

## Format for ANSWERING REVIEWERS

9, Jan, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 7418-review.doc).

**Title:** A simple scoring system for predicting cirrhosis in nonalcoholic fatty liver disease

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

**ESPS Manuscript NO:** 7418

Thank you for your letter concerning the above-mentioned manuscript. I received your letter on 17-Jan-2013, and I have revised the manuscript accordingly. I am pleased to note the favorable comments of the reviewers and have made the necessary corrections, as described in detail on the following pages. In addition, I received some comments and suggestions from reviewers and have addressed these as thoroughly as possible.

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

Thank you very much for your useful suggestions. That have been addressed in the revised manuscript, which we feel is now greatly improved as a result.

(1) Since the cohort of the patients with cirrhosis is significantly under represented ( about 4%), I assume that the majority of cirrhotics were identified with imaging studies instead and never undergone a liver biopsy.

Thank you for your useful suggestion. We apologize for our confusing statements. As you pointed out, patients with cirrhosis are represented about 4% in our cohort. Actually, Stuart McPherson et al previously reported patients with NASH-related cirrhosis is 9% (13/145) in their cohort, and there is extremely little NASH with cirrhosis among overall cohort (Stuart McPherson et al. Gut 59:1265, 2010). In addition, we performed liver biopsy under ultrasound guidance for all NAFLD patients and diagnose cirrhosis by using the NASH Clinical Research Network (CRN) scoring system, which diagnose the stage of fibrosis. Actually, we identified stage 4 as cirrhosis according to CRN scoring system.

Therefore, we proved cirrhosis by using liver biopsy, but not imaging studies. Therefore, we showed the above contents in the methods section (page 7, line 8 to 21. MATERIALS AND METHODS section) .

(2) Thus the cut offs of such high values and almost close to normal range were over represented in the cohort. In a sense it is very less likely in a clinical practice to find a patient with moderate or advanced fibrosis with such close to normal values.

Thank you for your useful suggestion. As you pointed out, it is an important question that it is very less likely in a clinical practice to find a patient with moderate or advanced fibrosis with such close to normal values. However, in our previous study, the platelet count was higher in patients with NAFLD-related severe fibrosis or cirrhosis than that in patients with HCV-related severe fibrosis or cirrhosis (Mawatari et al. J Gastroenterology 47:606, 2012). In addition, Kaneda et al reported that a cut-off value of  $16 \times 10^4/\mu\text{L}$  for platelet count was an independent predictor of cirrhosis in patients with NAFLD (Kaneda et al. Journal of Gastroenterology and Hepatology 21:1459, 2006). Furthermore, albumin and AST/ALT ratio as well as platelet count show the cut offs of high value and close to normal range. As you pointed out, to diagnose NAFLD-related cirrhosis by using only one variable with close to normal value may appear false positive to find patients with cirrhosis in a clinical practice. Thus, we propose the PLALA score, which is combined these three variables (platelet count, albumin and AST/ALT ratio), to predict cirrhosis. We indicated that the PLALA score of 2 or 3 points is highly diagnostic performance for NAFLD-related cirrhosis.

(3) Also we are in an age that are not devoid of multiple scoring systems that all have their limitations.

As you pointed out, a variable of age is used for major scoring systems, such as FIB4 score and NAFLD fibrosis score to diagnosis fibrosis. Actually, in our study, we showed that age was significantly higher in patients with NAFLD with cirrhosis (fibrosis stage 4) than that in patients with NAFLD without cirrhosis (fibrosis stage 0–3), by univariate analysis ( $P < 0.0001$ ) (Table 2). However, multiple logistic regression analysis by using age, AST/ALT ratio, serum ChE, albumin, hemoglobin, platelet count, hyaluronic acid, and type IV collagen 7s domain, which was significantly different between patients with or without cirrhosis in univariate analysis, showed that age was not an important factor for identifying cirrhosis in our study ( $P = 0.2610$ ). Therefore, the PLALA score is composed from platelet count, Alb, and AST/ALT ratio.

3 References and typesetting were corrected

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

Sincerely yours,

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