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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 28669
Title: Non-invasive evaluation of liver stiffness after splenectomy on CCl4-induced liver fibrosis in rabbits
Reviewer's code: 02663375
Reviewer's country: Italy
Science editor: Ze-Mao Gong
Date sent for review: 2016-07-13 09:29
Date reviewed: 2016-07-15 01:15

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Please note that ElastPQ, which is a proprietary software of Philips, is basically an ARFI technique and not a "new shear wave-based elastography" as stated in the introduction and the discussion. On this aspect, please check and cite: Barr RG et al. Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. Radiology 2015; 276(3): 845-61; Ferraioli G et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 3: liver. Ultrasound Med Biol 2015;41(5):1161-79. Please, not that the use of ElastPQ in the clinical practice is very well-established! The seminal papers should be cited: Ferraioli G et al. Point shear wave elastography method for assessing liver stiffness.World J Gastroenterol 2014;20(16):4787-96; Ma JJ. Assessment of liver fibrosis with elastography point quantification technique in chronic hepatitis B virus patients: a comparison with liver pathological results. J Gastroenterol Hepatol 2014; 29(4):814-9. Since then, several articles have been published. The references given to support the statement that macrophages play a pivotal role in liver fibrosis are not recent. Please, reword or give more recent references. Give reference to the statement "few data

pertaining to the evidence of changes in fibrotic liver stiffness after splenectomy at different pathological stages from ElastPQ is available" otherwise state that no data are available. Materials and Methods Were both probes used or only one? This is very important to know since different frequencies give different values for the same degree of stiffness. Discussion Give references for the statement "However, to our knowledge, until now few literature resources with respect to the relationship between the liver stiffness measurement via ElastPQ and liver fibrosis stages are available" (see comment above: the use of ElastPQ in the clinical practice is very well-established! The seminal papers should be cited: Ferraioli G et al. Point shear wave elastography method for assessing liver stiffness.World J Gastroenterol 2014; 20(16):4787-96; Ma JJ. Assessment of liver fibrosis with elastography point quantification technique in chronic hepatitis B virus patients: a comparison with liver pathological results. J Gastroenterol Hepatol 2014; 29(4):814-9. Since then, several articles have been published). It is not correct to state that "In this study, a trend that splenectomy can delay the progression of early liver fibrosis (especially F1) was detected". In fact, elastography assesses the stiffness which is directly related to liver fibrosis but may change also for other factors, including the quantity of blood in the portal vein. After splenectomy there is a reduction of portal blood flow. On this aspect, in the results it stated that "For the nine rabbits with F1 liver fibrosis (five in splenectomy group vs. four in sham group), the increase of ElastPQ values was delayed in the splenectomy group compared with that in the sham group during a period of 10 weeks following operations" but no information is given about the histology. Was it improved as well? It is preferable not to state that "So far, a number of clinical researches have clarified the feasibility, safety, and effectiveness of splenectomy for liver cirrhosis patients with hypersplenism, suggesting that patients will benefit in terms of short- and long-term outcomes". This issue is still controversial and it should be presented like so [Boyer TD, Habib S. Big spleens and hypersplenism: fix it or forget it? Liver Int. 2015 May;35(5):1492-8]. I would like to underline that it has been shown that the spleen-derived macrophages have a positive role in lung inflammation, thus to recommend splenectomy without any doubt is not advisable [Venosa A, et al. Protective role of spleen-derived macrophages in lung inflammation, injury, and fibrosis induced by nitrogen mustard. Am J Physiol Lung Cell Mol Physiol. 2015 Dec

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 28669
Title: Non-invasive evaluation of liver stiffness after splenectomy on CCl4-induced liver fibrosis in rabbits
Reviewer's code: 00006459
Reviewer's country: Australia
Science editor: Ze-Mao Gong
Date sent for review: 2016-07-13 09:29
Date reviewed: 2016-08-23 16:35

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
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COMMENTS TO AUTHORS

This manuscript (ms) shows data from a new method of LSM; ElastPQ. This study is well powered and the statistics are appropriate. A strength of this ms is that the model of fibrosis is improved from a previous publication. This ms shows no benefit of splenectomy in this model. A strength of this ms is that the measurements are very careful to ensure the maximal precision by using two experts for biopsy score and for LSM. The data is interpreted very well . I like the discussion of fibrosis resolution and macrophages. A strength of this ms is that it is well written and the data are carefully interpreted. Revision comments: 1. The exception regarding writing quality is that parts of the Discussion need improved English, in particular the 4th paragraph and 8th paragraph must be re-written. Also, the phrase , "can be alleviated " is unclear and must be explained [Discussion para 7]. An example in para 8 is that the phrase beginning, "recently confirmed ….. " is unclear and must be explained. The last 3-4 sentances of para 8 need to be clarified [Discussion para 8]. 2. The weakest part of this ms is the discussion. The first two paragraphs are introductory and are redundant when placed in the Discussion Section. The second sentence of 3rd para of Discussion is

where the Discussion Section should start. 3. Discussion needs to comment on CCl4 fibrosis models and on rabbit models of liver fibrosis. 4. Please explain in the ms why collagen IV was chosen as a measure. General comments: It would have been interesting to measure blood pressure, in particular portal pressure, in these animals. This ms would be greatly strengthened by adding a direct comparison with TE.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 28669
Title: Non-invasive evaluation of liver stiffness after splenectomy on CCl4-induced liver fibrosis in rabbits
Reviewer's code: 02860653
Reviewer's country: Ukraine
Science editor: Ze-Mao Gong
Date sent for review: 2016-07-13 09:29
Date reviewed: 2016-08-25 20:46

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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COMMENTS TO AUTHORS

The manuscript `Non-invasive evaluation of liver stiffness after splenectomy on CCl4-induced liver fibrosis in rabbits` by Wang MJ et al. is an interesting and well-elaborated paper presenting study of utilizing CCl4-induced liver fibrosis with liver stiffness measurement. The approach is not new and model might be most likely considered as reliable for the liver research. Sonoelastography should strongly expand a potential of the longitudinal experiment. However, some minor corrections might improve the paper quality via focused discussion/correction the following points: 1. Ultrasound image would appreciated, best option would to present side-by-side comparison sonoelastography–histology for fibrosis grades. 2. Why splenectomy was included to the experiment? Authors claim that `Splenectomy is one of surgical interventions for liver cirrhotic patients with hypersplenism`, but how hypersplenism was evaluated in included animals? Did animals demonstrated signs, lab tests relevant to hypersplenism? Was the portal hypertension and visceral blood flow redistribution considered? This is major point in the liver stiffness increasing mechanism. Statement that `splenectomy can delay the progression of early liver fibrosis` is very confusing. 3. The

design of invasive part has many unclear points, bias: - `To obtain different stages of liver fibrosis at different time intervals, the same surgical process was repeated for the remaining rabbits every two weeks until the 20th week.` - can alter hepatic tissue and evoke fibrosis as well - `Along with the increase of operation times, it was more and more difficult to get the liver tissue along the original midline incision because of adhesion` - taking tissue samples in one area might bias results be due to the postoperative scars. - Did you measure liver stiffness in biopsy samples for comparison? Did you consider that post mortem stiffness might be strongly altered to be properly compared. - authors did the biopsy in the subxiphoid region `to reduce the biases`. And where sonoelastography assessment was performed? - Another relevant bias is giving penicillin intramuscularly in doses of 40 U/rabbit to prevent infection. Translation issues and potential treatment options to be tested could be discussed The reference list might be expanded with newest studies on using sonoelastography in human and using ultrasound in animal models. Some language quality might be improved and spelling corrections to be done.