

October , 2014

Dear Editor,

Thank you for reviewing our manuscript and inviting revision. We are resubmitting our manuscript after making a new version according to your recommendations. Please find enclosed the edited manuscript in Word format (file name: 13238-review.doc). Revised contents were written in Red.

Title: Diagnostic value of PIVKA-II and AFP in Hepatitis B Virus-associated hepatocellular carcinoma

Author: Seung In Seo, Hyoung Su Kim, Won Jin Kim, Woon Geon Shin, Doo Jin Kim, Kyung Ho Kim, Myoung Kuk Jang, Jin Heon Lee, Joo Seop Kim, Hak Yang Kim, Dong Joon Kim, Myung Seok Lee, Choong Kee Park

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13238

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
We revised the manuscript as one reviewer's comments.

Major comments

The manuscript was written with precision, objectivity and clarity. Only minor language polishing is required. (1) The research is important and the research findings are significant (2) The novelty and innovative nature of the research is acceptable because there other similar reports but this one depicts an interesting number of patients. (3) The manuscript's presentation and readability are adequate. (4) The ethics-related aspects of the research have been addressed by the author's declaration.

Answer) Thank you for your comment.

Minor comments

1) Major concerns; The comparison between the three groups of patients revealed that there were statistical significant differences in several basal parameters (age, gender, biochemical parameters) behind AFP and PIVKA-II. An alternative mode for comparison should be carry out by stratifying the patients according the coincidence (total or partial), or alternatively difference (total o partial) between AFP and PIVKA-II cut-off values. Hence four groups could be advised according to median levels such as: normal/normal; normal/elevated; elevated/normal; elevated/elevated.

Answer) Thank you for valuable comments. Total patients were divided by 3 groups: 1) non-cirrhotic chronic hepatitis B (CHB), 2) cirrhosis without hepatocellular carcinoma (HCC) and 3) HCC. Thus, the baseline characteristics were different significantly according to disease status. As your comment, we grouped total patients by optimal cut-off values of PIVKA-II and AFP that calculated from ROC curve for differentiating HCC from nonmalignant CHB. We added this result to page 10 of RESULT and Table 2 in page 24. However, the baseline characteristics were different significantly when grouped by cutoff-values of PIVKA-II and AFP.

2) No data about HBV infection, cirrhosis, HCC treatment were mentioned.

Answer) Thank you for your comment. We enrolled 1255 patients with chronic hepatitis B. Our aim was to determine the optimal cutoff values of PIVKA-II and AFP for differentiating HCC from nonmalignant CHB and to compare the diagnostic role of AFP and PIVKA-II. Hence, we obtained the laboratory data at the time of diagnosis of HCC and we did not investigate about the treatment. Unfortunately, we could not present the accurate information about the treatment of HBV infection, cirrhosis and HCC. Roughly speaking, 50% of patients with nonmalignant CHB received antiviral therapies like lamivudine, adefovir, entecavir and tenofovir. In addition, approximately 50% of total patients with HCC were treated by transarterial chemoembolization (TACE) and the remainder of patients were treated by operation, radiofrequency ablation (RFA), liver transplantation or sorafenib. I wish your considerate understanding about this.

3) No data about severity of liver damage was scored (MELD ?)

Answer) Thank you for your kind attention. As your recommendation, we supplemented the MELD score to Table 1 and Table 2 (See page 23, 24) and page 7 of MATERIALS AND METHODS.

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*. We are looking forward to hearing a positive reply from you shortly.

Sincerely yours,

A handwritten signature in black ink, consisting of several fluid, connected strokes that form a stylized, cursive shape.

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