

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 36245

**Title:** 1H NMR-based Metabonomic Models for Non Invasive Diagnosis of Liver Fibrosis in Chronic Hepatitis C: Optimizing the Classification of Significant Fibrosis

**Reviewer's code:** 01560058

**Reviewer's country:** Japan

**Science editor:** Li-Jun Cui

**Date sent for review:** 2017-09-27

**Date reviewed:** 2017-10-01

**Review time:** 4 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

This study demonstrates the utility of metabonomic models (MMs) derived using 1H NMR spectroscopy as tools to evaluate liver fibrosis stages in HCV patients. The Reviewer has the following comments. 1. If the authors expect the clinical use of these MMs, they should discuss their cost-effectiveness. 2. In this study, the authors excluded HCV patients treated with antiviral agents. However, nowadays, sustained viral response can be achieved for most HCV patients treated with direct-acting antiviral agents. Studies have demonstrated that elastography can help monitor liver fibrosis stages after antiviral treatment. Are the MMs useful in this setting? Please discuss this point. 3. The results of this study suggest that the MMs can more accurately distinguish intermediate fibrosis stages in HCV patients than the APRI and the FIB-4 index. However, the Reviewer has found a paper indicating that the measurement of

serum osteopontin levels may be useful for this purpose (PLoS One, 10 : e0118744, 2015). Please cite this paper and discuss other measures to distinguish intermediate fibrosis stages.

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**Manuscript NO:** 36245

**Title:** 1H NMR-based Metabonomic Models for Non Invasive Diagnosis of Liver Fibrosis in Chronic Hepatitis C: Optimizing the Classification of Significant Fibrosis

**Reviewer's code:** 02943235

**Reviewer's country:** Japan

**Science editor:** Li-Jun Cui

**Date sent for review:** 2017-09-27

**Date reviewed:** 2017-10-10

**Review time:** 13 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input checked="" type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

I carefully reviewed the manuscript. In this study, the authors demonstrated the usefulness of 1H NMR-based metabonomic models for diagnosis of liver fibrosis in chronic hepatitis C patients. The study is potentially interesting. However, there are some concerns that should be addressed by the authors. 1. The authors should show diagnosis criteria of clinical cirrhosis and Child-Pugh score of cirrhosis patients, because the cirrhosis group mostly consists of clinically diagnosed cirrhosis patients 2. Although, in the manuscript, the results of the LDA MM for SF were compared to the APRI score, the comparison between the LDA MM and the FIB4 index for SF was not shown. How was the result of comparison between LDA MM and the FIB4 index? Similarly, the authors should show the result of comparison between LDA MM and the APRI score for AF. 3. The authors showed high accuracy and performance of the MM to diagnose liver

fibrosis. But, external validation of the models has not been yet conducted. Regarding this points, I think that the comparison between the MM, APRI score and FIB4 index may be premature. The authors should describe the accuracy and performance of the MM without comparisons with other models. I hope these comments will be helpful.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 36245

**Title:** 1H NMR-based Metabonomic Models for Non Invasive Diagnosis of Liver Fibrosis in Chronic Hepatitis C: Optimizing the Classification of Significant Fibrosis

**Reviewer's code:** 00054986

**Reviewer's country:** Portugal

**Science editor:** Li-Jun Cui

**Date sent for review:** 2017-09-27

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**Review time:** 16 Days

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

## COMMENTS TO AUTHORS

The manuscript deals with an interesting aspect of staging of chronic liver disease in patients with viral hepatitis C. I have a few comments: - Transient elastography was not used / mentioned as a tool for staging chronic liver disease in these patients. Authors should comment on their choice of FIB4 and APRI without including transient elastography - Liver biopsy was performed in 54 out of 69 patients. How did the remaining patients who did undergo liver biopsy have their liver disease staged and how accurate could that staging be? - The results of MM seem very good. I believe however, that this study would be much more useful with an external validation. -Severity of cirrhosis was not mentioned. Were these all Child Pugh A patients?