Peer Review File

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Reviewer A

This study investigated the diagnostic accuracy of Contrast-Enhanced Ultrasound for HCC. The major limitation of this work is lacking of novelty because this topic has been discussed in several articles. Furthermore, the language quality of this manuscript is too poor and it needs to be edited.

λ Please do not use the word "liver cancer". It should be "hepatocellular carcinoma".
Reply: Thanks for your comment. We have revised it.
Changes in the text: The full text involves the word "liver cancer".
λ Abstract: the statistical methods, as well as the diagnostic accuracy metric, need should be reported.
Reply: Thanks for your comment. We have revised it. Meta analysis used STATA 17.0 to fit the bivariate mixed effects model, calculated sensitivity, specificity, PLR, NLR, DOR, and corresponding 95% CI, SROC, AUC, and their 95% CI. The publication bias of the included literature was evaluated using the DEEK funnel plot
Changes in the text: Paragraph 2 / Abstract
λ Meta-analyses have been performed to discuss the diagnostic value of Contrast-Enhanced Ultrasound for HCC (J Ultrasound Med. 2022 Jun;41(6):1537-1547; Liver Int. 2020;40(10):2345-2352.). Please indicate the strength of this meta-analysis.
Reply: Thanks for your comment. We have revised it. This article (J Ultrasound Med. 2022 Jun;41(6):1537-1547) mainly compares the diagnostic value of hepatocellular carcinoma without staging, while our article focuses on the diagnostic value of early hepatocellular carcinoma; and the article (Liver Int. 2020;40(10):2345-2352.) is a combined system of contrast-enhanced ultrasound (CEUS) liver imaging reporting and data system (LI-RADS) for the diagnosis of hepatocellular carcinoma. We have included relevant literature explanations in the discussion.
Changes in the text: Paragraph 3 / Discussion

λ LineS 130 to 131: the original data should be sensitivity, specificity, sample sizes of HCC and non-HCC, rather than TP/FP/FN/TN.
Reply: Thanks for your comment. We have revised it. The original data used in this article are indeed true positive numbers, false positive numbers, false negative numbers, and true negative numbers (TP/FP/FN/TN) rather than the sensitivity, specificity, sample sizes of HCC and non-HCC.
Changes in the text: None

λ Lines 138 to 139, full text of the article could not be obtained. -----this is not a reasonable exclusion criterion.

Reply: Thanks for your comment. We have deleted it.

Changes in the text: Paragraph 3 / Methods

λ Lines 149 to 150, a reference should be cited there.

Reply: Thank you for the suggestion. We have added the citation.

Changes in the text: Paragraph 5 / Methods

λ Line 157, a reference should be cited there.

Reply: Thank you for the suggestion. This is a commonly used algorithm in STATA software and does not require specific references to be added.

Changes in the text: None

λ Lines 159 to 161, a reference should be cited there.

Reply: Thank you for the suggestion. we have added the citation.

Changes in the text: Paragraph 6 / Methods

λ Lines 161 to 162, a reference should be cited there.

Reply: Thank you for the suggestion. we have added the citation.

Changes in the text: Paragraph 6 / Methods

λ The discussion section is insufficient. The clinical implications and the strength of this study is not discussed.

Reply: Thank you for the suggestion. We have discussed it.

Changes in the text: Paragraph 2,3 / Discussion

λ The results of meta-regression should be listed in a table.

Reply: Thanks for your comment. The main results of Meta regression have been explained in the description, but this result is not applicable and there is no need to present it in a table.

Changes in the text: None

λ Lines 208 to 211: the statement is confusing and it is not supported by data.

Reply: Thanks for your comment. We have revised it. This means that we used Meta regression to identify sources of heterogeneity, where the published country and nodule size calculations showed $P>0.05$, indicating that it is not a source of heterogeneity. Therefore, it can only be inferred from the literature that the possible reason may be the heterogeneity of the analysis results caused by differences in the testing instruments used by medical units and the technical proficiency of operators.

Changes in the text: Paragraph 5 / Results

λ Lines 181 to 189: references should be cited to indicate the quality of included studies. For example, which studies have patient selection bias?
Reply: Thanks for your comment. We have added them.
Changes in the text: Paragraph 2 / Results

λ Large portion of included studies are from China, and the included studies in this systematic review seems to be different from that in previously published meta-analysis (J Ultrasound Med. 2022 Jun;41(6):1537-1547; Liver Int. 2020;40(10):2345-2352. Ultraschall Med; 2021;42(2):187-193; Clin Hemorheol Microcirc. 2021;79(2):293-309; Medicine (Baltimore). 2021;100(6):e24602; Hepatol Int. 2020;14(6):1104-1113; Liver Int. 2020;40(10):2345-2352; J Cancer Res Ther. 2016;12(Supplement):C274-C276.). Please explain the possible reasons
Reply: Thanks for your comment. This article mainly focuses on early hepatocellular carcinoma. When screening the literature, early limitations were added, so any literature that did not meet the criteria for early liver cancer was excluded.
Changes in the text: None

Reviewer B

First, the abstract needs further revisions. The background did not indicate the clinical controversy regarding the diagnostic accuracy of CEUS for liver cancer and what the clinical significance of this research focus is. The methods need to describe the inclusion of related studies according to the PICOS principle and data extracted from included studies. The results need to briefly summarize the numbers of subjects with and without liver cancer in included studies and test results of heterogeneity. The conclusion needs more detailed comments for the clinical implications of the findings.
Reply: Thank you for your suggestion. In the background we have added the clinical controversy about the diagnostic accuracy of CEUS for hepatocellular carcinoma and the clinical significance, in the methodology we have modified the content, and in the conclusions we have added more detailed clinical significance.
Changes in the text: Paragraph1,2,3 / Abstract

Second, the introduction is not adequate. Because meta-analysis is often used to address controversy, the authors need to present detailed examples on the inconsistent findings on the diagnostic accuracy of CEUS for liver cancer, analyze the potential reasons for the controversy, and explain why a meta-analysis is suitable for this research focus.
Reply: Thank you for your suggestion, we have added the reasons for the controversy in the introduction section and explained the reasons why Meta-analysis is appropriate to analyse the controversy over the diagnostic accuracy of CEUS for liver cancer.
Changes in the text: Paragraph 2 / Introduction

Third, in the methodology of the main text, the authors need to specify the control groups in the inclusion criteria for eligible studies, i.e., those with benign tumor, healthy controls, or with other conditions. Please specify the items in the QUADAS-2 and the criteria for high, low, and unclear risk of bias. In statistics, please consider sub-group

analysis to text the sources of heterogeneity and ensure P<0.05 is two-sided. The potential sources of heterogeneity should consider the subtype of controls in included studies.

Reply: Thank you for your comment. The meta-analysis method used in this article is not applicable to subgroup analysis. Instead, Meta regression was used in the article, and the results showed that the heterogeneity sources we included were calculated to be P>0.05, confirming non heterogeneity sources. Therefore, this subsequent article conducted a possibility analysis on other possible sources of heterogeneity. P<0.05 is a bilateral test.

Changes in the text: Paragraph 6 / Methods.

Reviewer C

1. Please check all abbreviations in the abstract, such as below abbreviations in the abstract. All abbreviated terms should be full when they first appear.

> assessment tool. The meta-analysis was performed using STATA 17.0 to fit the bivariate mixed effects model, calculated sensitivity, specificity, PLR, NLR, DOR, and corresponding 95% CI, SROC, AUC, and 95% CI. The publication bias of the included

Reply: Thanks for your comment. We have added them.

2. Please check all abbreviations in the main text, such as below abbreviations. All abbreviated terms should be full when they first appear.

> of hepatocellular carcinoma in patients with cholangiocarcinoma (11). The detection rate of liver CEUS in detecting early hepatocellular carcinoma has been questioned, and it is still necessary to combine CT, MRI, and some biomarkers to improve the

Reply: Thanks for your comment. We have added them.

3. The below cited references should be (5,6,16-22).

> co-infections were excluded. Ultimately, 9 articles (5,6,12-18) were included in the meta-analysis. The screening process is shown in Figure 1.

Reply: Thanks for your comment. We have revised it.

4. Table 1:

1) The author's name doesn't match with the reference 22. Please check.

Shan-Sha 2005, (22)	China	48	146

Reply: Thanks for your comment. We have revised it.

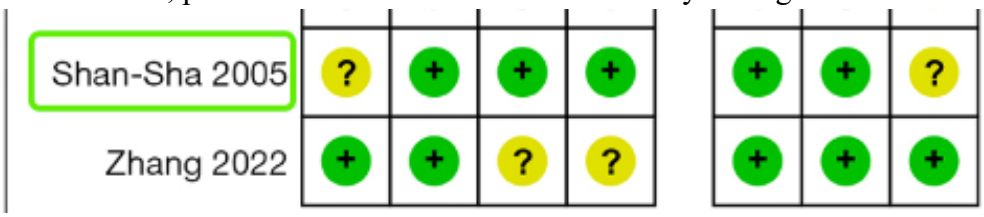
2) Please indicate how the data are presented for Age and Nodule size in Table footnote.

For example, Data are presented as mean ± SD or range for Age and Nodule size.

Reply: Thanks for your comment. We have added it.

5. Figures 2-5:

Same with Table 1, please also check the author's name in your Figures.



Reply: Thanks for your comment. We have revised it.

6. Figures 6-7:

Figures 6-7 legends are wrong. It should be "Numbers 1–9 in the figure represent references 5,6,16-22.".

522 **Figure 6 Summary receiver operating characteristic curve of contrast-enhanced**
523 **ultrasound diagnosis of early liver cancer.** Numbers 1–10 in the figure represent
524 references 12–16, 5, 17, 18, 6. SENS, sensitivity; SPEC, specificity; SROC, summary

Reply: Thanks for your comment. We have revised it.