

Dear Editor;

25.11.2014

Name of journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13814

Importance of imaging and recent developments in diagnosis of non-alcoholic fatty liver disease

Enclosed is the revised version of our manuscript entitled "**Importance of imaging and recent developments in diagnosis of non-alcoholic fatty liver disease**" (Manuscript no 13814). Thanks for your interest in our manuscript.

We evaluated the comments of the reviewer's, and the changes are done when was necessary. In the following papers you will find our point by point replies to the comments of the reviewers.

Best regards,

Reply to Reviewer 1

1. A number of recent studies have questioned two-hit hypothesis of NASH development. There is growing evidence that this hypothesis is likely incorrect, because simple fatty liver and NASH are probably two distinct clinical entities. Please refer to Curr Hepatol Rep. 2014 Jun 1;13(2):151-158.and Aliment Pharmacol Ther. 2012 Nov;36(9):815-23. Just because a theory is popular does not mean that it is correct.

-Changes are done and references are added.

2. Reference 5 on vitamin B12 is cited like a kind of afterthought and seems to be out of place. Please delete.
 - In a study, Koplay et al.,(5) shows that serum vitamin B12 levels may decrease in patients with NAFLD. This decrease in vitamin B12 levels may be connected with insulin resistance, endothelial dysfunction and hepatocyte injury. **This sentence is deleted.**

3. Biopsy is probably not the gold standard, but only the best standard for the diagnosis of NASH. Non expert physicians and patients are waiting for an almost perfect noninvasive test, which is a biomarker with less than 10% of false positive or false negative results and more than 99% applicability. This is not possible, even with liver biopsy. Therefore, it is an illusion to wait for an almost perfect biomarker with an adjusted AUROC greater than 90% for the diagnosis of NASH. This point must be explained in the paper. This is crucial for physicians interested in NAFLD imaging.

- Changes are done.

4. It is regrettable that the authors did not mention the Controlled Attenuation Parameter (CAP), an elastography-derived parameter, for the noninvasive assessment of hepatic steatosis. It is currently a hot topic with several papers to be cited (see J Gastroenterol

Hepatol. 2014 Jul;29(7):1470-6). Notably, CAP is a promising marker as it can detect steatosis even in subjects who are negative on ultrasound (see Eur J Gastroenterol Hepatol. 2013 Nov;25(11):1330-4).

- Changes are done.

5. The paper lacks a critical discussion of the pros and cons of the reviewed imaging modalities. The authors should add a final paragraph outlining the main advantages as well as caveats of the various imaging methods. Need also to add a section discussing cost-effectiveness of each modality. Otherwise the manuscript is purely narrative and does not present any point of discussion for anyone involved in the clinical aspects of NAFLD.

- Additions were made.

6- The manuscript includes principles for the future of NAFLD imaging.

7- The changes were ordered in manuscript. The changes were showed with red color in manuscript.

8. We also tried to improve the spelling and grammatical errors.

9. References were reordered according to World Journal of Hepatology format.

Best regards,

Reply to Reviewer 2

1. One major point is missing concerning the controlled attenuation parameter (CAP) which is a recent method for non-invasive assessment of steatosis with transient elastography. Moreover the two-hits hypothesis is currently controverted, this point must be discussed.

- Changes are done.

2. The changes were ordered in manuscript. The changes were showed with red color in manuscript.

3. We also tried to improve the spelling and grammatical errors.

4. References were reordered according to World Journal of Hepatology format.

Best regards,