

## PEER-REVIEW REPORT

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

**Manuscript NO:** 37238

**Title:** Survival outcomes of liver transplantation for hepatocellular carcinoma in patients with normal, high and very high preoperative alpha-fetoprotein levels

**Reviewer's code:** 03656588

**Reviewer's country:** China

**Science editor:** Na Ma

**Date sent for review:** 2017-11-25

**Date reviewed:** 2017-11-28

**Review time:** 2 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 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 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 type="checkbox"/> No	

### COMMENTS TO AUTHORS

1) The authors analyzed retrospectively the data from totally 250 adult patients underwent LT for HCC in their center . It indicated that AFP level of 54 ng/mL was associated with disease recurrence, and AFP level of 105 ng/mL was found to be the cut-off value for overall survival difference. The results are reliable , and the conclusions are convincible . 2) Using AFP alone to predict the tumor recurrence and overall survival would result in bias in selection of patients for LT. How about are the other tumor markers such as PIVKA-II, GPC-3 etc. , tumor size and number to predict the tumor recurrence and overall survival after LT ?

**Answer:**

Thank you very much for your comments.



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As to “Using AFP alone to predict the tumor recurrence and overall survival would result in bias in selection of patients for LT. How about are the other tumor markers such as PIVKA-II, GPC-3 etc. , tumor size and number to predict the tumor recurrence and overall survival after LT ?”, we would like to reiterate that we did not advocate using AFP as the only factor to predict recurrence and survival after LT; what we proposed was adding AFP to the armamentarium of assessment tools for LT listing. Other tumor markers and prediction factors were not included in this paper since, as the title of the paper suggests, this study focused on the influence of AFP on HCC recurrence and patient survival after LT.

We have made modification to the second last paragraph of the paper. The modified paragraph now reads:

*The findings of this study may not be universally applicable, as AFP 105 ng/mL is a value calculated from our cohort of 250 patients. Moreover, this is a retrospective cohort study with inevitable selection bias. Furthermore, the different levels of AFP (normal, high and very high) were arbitrarily defined. Before adopting AFP as a decision-making tool based on current selection criteria, we have to balance the risk of disease recurrence (hence overall survival) and the patients’ expectation. Still, it is hoped that this study can shed some light on the importance of adding AFP to the armamentarium of assessment tools for LT listing.*

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

**Manuscript NO:** 37238

**Title:** Survival outcomes of liver transplantation for hepatocellular carcinoma in patients with normal, high and very high preoperative alpha-fetoprotein levels

**Reviewer's code:** 00005191

**Reviewer's country:** United States

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" 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 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
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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 on "Survival outcomes of liver transplantation for hepatocellular carcinoma in patients with normal, high and very high preoperative alpha-fetoprotein levels" is a retrospective cohort study where the Authors investigate the impact of alpha-fetoprotein (AFP) on HCC long-term recurrence rate and overall survival after liver transplantation (LT). They also aim to define the level of AFP leading to a higher risk of disease recurrence and affecting patient survival. Patients with hepatocellular carcinoma (HCC) are currently listed for liver transplant (LT) based on Milan criteria. However, according to the Authors, also other biological markers should be explored to predict disease recurrence and patient survival. Data of 250 adult patients who received LT for HCC at the Authors' hospital from January 2000 to December 2013 were reviewed. The patients were divided into 3 groups: Group A, AFP <10 ng/mL (n=83); Group B,



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AFP  $\geq 10$  -  $< 400$  ng/mL (n=1); Group C, AFP  $\geq 400$  ng/mL (n=36). Results showed that higher AFP level was associated with tumor recurrence. The optimal cut-off value was set at 54 ng/mL. However, on further discriminative analysis, 105 ng/mL was set as the cut-off value and it demonstrated significant survival difference despite same amounts of patients who were within the Milan and UCSF criteria. No exact cut-off value could be indicated as an absolute value for contraindication to LT. The Authors maintain that their study suggests the importance of using AFP as one of the preoperative surrogate markers to evaluate LT candidates, as it represents additional information on identifying high-risk patients preoperatively so as to predict the risk of recurrence and to let patients have realistic anticipation regarding their long-term outcomes. Therefore, in addition to morphological consideration of tumor, the Authors conclude that the adoption of biological markers such as alpha-fetoprotein (AFP,) should be integrated into transplant criteria. As the Authors themselves stress, the study has its limitations, being a retrospective one. Their findings cannot be generalized, also because of inevitable selection bias. Nonetheless, the study sheds some light on the importance of AFP as an assessment tool for LT listing and it is certainly worth publication. Not only is the manuscript very well-written and includes plenty of pertinent and useful literature sources; it also brings new, meaningful information to all clinicians involved with care and management of HCC patients and LT candidates. If confirmed by further research, this message could affect LT evaluation and listing criteria, hence affect thousands of patients globally.

**Answer:**

Thank you very much for your comments.