

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 37107

**Title:** Pre-transplant BALAD and BALAD-2 in predicting hepatocellular carcinoma patients recurrence and survival

**Reviewer's code:** 02937050

**Reviewer's country:** United Kingdom

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-12-04

**Date reviewed:** 2017-12-04

**Review time:** 3 Hours

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"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

The authors investigate the BALAD and BALAD-2 models and their constituent variables as predictors of outcome in patients undergoing hepatic transplantation. The authors note that whilst the models have been validated extensively in most forms of HCC treatment, there is very little information on their performance in patients undergoing transplantation. The paper is clearly written, the analysis is sound and the conclusions reasonable. Specifically, they conclude that the models do have predictive value but a model combination of the biomarkers and tumour size performs better. Comment The BALAD models were designed to predict survival in patients with HCC. There are two elements to BALAD reflecting the major prognostic features for HCC - liver function (as measured by Bilirubin and Albumin) and the tumor-related factors (LAD i.e. the biomarkers). In patients undergoing liver transplantation, there is a 'new'



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liver and there is, therefore, no reason to believe that the preoperative liver function will impact on overall survival/outcome – other than, perhaps, as some indication of ‘overall health/performance status’. This has been well documented in studies that used just ALB and BILI (‘ALBI’) as a measure of liver function. In the initial publication (Johnson et al., J Clin Oncol. 20;33(6):550-8 2015) it was shown that ALBI had a major influence on survival in all therapeutic situations, except liver transplantation where there was no impact. Thus BALAD scores would appear, ‘a priori’, to be inappropriate in the transplant setting. I would suggest therefore that the paper just focuses on the biomarkers and their combination with tumour size (S-LAD). If the authors wish to retain the section on BALAD then this should not be the main feature of the paper but included to demonstrate the validity of the above argument that is to suggest that its application in the transplant setting is inappropriate.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 37107

**Title:** Pre-transplant BALAD and BALAD-2 in predicting hepatocellular carcinoma patients recurrence and survival

**Reviewer's code:** 02099384

**Reviewer's country:** Japan

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-12-04

**Date reviewed:** 2017-12-06

**Review time:** 1 Day

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 checked="" 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		[ Y ] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[ Y ] No	

## COMMENTS TO AUTHORS

Wongjarupong et al analyzed the value of BALAD and BALAD-2 in predicting the recurrence of HCC after liver transplantation. I have some comments. 1. (Material and methods) What is the definition of the elevation of each tumor marker in BALAD score? It should be clarified in the figure 1. Is it the same with that in figure 2? If so, how was the cutoff level calculated? 2. (Material and methods) What is the definition of HCC recurrence after liver transplantation? 3. The formula for GALAD and GALAD-z should be clarified. 4. (Discussion section, the 6th paragraph) The authors described that 'with and without HCC recurrence, We compared ...' should be 'with and without HCC recurrence. We compared ...' 5. Figure 1 is not a figure but a table.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 37107

**Title:** Pre-transplant BALAD and BALAD-2 in predicting hepatocellular carcinoma patients recurrence and survival

**Reviewer's code:** 02530754

**Reviewer's country:** Spain

**Science editor:** Ze-Mao Gong

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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 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
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<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 type="checkbox"/> No	

## COMMENTS TO AUTHORS

The manuscript Nicha Wongjarupong and co-workers is a retrospective evaluation of 113 patients with HCC who underwent liver transplantation at a single institution from 2000 to 2008. The authors aimed to validate BALAD and BALAD-2 scores as tools for predicting post-liver transplant tumor recurrence. In absence of any post-transplant intervention able to impact significantly on tumor recurrence, an optimization in the selection of candidates is central and therefore the topic is of great interest. The manuscript is well written and informative. However there are relevant flaws in the study design and methodology that have weakened the evidence. As a result the main conclusion of the study is not sufficiently supported by the results obtained. The authors are kindly invited to consider the following comments: - The authors aimed at validating BALAD and BALAD 2 scores but instead they modified the original scores by



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re-weighting their components in a different formula. There is no true validation. If the original aim is to be pursued, BALAD and BALAD 2 scores should be individually calculated for each patient and be included as such in the multivariate Cox's regression analysis, where other well known predictors of HCC recurrence may be controlled (diameter of the main nodule, number of nodules, microvascular invasion, macrovascular invasion, histological tumor differentiation...). In contrast, if the authors aim at re-weighting the score formula, it would be mandatory to validate the new resulting scores in an external cohort (otherwise external validity is compromised). None of these options are successfully accomplished in the present version of the manuscript.

- The cohort of patients is not consecutive (only 113 patients out of 299 were included because of missing data). Clearly the study is based in a subpopulation with more advanced HCC (with unusually high tumor recurrence rates), which does not represent the entire HCC transplanted population from the Mayo Clinic. Internal validity may be therefore compromised. This fact becomes apparent in the discussion where it can be read: "Thirty-eight of 113 patients (33.6%) with available serum had recurrence. However, when considering all HCC patients who underwent liver transplant during the same period, 43 of 299 patients (14.4%) had recurrence".
- Some authors have suggested that HCC after 3 years post-transplant may not be considered recurrence, but "de novo" HCC. In the present study there was a prolonged surveillance after transplantation and a significant proportion of patients were transplanted with chronic hepatitis C. Since the study was performed in the pre-DAA era, it may well be that some of the patients with late HCC recurrence were actually new HCCs within a recurrent hepatitis C. I would recommend removing late HCC recurrence from the analysis and controlling hepatitis C status in the multivariate analysis.
- The methodology for sample size calculation is not described.
- "Tumor size and tumor number were also determined from the most recent imagins prior to the transplant." Why not from the explanted liver?
- In results it can be read: "The transplant selection criteria for the HCC patients during the study period were mainly based on the Milan criteria and extended criteria, the UCSF criteria, in some patients". This information should be transferred to the methods' section. In addition, it is unclear in which situations were UCSF criteria allowed. Please clarify.
- In addition, there were some patients beyond UCSF criteria both at listing and at the time of transplant (15% and 7%). I understand that this information comes from pre-transplant imaging assessment. In most transplant institutions, these patients would have been removed from the waiting list in line with current guidelines. Please clarify the reason for not excluding these patients.
- Was there any protocolized follow-up after LT to detect tumor recurrence? Please describe.
- Describe the policy for prioritization within the waiting list and the length within the waiting list of the included patients.
- Regarding locoregional bridging therapies within



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the waiting list, please provide indication criteria. - The term “maximal tumor size” is confusing. Do the authors mean the diameter of the largest nodule or total tumor size (sum of the diameters of each detected nodule)? - Information about microvascular invasion and histological tumor differentiation is missing. These histological features are tightly associated with tumor recurrence. The authors should consider this information for the analysis. It would be interesting to know the interaction between BALAD score and histological features of HCC (if any). - The conclusion “The BALAD score and BALAD-2 class is valid to predict recurrence and death in HCC patients with liver transplant” is not supported by the findings of the study. As outlined above the model was not analyzed as such, but instead was re-weighted and not externally validated.