razek, Mohammed Saad Hashem, Imam Waked

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 15223

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. We solicited one of the language editing service suggested by the journal, and had them correct the manuscript for language and grammar. The attached revised manuscript is the output of their editing after we revised the manuscript and incorporated all other comments and modifications. We attach a certificate from the language editing service.
3. Revision has been made according to the suggestions of the reviewers. Our response is in blue below:

1. Reviewer 00068044

We thank the reviewer for his time and for evaluating the manuscript and his valuable comments.

(1) The result part of abstract is not detailed in several locations.

We thank the reviewer very much for his comment. We realized that the format of the abstract needs modification to satisfy the journal requirements. We modified the abstract, expanded the results part, and adhered to the word count thresholds indicated in the format to prospective study.

(2) The BCLC stage include Child-Pugh classification, ascites is a parameter of Child-Pugh classification. Is it appropriate to add ascites as a independent parameters of the BCLC stage?

We thank the reviewer for highlighting this. Although ascites is part of the CTP score, the BCLC categorized patients according to the total CTP score, not according to individual items of the score (including ascites, albumin and bilirubin). Patients in BCLC stage A can be CTP class A or B, with or without ascites. Here we examined whether the presence of ascites in the same CTP score and BCLC stage had an impact on outcome of HCC patients. We had previously reported that the presence of ascites, AFP above 200 ng/ml, portal vein invasion and extra-hepatic spread were independent predictors of survival, and that the BCLC staging system provide the best prognostic stratification for early (stage A) and intermediate (stage B) HCC stages. Presence of ascites and AFP above 200 ng/ml are occasionally encountered in early and intermediate stages of HCC patients, whereas portal vein invasion and extra-hepatic spread assign patients to advanced (stage C) and terminal (stage D) stages, where we found the CLIP score had the highest stratification ability highlighting the importance of including AFP in the best staging system. Hence, we believed that ascites and AFP level may be important independent prognostic parameters in patients with stage A and B HCC (who are all within CTP class A and B). We tried to highlight this in the last paragraph of the discussion.

- (3) *What is the standard to judge clinically detectable large ascites or mild ascites in the study?*
We thank the reviewer for his comment. We followed the EASL guidelines to judge the grades of ascites. Mild ascites is only detectable by ultrasound (grade 1), moderate ascites is evident by moderate symmetrical distension of abdomen (grade 2), while, large or gross ascites is evident by marked abdominal distension (grade 3). In this study, large ascites were assigned to BCLC stage D and excluded from the analysis.
- (4) *Which parameters of the comparative results is " $P < 0.001$ " in table 5?*
We thank the reviewer for this comment. There was a highly significant difference ($P < 0.001$) in survival in the three sub-groups (patients without ascites or elevated AFP > 200 ng/ml, patients with either ascites or elevated AFP > 200 ng/ml, and patients with both ascites or elevated AFP > 200 ng/ml) in either BCLC stage A or B patients. We highlighted this in the footnote of the table in the revised manuscript.
- (5) *What is the possible mechanism of AFP and ascites discriminate patients to subclasses with significantly different prognosis? Can you increase relative mechanisms in the discussion?*
We thank the reviewer very much and we added other relevant mechanisms in the discussion.

2. Reviewer 01852833

- (1) *The figures were poorly made, especially figure 2 and figure 3, the authors should pay attention to improve the quality of them.*
We thank the reviewer very much. We improved the quality of the figures in the revised manuscript.
- (2) *The lack of early stage patients is a shortage, the authors should increase the number of observed patients.*
We thank the reviewer for this comment. Actually, the early stage HCC patients were 496 (about half of the included patients). What is lacking is patients in the "very early" stage, and this is due to the absence of a screening program for HCC in Egypt except in some centers. Most of the patients are discovered outside a screening program, and in late stages.
- (3) *The introduction of the paper is not comprehensive enough, the authors can refer to the other paper [PMIDs: 25074882, 23506690, 24666672]*
We thank the reviewer very much. We added to introduction in the revised manuscript to make it comprehensive. We hope that this is in accordance with the reviewer's requirements.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Asmaa Gomaa

Asmaa Gomaa, MD

Hepatology Department

National Liver Institute

Menoufiya University

Shebeen El-kom, Menoufiya, 32111 Egypt.

Fax: +20-48-2234586

Email: aibrahim@liver-eg.org