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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 33929
Title: Improved Hepascore in HCV predicts reversal of risk of hepatocellular carcinoma, liver decompensation and liver death.
Reviewer's code: 00033049
Reviewer's country: United States
Science editor: Xiu-Xia Song
Date sent for review: 2017-03-15
Date reviewed: 2017-03-21

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] 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
[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

Current study was from the group who originally described Hepascore as a non-invasive marker of fibrosis in patients with chronic hepatitis C. In the current study, the authors use "baseline" Hepascore as a prognostic indicator. In addition, the authors also found the change in Hepascore over time ("Delta Hepascore") was also a predictor of liver related events or death. There were several concerns of the current study: 1. Study population: the median Hepascore was 0.48 with range of 0.02 to 1.0. According to the original articles on Hepascore, majority of the subjects would have significant fibrosis. However, there was no detail on the distribution of the study population. For example, how many has cirrhosis by Hepascore and/or clinically? How many patients is in each quartile as defined by the authors (Figure 1)? Readers need to know more about the distribution in order to interpret the findings. 2. According to table 1, 38 patients achieved SVR. This complicated the interpretation since achieving SVR had been shown to change the natural history and reduced risk of HCC. It was also not

clear how many were treated but did not achieve SVR. Should show additional data on the treated vs untreated group. This is particularly important with regard to HCC (as one of the endpoints). 3. What was the relationship, if any, between changes in Hepatoscore over time and variable such as HCV treatment, elements of metabolic syndrome (e.g. BMI), alcohol consumption? Alcohol use can increase the GGTP which is one of the variables in Hepascore. 4. The primary endpoint is liver related death or liver transplant. According to table 1, it was 28. However, there was only 8 LRD, so does it mean that 20 received liver transplant? There were 16 decompensation and 15 HCC, does it also mean patients had multiple events (i.e. LD and HCC)? 5. It would be useful to have a table summarizing the characteristics of each of the 4 quantile e.g. number of patients, mean age, ALT, platelet count. 6. Not clear why the second Hepascore was done and under what circumstance. For example, were they mostly done among those who achieved SVR looking for fibrosis regression and those whom clinician suspected clinical progression (in consideration of anti-viral therapy)? There was not enough detail about the group who had repeat Hepascore done. Also, of note, the range was very wide (0.03 to 12.5). Since fibrosis progression (assuming that is what the Hepacore is measuring) is a very slow process, should the analysis include only those with repeat Hepascore, say, more than 2 years apart? However, it looked like there might only be ~50 patients and not clear how many event occurred. 7. Table 2, the 95% CI for the second Hepascore was very wide (e.g. 0.0-4.6E+53), no doubt due to very small sample size. Could this be correct? 8. If Hepascore is truly a reliable reflection of fibrosis, only patients with advanced fibrosis (F3 or F4) is at risk for HCC, and only F4 patients are at risk for decompensating events and liver related death. Should the analysis be focusing on this group (e.g. Hepascore score >0.8) instead of the entire cohort? This is also suggested by figure 1. What is the sensitivity and specificity of Hepascore >0.75 for cirrhosis? Again, how many patients is in this category? 9. The delta Hepascore is intrinsically fraud. The variable that is missing is time. A 0.1 change over 1 year or over 5 years have different implication.

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COMMENTS TO AUTHORS

Could you mention about HCV genotype? Could you mention about treatment modality and therapeutic response?