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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 37676
Title: Digital liver biopsy: standardized bio-imaging for translational and clinical research on fatty liver
Reviewer's code: 00053659
Reviewer's country: Japan
Science editor: Li-Jun Cui
Date sent for review: 2018-01-04
Date reviewed: 2018-01-05
Review time: 16 Hours

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

COMMENTS TO AUTHORS

Mancini et al. reviewed various imaging modalities for assessing fatty liver. The manuscript is well written and the entire concept is interesting. But samples of each image and the differences among the modalities are hardly understood. Please add representative images for each tool and add table that represents diagnostic values such as AUC or c-statistics. Minor point. Author contributions could hardly understand what each author contributed equally. Please identify the section where each author provides it. Company name is missing for Fibroscan.

Answer:

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Representative images of the different techniques are provided in the Figures and Table ! was added with AUC statistics and references.

Table 1

			ROC-derived parameters*		
Paper	**Imaging modality**	**Classification**	**AUC**	**Sensitivity (%)**	**Specificity (%)**
Mancini M *et al* 2009 [60]	US	^{1}H-MRS fat content > 5%	0.996	100	95
Xia MF *et al* 2012 [61]	US	^{1}H-MRS fat content > 5.56%	n.a.	95.1	100
Edens MA *et al* 2009 [62]	US	^{1}H-MRS fat content > 5.56%	n.a.	66.7	100
Di Lascio N *et al* 2018 [65]	US	*^{1}H-MRS fat content* > 5%	0.97	89	94
Sasso M *et al* 2012 [108]	CAP score (imaging derived)	Liver Biopsy S_0: <10% of hepatocytes S_1: 11-33% of hepatocytes S_2: 34-66% of hepatocytes S_3: 67-100% of hepatocytes	$S_0 vs S_1S_2S_3$: 0.80 $S_0S_1 vs S_2S_3$: 0.86 $S_0S_1S_2 vs S_3$: 0.88	$S_0 vs S_1S_2S_3$: 76 $S_0S_1 vs S_2S_3$: 87 $S_0S_1S_2 vs S_3$: 78	$S_0 vs S_1S_2S_3$: 71 $S_0S_1 vs S_2S_3$: 74 $S_0S_1S_2 vs S_3$: 93

Table 1. **Intrahepatic Fat Measurements**

Both histologic and digital liver biopsy provide reliable measures of intrahepatic fat that are significantly correlated, but categorically different. Liver biopsy describes the histologic

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characteristics of the pathologic lesions and accounts for the percentage of hepatocytes with intracellular fat-derived vacuoles using categorical grading systems that are not directly representative of the hepatic triglyceride concentration [19-21]. On the other hand ^{1}H-MRS measures protons in acyl groups of liver tissue triglycerides and provides continuous quantitative values expressed as mg/g of hepatic tissue [109]. Moreover, ^{1}H-MRS uses a much larger volume of liver tissue than biopsy reducing sampling error and representing the most accurate measure of the overall liver triglyceride content.

The specific contributions of each Author are specified:

Marcello Mancini, Paul Summers and Francesco Faita equally contributed in the manuscript organization and writing for the imaging technique part in relative proportions as listed as 1st, 2nd and 3rd authors of the manuscript;

Ferruccio Bonino contributed to organize, coordinate the work and overall writing of the manuscript and is the last and addressing Author.

The remaining coworkers are listed in alphabetic order and their contributions were:

Maurizia R Brunetto, Fabio Farinati, Bruno Gridelli and Claudio Tiribelli equally contributed for liver pathology part writing and editing amd listed in alphabetic order;

Peppino Mirabelli, Piero A Salvadori, Emanuele Neri and Marco Salvatore equally contributed the biobanking part writing and editing;

Francesco Callea contributed for the histopathology part writing and editing;

Andrea De Nicola, Nicole Di Lascio, , Amalia Gastaldelli, Eleni Rebelos and Luca Valenti equally contributed for the writing and editing of the metabolic pathophysiology part;

Authors listed in the Appendix as Collaborators (Stefano Bellentani, Luigi Coppola and Valerio Nobili contributed equally to the critical revision and approval of the review.

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The company name of Fibroscan Echosense was added.

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 37676
Title: Digital liver biopsy: standardized bio-imaging for translational and clinical research on fatty liver
Reviewer's code: 01555255
Reviewer's country: Italy
Science editor: Li-Jun Cui
Date sent for review: 2018-01-04
Date reviewed: 2018-01-08
Review time: 4 Days

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

COMMENTS TO AUTHORS

- Liver elastography section: elastography is an easy, non invasive and well accepted tool to evaluate the degree of liver diseases in general and of NAFLD/NASH in particular. A review report the elastographic cut-off to define different degrees of the disease (Abenavoli et al. Ann Hepatol 2012). In this section I also suggest to briefly report the role of ARFI. - Intrahepatic fat measured by ultrasound (US) section: literature report the accuracy of US score to define the fat accumulation on the liver (e.g. Hamaguchi et al. Am J Gastroenterol. 2007). I suggest to brief report the most important US score. - Conclusion section: this section is pivotal for the reader. I suggest the Author to highlight the point that the described techniques present a real clinical impact in NAFLD management. However, many of these tools are limited in selected Centers. In this way, is important to increase the accessibility by reducing the costs.

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Answer:

The review report of the elastographic cut-off to define different degrees of the disease has been cited and referenced at ref. n. 29 Abenavoli L, Beaugrand M. Transient elastography in non-alcoholic fatty liver disease. Ann Hepatol. 2012 Mar-Apr;11(2):172-8.[PMID:22345333].

We briefly reported also the comparison with the ARFI method as suggested and cited a new ref. n. 37 Lee MS, Bae JM, Joo SK, Woo H, Lee DH, Jung YJ, Kim BG, Lee KL, Kim W Prospective comparison among transient elastography, supersonic shear imaging, and ARFI imaging for predicting fibrosis in nonalcoholic fatty liver disease. PLoS One. 2017 Nov 27;12(11): e0188321. [PMID: 29176844 PMCID:PMC5703509 DOI: 10.1371/journal.pone.0188321

In the intrahepatic fat measured by ultrasound (US) section the literature report on the accuracy of US score to define the fat accumulation on the liver was cited and refereced at Ref. n. 20 Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, Kato T, Takeda N, Okuda J, Ida K, Kawahito Y, Yoshikawa T, Okanoue T. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol 2007 Dec; 102(12):2708-15. Epub 2007 Sep 25.[PMID:17894848 DOI: 10.1111/j.1572-0241.2007.01526.x]

A brief report of the most important US score for intrahepatic fat and their relations have been reported and table 1 was added.

Table 1. **Intrahepatic Fat Measurements**

Both histologic and digital liver biopsy provide reliable measures of intrahepatic fat that are significantly correlated, but categorically different. Liver biopsy describes the histologic characteristics of the pathologic lesions and accounts for the percentage of hepatocytes with intracellular fat-derived vacuoles using categorical grading systems that are not directly representative of the hepatic triglyceride concentration [19-21]. On the other hand ^{1}H-MRS measures protons in acyl groups of liver tissue triglycerides and provides continuous quantitative values expressed as mg/g of hepatic tissue [109]. Moreover, ^{1}H-MRS uses a much larger volume of liver tissue than biopsy reducing sampling error and representing the most accurate measure of the overall

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liver triglyceride content.

We highlighted the point that the described techniques present a real clinical impact in NAFLD management and indicated their limitations with the need to increase their accessibility by reducing the costs in the conclusions.

"We foresee the combination of image-based digital liver biopsy with liver histology and liquid biopsy in a multimodal approach to the study of the fatty liver in clinical pathology as a key to personalizing patient care in NAFLD. To foster this approach in clinical and translational research there is a need to standardize the methods of acquisition, processing and storage of bio-images of the liver. A number of imaging techniques that offer a starting point for acquisition have been identified and their use in combination in prospective studies will open a new venue of translational and clinical research. However, many of these tools are still limited to selected Centres and it is important to increase their accessibility by reducing costs."

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 37676
Title: Digital liver biopsy: standardized bio-imaging for translational and clinical research on fatty liver
Reviewer's code: 01919991
Reviewer's country: Afghanistan
Science editor: Li-Jun Cui
Date sent for review: 2018-01-04
Date reviewed: 2018-01-09
Review time: 5 Days

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

COMMENTS TO AUTHORS

The manuscript is well written in the whole and follows a logical projection, with general views of different imaging approaches useful in the diagnosis and staging fatty liver disease and, in a wider view, liver disease progression. I suggest that the authors emphasize the benefits of adopting a common image acquisition and processing standard in their conclusions. A careful check for typos is recommended

Answer:

We emphasized the benefits of adopting a common image acquisition and processing standard in the conclusion of the revised manuscript. "We foresee the combination of image-based digital liver biopsy with liver histology and liquid biopsy in a multimodal approach to

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the study of the fatty liver in clinical pathology as a key to personalizing patient care in NAFLD. To foster this approach in clinical and translational research there is a need to standardize the methods of acquisition, processing and storage of bio-images of the liver. A number of imaging techniques that offer a starting point for acquisition have been identified and their use in combination in prospective studies will open a new venue of translational and clinical research. However, many of these tools are still limited to selected Centres and it is important to increase their accessibility by reducing costs."

A careful check of typos was made and we corrected them.

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 37676
Title: Digital liver biopsy: standardized bio-imaging for translational and clinical research on fatty liver
Reviewer's code: 02441021
Reviewer's country: Egypt
Science editor: Li-Jun Cui
Date sent for review: 2018-01-04
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Review time: 7 Days

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

COMMENTS TO AUTHORS

Needs better division into shorter, concise paragraphs

Answer:

A better division in 12 more concise paragraphs was made in the revised manuscript as follows:

1) **INTRODUCTION, 2) ACQUISITION OF HEPATIC BIO-IMAGES, 3) LIVER ELASTOGRAPHY FOR ASSESSMENT OF FIBROSIS, 4) MAGNETIC RESONANCE RELAXOMETRY FOR ASSESSMENT OF FIBROSIS, 5) MAGNETIC RESONANCE**

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SPECTROSCOPY (MRS) FOR ASSESSMENT OF STEATOSIS, 6) PROTON-DENSITY FAT FRACTION MEASUREMENT, 7) INTRAHEPATIC FAT MEASURED BY ULTRASOUND, 8) PET TO STUDY LIVER METABOLISM, IMAGING MASS SPECTROMETRY (IMS), 9) RADIOMICS, 10) BIO-BANKING FOR LIVER DISEASE, 11) DIGITAL BIOPSY-THE ROAD AHEAD, 12) CONCLUSIONS