

Format for ANSWERING REVIEWERS



September 8, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4908-review.doc).

Title: Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

Author: Yoshio Sumida, Atsushi Nakajima, Yoshito Itoh

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4908

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

Reviewed by 00504699

Very well done. I only found one minor typographic error on page 10 line 11 states:

"degeneration of hepatocytes; and type 4, type 3 and Mallory-Denk bodies or fibrosis."

should read: "degeneration of hepatocytes; and type 4 Mallory-Denk bodies or fibrosis."

Otherwise this is a very thorough and well thought out review.

Answer: The sentence " type 4, type 3 and Mallory-Denk bodies or fibrosis." was replaced by the sentence "type 4, type 3 plus Mallory-Denk bodies or fibrosis." (revised manuscript, page15, last paragraph- page 17, line 10).

Reviewed by 02462531

In the present review, the authors focus on the limitations of liver biopsy and on the potential noninvasive strategies for the detection of NASH. Overall the manuscript addresses a very important topic, which has been largely reviewed in recent publications.

Major points

1. One the major issues inherent in this paper is its limited novelty. Many excellent review have already addressed the topic of noninvasive diagnosis of NASH (see Clin Liver Dis. 2012 Aug;16(3):567-85; Hepatology. 2011 Jan;53(1):325-35; Curr Med Chem. 2011;18(5):725-32). These papers should be cited and the points of novelty inherent in these papers explicitly highlighted.

Answer: In agreement with you, suggested papers were cited (revised manuscript, page, line). To highlight novelty of our manuscripts, the sentence "Several extensive reviews from western countries already discussed noninvasive diagnostic methods for NASH or advanced fibrosis^[44-46].However most of these papers described a simple enumeration of noninvasive tests. Thus, we here review biomarkers or scoring systems with critical appraisal in order to establish diagnostic algorithms which can be applicable even for Asian patients with NAFLD in clinical practice." was inserted (revised manuscript, page20, line1-5).

2. The statement that "A combination of these scoring systems is expected to contribute to the establishment of a noninvasive diagnostic method for NASH" is questionable; such systems are difficult to implement even when used alone, so it is unlikely that different scoring systems may be efficiently combined.

Answer: In agreement with you, the sentence "A combination of these scoring systems is expected to contribute to the establishment of a noninvasive diagnostic method for NASH." was deleted in the abstract.

3. Concerning the diagnostic algorithm for NAFLD, the authors should Rafiq N, Younossi

ZM. Nonalcoholic fatty liver disease: a practical approach to evaluation and management. Clin Liver Dis 2009;13:249–66. PMID: 19442917.

Answer: In agreement with you, we cited and discussed the reference: Rafiq N, Younossi ZM. Nonalcoholic fatty liver disease: a practical approach to evaluation and management. Clin Liver Dis 2009;13:249–66. PMID: 19442917. (revised manuscript, page , line) (revised manuscript, page26, line 1-5)

4. One of the most reliable biochemical test for distinguishing NASH from simple steatosis is CK-18. Although this issue is briefly mentioned, the authors should expand this point and refer to Clin Chim Acta. 2011 Nov 20;412(23-24):2031-6 and Hepatol Res. 2013 Jul 9. doi: 10.1111/hepr.12197.

Answer: In accordance with your suggestion, we cited and discussed suggested papers (revised manuscript, page31, line5-9).

5. Please proof the manuscript because there are several typos.

Answer: we checked spelling.

Minor points

1. Consider replacing "NAFL" with "simple steatosis".

Answer: In accordance with your suggestion, “NAFL” was replaced by “simple steatosis” throughout the revised manuscript.

2. Please replace "gender" with "sex" (see CMAJ. 1997 June 15; 156(12): 1695)

Answer: In accordance with your suggestion, “gender” was replaced by “sex” throughout the revised manuscript.

For the authors:

1) P.5. Consider clarification or commitment of the phrase “lifestyle related diseases”.

Answer: The phrase “lifestyle related diseases” was replaced by “metabolic syndrome”(revised manuscript, page8, line4-5).

2) According to the title, the main purpose of the article is to review the limitation of invasive and non-invasive methods in diagnosis of steatohepatitis. Thus, the diagnostic scores for the evaluation of NAFLD should be minimized in order to avoid confusion. Otherwise, consider modification of the title.

Answer: In accordance with your suggestion, the title was changed into “Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis”

3) P9. For the paragraph with references #20 and #21 provide exact numbers with statistics, instead of words “highly consistent” and “high”. Let the reader make their own conclusions about the significance of data.

Answer: In accordance with your suggestion, we showed kappa values (revised manuscript, page13, last paragraph-page14, 1st paragraph).

4) Check the tables’ order: Table2 is referred in the text after Table 3

Answer: In accordance with your suggestion, we made tables’ order appropriate.

5) P.13. Last paragraph. The last sentence is unnecessary

Answer: In accordance with your suggestion, the last sentence “In this section of the review, identification of NASH with advanced fibrosis.” was deleted

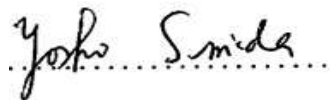
6) Figure 1 is not mentioned in the text manuscript, but twice following the text (p.24 and p.36)

Answer: In accordance with your suggestion, p.24 was deleted and figure legends were moved into the text (revised manuscript, page 32, line 1-4).

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink that reads "Yoshio Sumida". The signature is written in a cursive style and is positioned above a horizontal dotted line.

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