

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 58780

**Title:** Contrast-enhanced ultrasound in association with serum biomarkers for differentiating combined hepatocellular-cholangiocarcinoma from hepatocellular carcinoma and intrahepatic cholangiocarcinoma

**Reviewer's code:** 05038583

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-08-06

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-09-17 17:33

**Reviewer performed review:** 2020-09-19 15:49

**Review time:** 1 Day and 22 Hours

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

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

## SPECIFIC COMMENTS TO AUTHORS

Prognosis and treatment modality for CHC are different from HCC or ICC alone, therefore it is important to make a correct diagnosis. As imaging diagnosis is a main modality for HCC diagnosis, CHC is often misdiagnosed as HCC. In addition, as authors mentioned, even biopsy may lead to incorrect diagnosis due to sampling error. This study aims to study the utility of CEUS in differentiating CHC from HCC or ICC which is clinically very important. One potential bias for this study is that everyone had histologically confirmed CHC, ICC, and HCC from liver resection. This implies that everyone in this study had relatively compensated cirrhosis or had tumor without underlying fibrosis who were candidate for resection. I wonder if these findings can be generalizable for decompensated cirrhotic patients which are more common in non-Asian countries. I do understand that from the study design and the study population, I do not think authors are able to answer this question and they mentioned this in limitation which is appropriate. Another potential issue of this study is sample size which resulted in low AUC noted in discussion section and table 5. I understand that CHC is a rare disease and I do not think it is possible for authors to address this issue as they acknowledged in limitation. Although this may be an issue, I believe this study can give an insight into the future studies. Overall, this is a well written paper on a very important topic.

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**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 58780

**Title:** Contrast-enhanced ultrasound in association with serum biomarkers for differentiating combined hepatocellular-cholangiocarcinoma from hepatocellular carcinoma and intrahepatic cholangiocarcinoma

**Reviewer's code:** 01804834

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Germany

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-08-06

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-09-16 08:45

**Reviewer performed review:** 2020-09-22 13:40

**Review time:** 6 Days and 4 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

## SPECIFIC COMMENTS TO AUTHORS

Here, the present work of Yang and Coworkers evaluates diagnostic pathways using contrast-enhanced ultrasound (CEUS) as well as serum biomarkers in order to discriminate combined hepatocellular carcinoma (CHC) from hepatocellular carcinoma (HCC) as well as intrahepatic cholangiocarcinoma (ICC). This retrospective study includes patients with a chronic liver disease from 2016 to 2019. The main finding of this trial is that the use of CEUS and its classification system, the Liver Imaging Reporting and Data System (LI-RADS) in combination with serum biomarkers provides a high specificity. Thereby, CHC can be safely excluded and the diagnostic pathway using CEUS LI-RADS in combination with serum biomarkers is novel. In addition, the study helps to further characterize CHC, also in contrast to HCC and ICC. The authors analyzed ultrasound findings in detail and compared it in detail in between the entities. However, the number of patients included and used for statistics is very small. In order to make the work more comprehensive, the following topics should be addressed. 1) As the CHC is a rare primary liver cancer, background literature describing the significance with regard to prevalence and therapeutic consequences is missing. The clinical impact of the trial is not stated, neither in the introduction nor in the conclusion. One has difficulties to imagine, how this diagnostic tool will be implemented into the clinical routine. A scheme, representing the diagnostic pathway in order to differentiate HCC from CHC for example might help to implement these findings into clinical routine. 2) Statistical outcomes such as sensitivity, specificity as well as the positive and negative predictive value are summarized for the three diagnostic pathways. The application of these three constellations consisting of a liver nodule classified as LR-5 or LR-M and serum biomarkers AFP and/or Ca19-9 seems fairly complicated for the daily clinical

application. In order to raise the awareness, these constellations should be examined separately. 3) In the clinical routine, nodules at risk of an ICC or CHC might be subjected to a biopsy. How many of the patients did receive a biopsy and what was the histological diagnosis? 4) Moreover, these patients might have received a CT scan or MRI scan. Studies by Sagrini et. al. (2019) suggest that CEUS misdiagnosed a higher number as HCC in comparison to CT scans or MRI scan. How do the authors comment on this finding? 5) In order to fully understand the data in detail, the p-values for the separate echogenic degrees are needed (hypo- vs. hyperenhancement) 6) The unit used in table 4 for the serum biomarkers remains unclear. Taken together, the authors add a valuable puzzle piece to the understanding of CHC. Prospective studies investigating the effect of this diagnostic tool in patients at risk and in a large population will be of great interest. Therefore, there work could be considered for publication.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Gastroenterology

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**Title:** Contrast-enhanced ultrasound in association with serum biomarkers for differentiating combined hepatocellular-cholangiocarcinoma from hepatocellular carcinoma and intrahepatic cholangiocarcinoma

**Reviewer's code:** 05038583

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-08-06

**Reviewer chosen by:** Chen-Chen Gao

**Reviewer accepted review:** 2020-11-02 04:10

**Reviewer performed review:** 2020-11-02 04:22

**Review time:** 1 Hour

<b>Scientific quality</b>	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Very good <input type="radio"/> Grade C: Good <input type="radio"/> Grade D: Fair <input type="radio"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="radio"/> Grade A: Priority publishing <input type="radio"/> Grade B: Minor language polishing <input type="radio"/> Grade C: A great deal of language polishing <input type="radio"/> Grade D: Rejection
<b>Conclusion</b>	<input type="radio"/> Accept (High priority) <input checked="" type="radio"/> Accept (General priority) <input type="radio"/> Minor revision <input type="radio"/> Major revision <input type="radio"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="radio"/> Anonymous <input type="radio"/> Onymous Conflicts-of-Interest: <input type="radio"/> Yes <input checked="" type="radio"/> No

#### **SPECIFIC COMMENTS TO AUTHORS**

I reviewed a revised manuscript and comments from the other reviewer. Authors addressed reviewer's comments appropriately and this study should be accepted. No further comments for additional revision.