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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 22648
Title: Osteopontin: A non-invasive parameter of portal hypertension and prognostic marker of cirrhosis
Reviewer's code: 00002232
Reviewer's country: Spain
Science editor: Jing Yu
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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	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this study, Bruha et al. aimed to investigate the association between blood levels of osteopontin and portal hypertension measured by HVPG and to assess the prognostic value of osteopontin in cirrhotic patients. This study was performed in 154 portal hypertensive cirrhotic patients and in 137 healthy individuals. The authors conclude that osteopontin is a non-invasive parameter of significant portal hypertension and a prognostic indicator for survival in patients with liver cirrhosis. In addition, the combination of the variables HVPG and OPN has a higher prognosis value compare to that of either HVPG or OPN alone. The authors provide interesting information about the value of osteopontin measurement as a non-invasive biomarker of portal hypertension. As noted by the authors, this association has not previously been described. While the findings are interesting, there are some questions that the authors should address to strengthen the study. Comments: 1) In this study, there is a notable lack of comparison between osteopontin and other non invasive markers of portal hypertension. For example, transient elastography, alone or in combination with platelets count+spleen size, has a very good predictive value for clinically significant portal hypertension. In

addition, several blood biomarkers have been investigated as noninvasive testing for portal hypertension such as the AST/ALT ratio, BMP7, apelin, vWF, VCAM-1, IL-1beta, among others. The comparison of accuracy for predicting clinically-significant portal hypertension between osteopontin and other non-invasive biomarker is needed to strengthen the study. 2) The authors conclude that osteopontin is a non-invasive parameter useful in the stratification of significant portal hypertension. The authors reached this conclusion by performing univariate and correlation statistical test. However, the correlation coefficient between OPN and HVPG was weak (0.25), although significant. The authors should investigate further the robustness of this association. For example, I would recommend performing multivariate linear regression considering HVPG as response variable run for HVPG ≤10 and HVPG>10 mmHg and adjusting the model for possible confounding variables. 3) Positive and negative predictive values should be also reported together with sensitivity and specificity for osteopontin 4) Transaminase values for cirrhotic patients should be reported in table 1 5) In the discussion section, the authors state that "the clear relationship between single HVPG measurement and overall survival of patients with cirrhosis is not well documented". This information is not supported by the literature. For example, a reduction in the HVPG to less than 12 mm Hg or a reduction of more than 20% from the baseline value is associated with a decreased risk of variceal hemorrhage and improved survival. Therefore, I would recommend to modify appropriately this paragraph (Abraldes et al., Hepatology 2003;37:902-8. and D'Amico G, et al. Gastroenterology 2006;131:1611-24) 6) A "study limitations" section should be included in your manuscript. Some limitations to consider are the lack of a validation cohort and the strong regional focus of patients included in this study. 7) Some biochemical parameters do not necessarily follow a normal distribution and this seems to be the case for osteopontin, according to the boxplots shown in figure 1A and B. Therefore, all the parameters that do not follow a normal distribution should be reported as median and interquartile range in the table 1.

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		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The manuscript describes a study of the value of OPN as a non invasive indicator of portal hypertension. The patient size is reasonably large and the authors have made a good attempt to exclude indications associated with elevated circulation OPN such as alcohol abuse and HCC in their patient populations. However it is not clear from Table 1 what the constitution of each group is in terms of etiology (ie how many patients had viral related disease, NASH etc) and this table suggests that some patients did have alcohol-related cirrhosis. The numbers for each etiology should be clearly stated and the authors should comment on validity of grouping small numbers of patients with varying etiology of disease into such analyses. In particular the association of OPN and HCC is well described so discussion of etiologies particularly associated with development of HCC is warranted and more clarity regarding numbers of patients with each disease is important. The observation that HVPG is higher in cirrhosis is not new, and elevations of circulation OPN in patients with cirrhosis is also well described. The correlation between OPN and survival is clear but predictable based on associations with disease severity (and markers such as platelet count etc as noted by the

authors in the discussion) and has been demonstrated in cirrhotic patients with HCC in the past. It would be interesting to see a more detailed breakdown of etiology and survival linked to OPN levels and also cause of death data for the 62 who died (ie not just brief mention of incidence of HCC).