June 10, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 18880-revised.doc).

Title: Ultrasound-based elastography for the diagnosis of portal hypertension in cirrhotics

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Name of Journal: World Journal of Gastroenterology

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The manuscript has been improved according to the suggestions of reviewers:

Reviewer 01136482

1. key words: I suggest to synthesize it.

We reformulated the key words as follows: "portal hypertension, transient elastography, ARFI elastography, 2D-SWE elastography"

2. Introduction section: I suggest to report the data on the alcoholic cirrhosis, the first reason for liver transplantation in Europe.

The following fragment was added:

"Alcoholic cirrhosis is also a major cause of disease burden and death. In 2010, 493,300 deaths were attributable worldwide to alcoholic cirrhosis (7.2 for 100,000 people; 47.9% of all liver cirrhosis deaths) [5] . In Europe, also in 2010, 43,500 deaths were caused by alcoholic cirrhosis [5] . More than 5,500 liver transplants are performed in Europe each year, 59% of them for liver cirrhosis, 33% of them with pure alcoholic etiology and an additional 5% of mixed alcoholic and viral etiology [6]."

3. one of the most feared complications of cirrhosis is portal hypertension with development not only of esophageal, but also of gastric varices

We corrected as suggested: .... "esophageal and gastric varices (EV and GV, respectively)"

4. TE section: in this section is important to report the different diagnostic cut-off on the basis of the differente causes of cirrhosis (Abenavoli et al. Can J Gastroenterol 2007)

We added the suggested reference: "However, the cut-off values for diagnosing cirrhosis may vary according to the etiology[24]. Published studies found the following cut-offs...."

5. I suggest to report a section with a comparison of the costs/effectiveness of all the diagnostic tecniques reported in the text:

We thank the reviewer for the suggestion, but since only TE is a validated method for livers stiffness assessment, (the other methods are only being evaluated), there are no available data regarding the costs of the other elastographic methods so we were unable to make the cost/effectiveness analysis.

Reviewer 00032933

1. Please include several Tables or Figures to demonstrate the main concepts of this review.
Tables were added as suggested (Tables 1-3)

2. Different etiologies have different characteristic in development of liver cirrhosis or portal hypertension. It is important to mention the underlying etiologies of liver fibrosis at the description of each report.

We reported different cut-offs for TE for the diagnosis of cirrhosis according to the etiology, as well as different cut-offs for TE for the diagnosis EV according to the etiology:

"However, the cut-off values for diagnosing cirrhosis may vary according to the etiology[24]. Published studies found the following cut-offs: 12.5 kPa in HCV infection [25]; 13.4 kPa in HBV infection [26]; 10.3 kPa in NAFLD [27]; 22.4 kPa in ASH [28]; 17.3 kPa in cholestatic chronic diseases (primary biliary cirrhosis and primary sclerosing cholangitis) [29]." and

" Predictive LS values for significant EV were assessed according to cirrhosis etiology. The cut-off values were higher in alcoholic cirrhosis (47.2kPa; AUROC 0.77; 84.6% sensitivity, 63.6% specificity, 44% positive predictive value and 92.5% negative predictive value) than in patients with viral etiology (19.8kPa; AUROC=0.73; 88.9% sensitivity, 55.1% specificity, 26.7% positive predictive value, and 96.4% negative predictive value)[39]. The same thing was observed in a study from our group on almost 700 patients. In our study, the best LS cut-off value for predicting significant EV was 32.5 kPa (AUROC=0.836) in alcoholic cirrhosis as compared with 24.8 kPa (AUROC=0.867) in patients with viral etiology of liver cirrhosis[40].

In a study published in 2009 on HCV cirrhosis, Castera et al calculated a cut-off of 21.5 kPa to predict the presence of EV, but with only 76% sensitivity and 78% specificity, so that they concluded that TE cannot replace upper endoscopy for the diagnosis of EV[41]. In a smaller, more recent study that compared TE with FIB-4, Forns Index and Lok score for prediction of grade 2 and 3 EV in patients with HCV cirrhosis, TE showed the highest accuracy (80%) with a cutoff of 22.4kPa and AUROC of 0.801[42].

Chen et al evaluated 238 patients with HBV cirrhosis by TE and upper digestive endoscopy. For a cut-off of 36.1 kPa in patients with high levels of aminotransferases (≥ 5 × upper limit of normal), TE had 100% negative predictive value, and 72.7% positive predictive value for predicting grade 2 and 3 EV, AUROC 0.93[43]."

To our knowledge no data regarding different cut-offs for predicting portal hypertension according to etiology are available regarding ARFI elastography, 2D-SWE, ElastPQ and Strain Elastography.

3. Please give an explanation of how TE may predict portal hypertension while ARFI may not.
We added the following comment:

"Published studies did not explain why TE can predict portal hypertension while ARFI cannot. An explanation can be the wider range of TE, above the cut-off for cirrhosis (approximately from 12.5-13.5 kPa up to 75 kPa), than for ARFI (approximately from 1.8-2 m/s up to 5 m/s)."

Editor:

1. We provided certificate letter from a professional English language editing company.
2. We reformulated the Authorship section
3. We provided the conflict of interest statement
4. We provided PMID and or DOI for each reference in the list when available. When neither was available, we provided the first page of the paper cited.

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

Sincerely yours,

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