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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 42566

Title: Serum biomarkers and risk of hepatocellular carcinoma recurrence after liver transplantation

Reviewer's code: 02530754

Reviewer's country: Spain

Science editor: Jin-Lei Wang

Date sent for review: 2018-09-28

Date reviewed: 2018-10-02

Review time: 4 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The present manuscript by María José Citores et al. is a comprehensive review on the current state and potential utility of serum biomarkers of HCC in candidates for liver transplantation. The topic is of high interest given the inaccuracy of tumor burden, as

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assessed by dynamic imaging techniques, to predict tumor recurrence after liver transplantation. Not invasive surrogate markers of tumor biology, either alone or in combination with existing radiological criteria, may provide a more rational approach to select candidates for liver transplantation and to prioritize them within the waiting list. The authors are kindly invited to consider the following comments: - In the introduction it can be read: "preoperative biopsy… is not currently recommended for HCC evaluation because of the risk of needle tract tumor seeding". While such risk exists, tumor biopsy is still needed in patients with atypical radiological features. I agree that liver biopsy is not systematically needed, but it is still recommended in doubtful cases (and this trend will probably increase in the next years). Consider rephrasing. - Regarding the above referred paragraph: Microvascular invasion cannot be assessed or predicted by using a needle biopsy. The whole liver specimen (either resected or explanted) is needed for such evaluation. An unequivocal statement is needed. - Regarding systemic inflammatory markers, several meta-analyses of observational studies are quoted. It is fair to state in the manuscript that these studies are based in very low quality evidence and that they are limited by a high risk of publication bias. Indeed, those studies evaluating inflammatory markers with positive results are more likely to be published as compared with studies describing negative findings. In addition, abstracts presented in congresses but not published in full, which are more likely to report negative findings, are systematically not considered. In addition the referred meta-analyses do not provide a valid assessment of risk of publication bias (funnel plots or similar). The authors should therefore refer to these meta-analyses and derived results with great caution. - Aligning with the comment above, the main barrier for implementation of inflammatory markers to select candidates for LT or to prioritize them within the waiting list is their lack of specificity. As the authors acknowledge thereafter, these markers may be increased in other situations such as infections, which

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are frequent in patients with end stage liver disease. This limitation should be further highlighted in the manuscript. - In page 7, last line, the authors quoted a statement from the EASL-EORTC guidelines where AFP was considered a suboptimal marker but as far as I know this pertains to HCC screening only, whereas the authors referred to the whole HCC routine clinical practice. Please revise. - AFP-L3 has been invoked as more specific and may be particularly useful in patients with increased tumor burden but with normal or mildly increased conventional AFP. Please comment. - Another limitation of pre-transplant serum biomarkers to be considered by the authors is that the vast majority of studies published in the field did not implement a methodology to control for competing risks. When considering HCC recurrence as a time-dependent outcome, a patient who experience early death after LT, not related to HCC, may never have a chance to recur. Please comment. - A paragraph delineating further directions may be welcomed. In opinion of the authors, What would be the role of cutting edge biomarkers such as cell free DNA, miRNAs… in the near future? - I would recommend the authors to conclude the manuscript by claiming for an international consensus in this setting, which may provide with practical recommendations to implement serum biomarkers in local practice algorithms. - Minor English polishing is required.

INITIAL REVIEW OF THE MANUSCRIPT

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Reviewer's code: 00054465

Reviewer's country: United States

Science editor: Jin-Lei Wang

Date sent for review: 2018-09-28

Date reviewed: 2018-10-11

Review time: 13 Days

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[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[Y] Accept (General priority)	[Y] Anonymous
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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

This is a nice review of the current state and outcomes of liver resection and transplantation for hepatocellular cancer. Most of the data was retrospective review of biomarkers and the published outcomes of using the Milan criteria for transplantation.

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The authors conclude that using multiple biomarkers may be stronger data to predict the probability of recurrence of cancer after transplantation. A well analyzed conclusion that NOW REQUIRES A PROSPECTIVE STUDY.

INITIAL REVIEW OF THE MANUSCRIPT

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