

Format for ANSWERING REVIEWERS



December 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14993-review.doc).

Title: Non-invasive methods for the diagnosis of nonalcoholic fatty liver disease

Author: Marianthi Papagianni, Areti Sofogianni, Konstantinos Tziomalos

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 14993

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

Reviewer 02521807

This review from Papagianni M et al., is extensive and involves many different non-invasive strategies for the diagnosis of nonalcoholic fatty liver disease. They enumerate several approaches for serological and imaging-based techniques and they consider during their discussion the parameters involved on each valuation and for most of them, their statistical significance by ROC curves. Major observations: 1. In order to be able to evaluate the different approaches with their pros and cons, it would be interesting to include at least one Table for each field (serology and imaging) as well as differentiating when algorithms are considered. 2. Please indicate by the first time the meaning of the abbreviation (FIB-4; UV, etc) to facilitate the readability.

We added one table for serology and one table for imaging. We also indicate by the first time the meaning of the abbreviation.

Reviewer 02527608

The ultrasound and the FIB-4 score are probably the most appealing methods for detecting steatosis and for distinguishing NASH from simple steatosis, respectively. Can they more detail to describe the sensitivity and specificity under these two methods?

We added in the last paragraph of page 9 "In the above-mentioned studies, the sensitivity and specificity of a cut-off value of 1.30-1.45 of the FIB-4 score for detecting advanced fibrosis was 74-90 and 64-88%, respectively, whereas a cut-off value of 3.25 had sensitivity of 26-40% and specificity of 95-100%^[46-49]." We also added in page 13 "In a recent study in 79 patients (21 with NAFLD) who underwent both US and liver biopsy, the sensitivity and specificity of the US for detecting macrovesicular steatosis \geq 5% of total hepatocyte area were 82 and 100%, respectively, but the sensitivity and specificity for detecting microvesicular steatosis were only 59 and 74%, respectively^[61]. In patients with steatosis \geq 20% of total hepatocyte area, sensitivity increased to 96% for macrovesicular steatosis but only to 67% for microvesicular steatosis; specificity decreased to 98 and 66%, respectively^[61]. In contrast, a larger study in 94 patients with NAFLD reported an AUROC of 0.98 of US for detecting steatosis; the sensitivity and specificity was 92 and 100%, respectively^[64]. In a meta-analysis of 49 studies (n = 4,720), US had an AUROC of 0.93 for detecting steatosis; the sensitivity and specificity was 85 and 94%, respectively^[65]. Moreover, in 5 small comparative studies

(n = 215), US was as accurate as computed tomography (CT), magnetic resonance imaging (MRI) and MRS for detecting steatosis and had a sensitivity and specificity of 94 and 80%, respectively^[65]."

Reviewer 00181532

In the manuscript, the authors reviewed the current knowledge on the non-invasive diagnostic tests for NAFLD. The manuscript is well written. However, I would like to suggest the following to improve the readability of the article. 1. At the end of each section, the authors can add a short summary of the findings described. 2. The authors can add a few Tables to summarize the different diagnostic tests described in text.

We thank this Reviewer for stating "The manuscript is well written". At the end of each section, we added a short summary of the findings described. We also added one table summarizing the serologic markers and one table summarizing the imaging methods.

3 References and typesetting were corrected

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

Sincerely yours,



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