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March 26, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6835-revised.doc).

**Title:** Noninvasive assessment of liver fibrosis in patients with chronic hepatitis B

**Author:** Masaru Enomoto, Hiroyasu Morikawa, Akihiro Tamori, Norifumi Kawada

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6835

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**

**Responses to Reviewer #00007392**

1) Authors stated that serum markers can be influenced by comorbid conditions. Please explain more in detail using references. Severe hepatitis, hyperbilirubinemia, alcohol consumption and hemolysis may be important factors to affect the results of several algorithms.

→As the reviewer stated, severe hepatitis, hyperbilirubinemia, alcohol consumption, and hemolysis can affect the results of several algorithms by influencing the levels of serum markers including aminotransferase, bilirubin, GGT, and haptoglobin. We have discussed this important issue in the revised paper (page 7, lines 6–9). Thank you for your valuable suggestions.

2) Some texts are same as previous reports without citation (reference). For example, the text in page 6,

line 15-17 is exactly same to the text in reference 25. It may be unfavorable. Some consideration is needed.

→We have modified these sentences (page 8, lines 3–4).

3) Authors showed the result of Boursier's study (ref.25). However, this study did not focused on the result in patients with chronic hepatitis B. Authors should mention this point.

→Indeed, Boursier's study included not only patients with chronic hepatitis B but also patients with various other chronic liver diseases. We have mentioned this point in the revised paper (page 8, line 6).

4) Page 10; Authors stated on the issue of assessing the clinical stage of disease. However, the association between this issue and the aim of this review is somewhat difficult to understand.

→As the reviewer feels that the issue of *assessing the clinical stage of disease* does not fit the aim of this review article, we have shortened the corresponding section (page 12). We are willing to delete the section entirely if the editor agrees that we should do so.

5) Authors stated that liver biopsy can cause death (page 4). Please indicate the reference, if possible.

→The mortality rate associated with liver biopsy in large studies reported in this century ranged from 0 to 0.14% (typically 0.01%). We have cited two relevant papers [5,6] in the revised manuscript.

>Huang JF, Hsieh MY, Dai CY, et al. Gut. 2007 May;56(5):736–7.

>Myers RP, Fong A, Shaheen AA. Liver Int. 2008 May;28(5):705–12.

6) Conclusion is relatively long.

→We have shortened the Conclusion (page 15).

7) Please check the following words; ROC (in text) vs. AUROC (in Table 1). platelet count and platelets (in Forns index in Table 1).

→In the revised manuscript, the area under the receiver operating characteristic curve has been abbreviated as AUROC throughout the manuscript. The parameter "platelets" (in the Forns index in Table 1) has been changed to "platelet count."

### **Responses to Reviewer #00012516**

1) I noticed that the authors listed the biomarkers and transient elastography and their AUROC. However, these are still confusing. I need a definitive cut-off index, with this in each

marker/technique, I can get the sensitivity, specificity.

→We have added the cut-off index, sensitivity, and specificity to Tables 1 and 2 of the revised paper. Thank you for your valuable suggestions.

2) What about other techniques? Such as acoustic radiation force impulse, real-time tissue elastography and magnetic resonance elastography etc.

→Limited data are available regarding the usefulness of acoustic radiation force impulse, real-time tissue elastography, and magnetic resonance elastography in patients with chronic hepatitis B.

3) As the authors said, liver biopsy has been considered the “gold standard” for diagnosing chronic liver disease, grading necroinflammatory activity, and staging liver fibrosis. When assessing the diagnostic accuracy of various noninvasive tests, liver biopsy has to be a standard, the review also should choose the papers with liver biopsy.

→As the reviewer stated, liver biopsy must remain the standard because of conflicting data regarding the reliability of noninvasive alternatives especially in chronic hepatitis B. Furthermore, liver biopsy can provide information on necroinflammatory activity, steatosis, and iron deposition as well as on the degree of fibrosis. We have chosen two papers [3,4] concerning liver biopsy: one is the AASLD guideline on liver biopsy and the other is a review article about the utility of biopsy in chronic hepatitis B.

>Rockey DC, Caldwell SH, Goodman ZD, et al. Hepatology. 2009 Mar;49(3):1017–44.

>Mani H, Kleiner DE. Hepatology. 2009 May;49(5 Suppl):S61–71.

4) There are many English errors the authors need to pay more attention: The mean liver stiffness values obtained by ARFI were shown by Sporea et al. [48] to be similar between patients with chronic hepatitis B and those with chronic hepatitis C for the same stage of fibrosis. Should be: Sporea et al showed: the mean liver stiffness values obtained by ARFI were similar between patients with chronic hepatitis B and those with chronic hepatitis C for the same stage of fibrosis. [48] The harder the tissue is, the faster the shear wave spreads You don't have to parallel here. The sentence will be better without “is”

→We agree. We have changed the sentences in accordance with the reviewer's suggestions (page 10, lines 3–4 and 8–10). We uploaded a recommendation letter from a professional English language editing company when resubmitting the paper.

### **Responses to Reviewer #00185907**

1) Needs little language corrections by a native English speaking person.

→We used a copyediting service provided by a professional English language-editing company and uploaded a recommendation letter from the company when resubmitting the paper.

### **Responses to Reviewer #002860516**

We thank the reviewer for accepting our article.

### **3 References and typesetting were corrected**

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

A handwritten signature in black ink, appearing to read 'Norifumi Kawada', is written over a horizontal line.

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