PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 75525

Title: Clinical value of contrast-enhanced ultrasound in the early diagnosis of small hepatocellular carcinoma (≤2 cm) in patients with high risk factors

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

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Reviewer's code: 05230210

Position: Editorial Board

Academic degree: MD

Professional title: Associate Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I would like to thank the authors for their work.   The English language needs extensive revision. There are a lot of grammatical and spelling mistakes in the manuscript.   The presentation of the methodology and results is sometimes confusing, I recommend adding a flow chart for their presentation and adding the outcome of the patients (how the patients were managed) In abstract: • The authors stated in materials and methods: "632 nodules in 395 patients clinical data at high risk of HCC who underwent regular follow-up at *** Hospital were prospectively collected from January 2007 to December 2021." If this is a primary diagnosis then it is the number of patients with their end diagnosis that should be mentioned. And also could you elaborate how the nodules were diagnosed in the first place (ultrasound, triphasic CT, MRI?), and whether confirmation of the benign consistency of these lesions is confirmed by CT triphasic and AFP level or not (gold standard)? •   There is no mention of the type of the study only that it is a prospective study, (cross sectional, case control, etc)? • There   is   no mention how the authors categorized patients as high risk for HCC (previous HCV, HBV, cirrhosis, etc) , kindly elaborate. Introduction: • Could you elaborate more on the current HCC guidelines and their limitations, and the CEUS studies performed in this area? Materials and methods: •   The authors didn't mention how they diagnosed the dysplastic transformation and the HCC transformation? By biopsy or by CT triphasic, etc.?, please clarify, as the diagnostic tools is mandatory in judging the diagnostic accuracy of the text used. •   An important point to address: The number of nodules is very high as compared to the number of patients, as the authors stated "632 nodules in 395 patients clinical data at high risk of HCC" which means that each patient is most

likely to have multiple nodules, hence the prognosis is worse as compared to lesser number as the study of Huang et al, could explain the effect of this on the diagnostic yield? and AFP level? • Ref: Diagnostic Accuracy of CEUS LI-RADS for the Characterization of Liver Nodules 20 mm or Smaller in Patients at Risk for Hepatocellular Carcinoma. Jia-Yan Huang, Jia-Wu Li, Qiang Lu, Yan Luo, Ling Lin, Yu-Jun Shi, Tao Li, Ji-Bin Liu, and Andrej Lyshchik. Radiology 2020 294:2, 329-339 •

In the inclusion criteria the authors mentioned "increase in one of combined indicators of HCC (AFP or a new HCC marker Glypican-3), but imaging examination showed no space-occupying lesions">> but if there is no space occupying lesions how did you include for hypoechoic nodules in the first place? This statement means that the AFP was high with no ultrasound findings, then why did you include? Kindly explain.

• I advice to add a flow chart to know the number of patients diagnosed by clinical and ultrasound evaluation and by biopsy examination and by CT? Results: • In the results section the authors mentioned "Of the 93 patients who underwent surgery and needle biopsy">> why a cirrhotic patient with nodular lesion of <2 cm undergo a liver biopsy?? Could you expain the reason for biopsy and why did a surgical team do it? Not radiology or gastroenterology? And if that mean excision not just biopsy (as figure two shows a specimen of 5 cm)? • In table 3 you mention dysplastic nodule, does that include only the patients decided by pathology? Please see previous comment. • No mention of the AFP or other lab correlation? why • The result only contain correlation not roc curve and diagnostic accuracy testing which is more relevant to this type of study, could you explain and modify the results? • Could you add a table of CEUS LI-RADS results for all the patients? • Does the increased number of nodules in each patient correlate with the HCC diagnosis or not in this study? • If this is a prospective study then what was the treatment and prognosis of the patients? Lobe excision- liver transplantation or radiofrequency? It is important to add this follow up

data. Discussion: • Most parts of the discussion could be added to the introduction.

• Please focus in the discussion on the explanation of your results, and the comparison with other studies done in the same area and their diagnostic accuracy yield versus yours. Conclusion: Good References: add for discussion as mentioned before

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SPECIFIC COMMENTS TO AUTHORS

Exciting topic. Abstract has several sentences that may be unclear or hard to follow (example: "Use conventional ultrasonographyp plus CEUS to comparative analysis of the echo, size,location and enhancement characteristics of benign and malignant nodules, as well as enhancement methods for HCC of different diameters" It should be like: "Use conventional ultrasonography plus CEUS for comparative analysis of the echo, size, location, and enhancement characteristics of benign and malignant nodules and enhancement methods for HCC of different diameters"). Unfortanutalley, the whole manuscript needs to be revised for the English language. I cannot understand the "***" hospital. Please be more precise in the provided classification in the diagnostic criteria session. For example, the CEUS findings were classified into four different categories: 1. the lesion area was slower wash-in, and the portal and delayed phases showed isoechoic enhancement, and washed out isochronously as with the liver parenchyma, namely the "slow-in and isochronous-out" type, this suggested a dysplasia nodule. 2…….etc. You must, also, provide the reference data for this classification. Crucial information is missing in Table 1, like the etiology of liver disease, the presence of cirrhosis, and the grade of cirrhosis. In Table 2, the variables were supposed to be presented as "n (%)". The percentage is missing. Statistically, non-significant p-values should be presented as "NS," not as ">0.005". Otherwise, you can use the non-significant p-value itself (example, p=0.23). Figure 3 is missing? Authors conclude that the smaller the HCC nodule, the later the contrast agent began to wash out. They further indicate that the HCC nodule size was negatively correlated with the duration of enhancement of the contrast agent. However, as shown in Table 4, small size HCCs (≤1cm) had a more "typical" pattern

than those of 1-2 cm [Fast-in and fast-out pattern: 5 (76.92%) vs. 33 (63.46%)]. Is there any explanation for this? Thus, is the enhancement time the only statistically significant difference? In the discussion session, the study's main aim was to evaluate the contrast-enhanced ultrasound in the early diagnosis of small hepatocellular carcinoma. This should be clear. Unfortunately, the discussion session is not well organized and is chaotic. Therefore, it would help to start the discussion with the study's main findings. The crucial conclusion is the enhancement time differentiation between different size HCCs. You also should mention the role of the "wash-out" time, which is the standard of care: two paragraphs plus the conclusion.

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Please add explanations mentioned in the   answers to reviewer 2 in questions (5 and 6) to your discussion. Also, kindly modify (mo) to months in your manuscript.