

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 24432

Title: Hepatocellular Carcinoma: Review of disease and tumor biomarkers

Reviewer's code: 00182114

Reviewer's country: Japan

Science editor: Ya-Juan Ma

Date sent for review: 2016-01-23 08:47

Date reviewed: 2016-01-26 13:28

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 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"/> Duplicate publication	
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input 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

Dear Author 1. Serum biomarkers are striking potential tools to screen for and diagnose HCC early thanks to the non-invasive, objective, and reproducible assessments they can potentially enable. α -fetoprotein (AFP) is the biomarker most widely used to test for HCC, but the sensitivity and specificity of AFP vary widely, and total AFP is not always specific, especially when HCC is in its early stages. Whereas the sensitivity of AFP analysis used in conjunction with ultrasound to detect early-stage HCC has ranged from about 40% to 65%, the combination use of newer biomarkers, the Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and des-gamma-carboxy prothrombin (DCP) (PIVKA-II) plus ultrasound, provides a sensitivity of nearly 85% and a specificity of nearly 95%. I ask some questions. According to your Table 2, AFP1-3 is much higher in sensitivity and specificity compared to AFP, DCP and AFU. How about the sensitivity and specificity if you use the combination of AFP1-3 and DCP.? 2. Although DCP (PIVKA-II), AFP-L3, and Osteopontin (OPN) exhibit high specificity regarding the diagnosis of HCC, many clinicians use AFP values to follow-up patients with chronic liver diseases due to its higher sensitivity. The results of conventional tumor markers are negative for approximately 30% to 40% of HCC patients; therefore, searching for novel



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HCC markers must be continued. Squamous cell carcinoma antigen (SCCA) and HSP70 may be considered as key biomarkers for HCC patients when the results for traditional biomarkers are negative. (An Overview of Biomarkers for the Diagnosis of Hepatocellular Carcinoma, Hepatitis Monthly 2012) Please tell me how about SCCA and HSP70 for HCC biomarker? 3. HIF-1 plays important roles in many critical aspects of HCC tumorigenesis, progression, and metastasis. It is involved in cellular proliferation, angiogenesis, invasion, and resistance to radiotherapy and chemotherapy. Clinical data also indicate that HIF-1 overexpression is associated with poor prognosis of HCC. More importantly, HIF-1 is identified as a potential target for HCC therapy. (The Role of Hypoxia Inducible Factor-1 in Hepatocellular Carcinoma 2014) Please comment the biomarker and target therapy of HIF-1 for HCC. Author comment various kinds of biomarker for HCC. Please tell me about some specific biomarker .

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

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Title: Hepatocellular Carcinoma: Review of disease and tumor biomarkers

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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 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"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input 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 paper is quite interesting and highlights the unanswered need for a specific and cheap serum or urinary biomarker useful for early diagnosis of HCC especially in not developed countries. Some minor points should be clarified Core tip: write proton nuclear magnetic resonance and mass spectrometry instead of 1H NMR and MS Too many abbreviations are used throughout the paper and this makes the reading difficult. I think that a list of abbreviations should be reported. Furthermore, I do not understand the meaning of some abbreviations such as TSA, TCA, CA, GC-MS, HILIC, and RPLC Introduction: according to the present guidelines percutaneous ablation should be added to the curative treatments of HCC Paragraph The angiogenic switch: dysplastic nodules are often but not always hypoechoic on ultrasound; they can also less frequently appear as hyperchoic or isoechoic. Please, correct Paragraph Current surveillance and diagnosis: the Authors should specify that the present guidelines for non invasive diagnosis of HCC apply only to patients with established liver cirrhosis I looked for reference 76 in pubmed but I could not find it Discussion: I think that it is too much short. The Authors should add a paragraph highlighting which are at present the more promising candidate metabolites in the blood and urine that could be tested in large series of



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cirrhotic patients with HCC (especially in the very early and early stage) and without HCC



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COMMENTS TO AUTHORS

This is a nice review which comprehensive reviewed the literature. Several biomarkers for diagnosis HCC were described in this review. However, the sensitivity and specificity of some biomarkers were different between Eastern patients and Western patients. I think the authors should also describe such content.