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28 February, 2013

Lian-Sheng Ma
President and Editor-in-Chief
World Journal of Hepatology

Dear Prof Ma,

RE: Submission of Revised Version of Manuscript (ESPS Manuscript NO: 2146)

Please find enclosed the edited manuscript in Word format (file name: 2146-review.doc).

Title: Transient elastography: Kill two birds with one stone?

Author: Wong, Grace Lai-Hung

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 2146

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 (with changes highlighted in red, please see Appendix);

3 References and typesetting were corrected.

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

Sincerely yours,
Grace Lai-Hung Wong, MD

**Appendix: Responses to Editor's and Reviewers' Comments (ESPS
Manuscript NO: 2146)**

We would like to thank the Editorial Team and Reviewers again for their important comments. Our responses to the comments are as follows:

Editors:

Reviewer 1:

GENERAL COMMENT

The individual paragraphs are completely untied. A short sentence making clear the logical progression of thinking from each step to the next need to be introduced. For instance, the paragraph on liver biopsy should close with: "Given the above limitations to the practice of liver biopsy, a noninvasive transient elastography has been proposed as an alternative tool".

Response: A short sentence is added to the end of each section in order to improve the flow of the whole article.

This article is timely and of interest; however, it needs to be improved to a significant extent. In particular, I found it be too full of technical details and relatively lacking in defining the position of TE in the overall scenario of diagnostic-follow-up techniques, particularly in NAFLD. The potential and limitations of TE also need to be expanded and all recent relevant literature needs to be updated. Editing of English by a native speaker is strongly recommended.

Response: The technical details are now trimmed down, whereas a few sentences are added to define the position of TE in particulars in NAFLD (page 10, paragraph 2). The potential and limitations of TE are also expanded accordingly (page 13, paragraphs 1 and 2). English-language editing is performed as suggested.

SPECIFIC COMMENTS INTRODUCTION

This paragraph is confusing given that it does not specify adequately whether it refers to NAFLD alone or to other types of liver disease. Moreover there are two contrasting sentences which need to be improved. Liver steatosis is a usually reversible and benign condition, except in the setting of steatohepatitis which inflammation and hepatocyte changes co-exist. Both liver fibrosis and steatosis may eventually result in liver cirrhosis and its various complications. Comments 1) Which = WHERE 2) these two sentences are clearly contradictory: the first stating that steatosis is benign; the second claiming that it may end up with cirrhosis. The Authors are referred to recent reviews on the classification/definition, pathogenesis and natural history of NAFLD to rewrite these two sentences (Musso G, Ann Med. 2011 Dec;43(8):617-49; Lonardo A, Expert Rev Gastroenterol Hepatol. 2011 Apr;5(2):279-89; Vernon G, Aliment Pharmacol Ther. 2011 Aug;34(3):274-85).

Response: These two sentences are now rephrased to improve the clarity. The three suggested references are added (page 5, paragraph 1).

Liver biopsy –drawback of this“gold standard” This paragraph should - cite and the discuss the following papers: Campbell MS, Aliment Pharmacol Ther. 2004 Aug 1;20(3):249-59. Rockey DC, Hepatology. 2009 Mar;49(3):1017-44. Poynard T, Clin Gastroenterol Hepatol. 2012 Jun;10(6):657-63.e7; Poynard T, J Hepatol. 2009 Jun;50(6):1267-8. ; Ratziu V, Aliment Pharmacol Ther. 2007 Sep 15;26(6):821-30. Specifically discuss inadvertent puncture of gallbladder and choleperitoneum as a complication of liver biopsy

Response: The suggested references are added wherever appropriate (page 6, paragraph 1). The discussion of choleperitoneum is also added (page 5, paragraph 2).

Working principles of controlled attenuation parameter - The Authors should explain why they focus their attention steatosis. In doing so, they might be willing to discuss that not only is NAFLD among the most common liver diseases (Byron D, Hepatology. 1996 Oct;24(4):813-5.Bellentani S, Ann Hepatol. 2009;8 Suppl 1:S4-8.) but also that steatosis often coexists in liver diseases due to other etiologies (Clouston AD, Clin Liver Dis. 2007 Feb;11(1):173-89).

Response: The importance of steatosis in other liver diseases is now discussed. The suggested references are added accordingly (page 7, paragraph 2).

The role of TE in the screening for cirrhosis in asymptomatic people and in the setting of other non-invasive diagnostic techniques needs to be discussed by quoting and discussing the following papers: Festi D, Aliment Pharmacol Ther. 2013 Feb;37(4):392-4002; Ballestri S, Liver Int. 2012 Sep;32(8):1242-52.; Castera L. Gut. 2011 Jul;60(7):883-4. ; Roulot D, Gut. 2011 Jul;60(7):977-84. ; Stepanova M, Aliment Pharmacol Ther. 2010 May;31(10):1085-94.

Response: The role of TE in screening for cirrhosis in asymptomatic and NAFLD patients is now discussed based on the new references (page 10, paragraph 1).

The limitations of TE need to be highlighted by quoting and discussing: Gaia S, J Hepatol. 2011 Jan;54(1):64-71. Lebray P, Liver stiffness is an unreliable marker of liver fibrosis in patients with cardiac insufficiency. Hepatology. 2008 Dec;48(6):2089.

Response: The limitations of TE is further highlighted and discussed in more details, with references to the suggested publications (page 13, paragraph 2).

The bibliography needs to be updated by adding the following: Abraldes JG, Reverter E, Berzigotti A. Spleen stiffness: Towards a non-invasive portal

sphygmomanometer? Hepatology. 2013 Jan 21. doi: 10.1002/hep.26239. [Epub ahead]

Response: The discussion on spleen stiffness and the suggested reference is now added in a new section titled "Spleen stiffness – measures portal hypertension non-invasively" near the end of the manuscript (page 17, paragraph 2).

Reviewer 2:

1. The validity of TE in PBC/PSC is at best encouraging but certainly difficult to describe as well-validated as the main study quoted had only 29 PSC patients including and other studies in the literature are relatively lacking, particularly compared to HCV. Therefore, this assertion needs to be modified.

Response: We now highlight the small sample size of PSC cohort in Table 1.

2. Though there are drawbacks to liver biopsy as described, I think it is important to highlight that no activity information can be gained from TE as opposed to liver biopsy.

Response: The lack of activity information is now emphasized in the discussion of limitation of transient elastography (page 13, paragraph 1).

3. Though TE is the best studies, there are newer techniques emerging with excellent promise. This includes Acoustic Radiation Force Impulse (ARFI) for instance. Moreover, other new generation USS devices offer built in TE technology such as Hitachi. I think it would be useful to mention these to provide a more balanced view.

Response: These few new advances are now mentioned in a new section titled "New imaging technologies" (page 17, paragraph 3).

4. The conclusion should emphasis the usefulness of TE in looking for advanced fibrosis or cirrhosis but it is still not truly valuable in assessing fibrosis in general.

Response: The conclusion is now modified accordingly (page 17, paragraph 4).

Reviewer 3:

Wong presents an excellent review about the properties of the transient hepatic elastography. The review would benefit from outlining the method of data collection in the introduction or in a method section. In addition the author should mention some new data dealing with TE in rare liver diseases such as cystic fibrosis.

Response: New data concerning cystic fibrosis is now described in the text as well as Table 1.

Reviewer 4:

This is an important review article in the field of Transient elastography. Specific comments 1. This is very well written review article. 2. It will add to the strength of the article if author adds review on splenic stiffness also.

Response: A new section concerning splenic stiffness is now added (page 17, paragraph 2).

Reviewer 5:

In this interesting review, Dr. Lai-Hung Wong presents update about the transient elastography in the diagnosis of liver diseases. On one hand, data focus in the advantages of using the elastography but on the other hand, limitations of this diagnosing procedure are also highlighted. If data are available, a Table showing the sensitivity and specificity in the diagnosis of the different liver entities could add useful information. In the same way, information about costs as compared with costs of liver biopsy can be added.

Response: We now include sensitivity and specificity in Table 1 and 2. Discussion about the costs of TE vs. liver biopsy is also added (page 5, paragraph 1 and page 8, paragraph 1).