PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73990

Title: Contrast-enhanced ultrasound LI-RADS: lights and shadows in hepatocellular carcinoma and cholangiocellular carcinoma diagnosis

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05127202

Position: Peer Reviewer

Academic degree: PhD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Italy

Manuscript submission date: 2021-12-17

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-12-24 03:16

Reviewer performed review: 2021-12-24 03:30

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] 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

The article is good, but it is too long. I suggest it be shortened.

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Title: Contrast-enhanced ultrasound LI-RADS: lights and shadows in hepatocellular carcinoma and cholangiocellular carcinoma diagnosis

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05319716

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: Italy

Manuscript submission date: 2021-12-17

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-02 09:53

Reviewer performed review: 2022-01-04 04:05

Review time: 1 Day and 18 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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 [Y] Grade B: Minor language polishing [ ] 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

Comments to the Authors: The authors, Vidili G et al. report Accuracy of CEUS LI-RADS for HCC and ICC diagnosis. They evaluated the accuracy of CEUS LI-RADS in the differentiation between HCC and ICC.   Liver biopsy is the final diagnosis for HCC and ICC diagnosis, but it is an invasive test and building on the knowledge of contrast echocardiography is a very important part of clinical research.   Major comment   1. The fact that only 20% of the tissues were collected degrades the quality of this study. How CT and MRI were used to classify HCC and ICC should be described in the section   of   Contrast-enhanced ultrasound examination and CEUS LI-RADS classification.   2.The typical images of typical HCC and ICC from this study should be included in   figure as   the CT, MRI, and pathology.   3.In addition, the combined type of HCC and ICC and CoCC are likely to be mixed in this case, and although it is difficult to change the study design from now on, it should be added in the Discussion.

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Title: Contrast-enhanced ultrasound LI-RADS: lights and shadows in hepatocellular carcinoma and cholangiocellular carcinoma diagnosis

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03741383

Position: Peer Reviewer

Academic degree: N/A

Professional title: N/A

Reviewer's Country/Territory: China

Author's Country/Territory: Italy

Manuscript submission date: 2021-12-17

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-12-31 03:56

Reviewer performed review: 2022-01-11 16:43

Review time: 11 Days and 12 Hours

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

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

SPECIFIC COMMENTS TO AUTHORS

Comments to Author Title: Contrast-enhanced ultrasound LI-RADS: lights and shadows in hepatocellular carcinoma and cholangiocellular carcinoma diagnosis   The purpose of this retrospective study is to determine the diagnostic performance of CEUS LI-RADS using SonoVue in accurately differentiating ICC from HCC in patients with cirrhosis. Advantages: 1. A relatively large sample size (511 observations in 269 patients) were included in the study. 2. Refinement of CEUS LR-3 category   Disadvantages: 1. Although the manuscript was structured, it seemed to be lengthy. 2. The probability of HCC in CEUS LR-4 category was 97.4% in this study, which was better than the estimate value of LR-5 in other studies concerning CEUS and CT/MRI LI-RADS category (Shin et al. Liver International.2020,DOI: 10.1111/liv.14617;van der Pol et al, Gastroenterology, 2019,DOI: 10.1053/j.gastro.2018.11.020). That might be the cause that the specificity of CEUS LR-4/5 for diagnosing HCC remained 94.3% specificity and 98.8% PPV. The results cannot be generalized to other populations. 3. The process of patient selection was not clearly elaborated. Lesions that can easily be confused with HCC (eg, mixed HCC-CCA, FNH, hepatic adenoma, inflammatory pseudotumor, etc) were not included in the cohort, which might lead to overestimation of diagnostic accuracy. 4. Pathological diagnosis was only available for 102 (20%) cases.   Specific comments Abstract It was mentioned before, the abstract is lengthy. Please edit the text to make it as concise as possible. Pg 4 Ln12 The phrase 'even though' was not used appropriately.   Key words When available, please use controlled vocabularies, such as medical subject headings (MeSH). Pg 4 Ln25. Use 'cirrhosis' instead of 'hepatic cirrhosis'.   Introduction The authors did not give a full account of the innovativeness of the study.   Material and

Methods Pg 7 Ln4. How to confirm the presence of cirrhosis? Was the diagnosis of cirrhosis established by pathological diagnosis or by imaging with MRI or elastography in conjugation with laboratory and clinical findings? Pg 7 Ln3-5. How many patients with multiple lesions? And how to deal with cases with multiple intrahepatic foci in this study? How were target lesions selected? How many target lesions per patient were allowed? Pg 7 Ln6-7. Were patients consecutively or selectively included? Pg 7 Ln10-11. 'CT and/or MRI, when typical for HCC or definitely benign, were used as the gold standard imaging modalities, as per HCC international guidelines'. Indeed, different guidelines have slightly different imaging reference standard. Does 'definitely benign' refer to hemangioma? Pg 7 Ln15-17. What does it mean that 'The American Association for the Study of Liver Diseases (AASLD) guidelines were followed……until the end of our study'? Does it mean the imaging reference standard adopted before 2013 was different from that after 2013? If so, what's the differences? Pg 7 Ln 23-25. How many cases with deep-seated lesions or severe fatty liver were excluded? In these cases, it is difficult to review the main features. Pg 7 Ln 23-25. Were lesions with prior treatment for HCC included? Pg 8 Ln 21-22. 'The reviewers were blinded to patient identity and to the final diagnosis after CT, MRI or biopsy'. Were the reviewers blinded to study design? Pg 9 Ln 8-10. How these 50 cases were selected? Randomly or artificially? Pg 9 Ln 20-22. How these estimates of diagnostic accuracy were calculated? Was generalized estimating equations (GEE) used for adjusting aggregation effects? Results Please show the probability of HCC in each LR category. Pg 11 Ln29- Pg12 Ln2. The probability of HCC in CEUS LR-4 category was 97.4%, which was close to the estimate value of LR-5 in other studies concerning CEUS and CT/MRI LI-RADS category (Shin et al. Liver International.2020,DOI: 10.1111/liv.14617;van der Pol et al, Gastroenterology, 2019,DOI: 10.1053/j.gastro.2018.11.020). That might be the cause that the specificity of CEUS LR-4/5 for diagnosing HCC remained 94.3% specificity and 98.8%

PPV.   Pg 13 Ln 2-4. In this study, all nodules were greater than 10mm. Five nodules (1%) were categorized as CEUS LR-2 rather than LR-3. Please explain it. Pg 13 Ln 6-21. The interobserver agreement was substantial or almost perfect concerning LI-RADS category in this study. But in a study by Zhou et al (Ultraschall Med. 2020. DOI: 10.1055/a-1168-6321), the inter-reader agreement was not satisfactory concerning CEUS LI-RADS category and washout appearance.   Discussions Pg 15 Ln 17-19. In the current study, the most frequent CEUS pattern in the arterial phase was rim APHE. But it was only observed in 16% (55/354) cases in a study by Zheng et al (Radiology 2020; 294:299–307. DOI: 10.1148/radiol.2019190878).

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] 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	[ ] Yes [Y] No

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

SPECIFIC COMMENTS TO AUTHORS

This retrospective study aimed to evaluate the accuracy of CEUS LI-RADS in diagnosing HCC and ICC in patients with hepatic cirrhosis. The results reinforced the fact of high specificity of LR-5 for the diagnosis of HCC. The authors also found ICC could be predicted by LR-M with 91.3% sensitivity and 96.7% specificity. Moreover, the authors proposed to split the LR-3 into two subgroups due to the huge discrepancy of malignancy possibility. The paper is well written and discussed. However, there are some issues need to be clarified. 1. The feasibility to calculate the diagnostic ability of LR-4 or LR-3. Take LR-4 for example. A nodule should be regarded as HCC if it meets the feature of LR-4. If a nodule does not meet the feature of LR-4, should it be taken as non-HCC even if it meets the criteria for LR-5?   The same question exists for LR-3. That is why in most studies, only percentage of HCC was presented in these categories.   2. How to explain the low PPV of LR-M for the diagnosis of ICC? The composition of pathologic entities in LR-M has enormous impact for the diagnosis of ICC. This study not only has a relatively lower percentage of HCC, but also high percentage of ICC in LR-M group. So, the diagnostic power of LR-M for diagnosing ICC may be exaggerated and the finding needs outer validation before clinical application.   3. In this study, there was a much higher proportion of ICC in LR-M category compared with previous studies (including those with large sample) which HCC composed the majority of LR-M lesions. The authors should explain this discrepancy.   4. The issue of reference standard should be addressed in detail since most of the cases were diagnosed by CT/MRI. Are there any cases that diagnosed as CE/MRI LI-RADS 2 or 3 or 4? If so, the reference standard is not as robust as it should be.   5. In the methods part, how long

was the CEUS procedure observed?   As we observed in clinical practice, washout could be identified as late as 5 minutes after contrast agent injection. If the procedure was not observed long enough, some of the LR-5 cases could be taken as LR-4.   6. If patients have multiple nodules, especially those with more than 3 lesions, are all lesions included for analysis? Multiple target nodules might impact the effective evaluation of liver nodules in CEUS examination. The author should elucidate this issue.   7. Tables should be presented in form of three-line table.