Original Article

Diagnostic value of liver contrast-enhanced ultrasound in early hepatocellular carcinoma: a systematic review and meta-analysis

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Background: Hepatocellular carcinoma is the sixth most common cancer in the world, and its incidence rate will continue to increase. Contrast-enhanced ultrasound (CEUS) is feasible as a rapid examination for early hepatocellular carcinoma diagnosis. However, considering the possible causes of false positives caused by ultrasound, its diagnostic value is still controversial. Therefore, the study conducted a meta-analysis to evaluate the application value of CEUS in the early diagnosis of hepatocellular carcinoma.

Methods: The PubMed, Cochrane Library, Embase, Ovid Technologies (OVID), China National Knowledge Infrastructure (CNKI), Chongqing VIP Information (VIP), and Wanfang databases were searched to retrieve articles on the use of CEUS for the early diagnosis of hepatocellular carcinoma. The literature quality assessment was performed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) quality assessment tool. The meta-analysis was performed using STATA 17.0 to fit the bivariate mixed effects model, calculated sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and corresponding 95% CI, summary receiver operating characteristic curves (SROC), area under the curve (AUC), and 95% confidence interval (CI). The publication bias of the included literature was evaluated using the DEEK funnel plot.

Results: Ultimately, 9 articles, comprising 1,434 patients, were included in the meta-analysis. The heterogeneity test found that I^2>50%, using a random effects model. The results of the meta-analysis showed that the CEUS had a combined sensitivity of 0.92 (95% CI: 0.86–0.95), a combined specificity of 0.93 (95% CI: 0.56–0.99), a combined PLR of 13.47 (95% CI: 1.51–120.46), a combined NLR of 0.09 (95% CI: 0.05–0.14), a combined DOR of 154.16 (95% CI: 15.93–1,492.02), a diagnostic score of 5.04 (95% CI: 2.77–7.31), and a combined AUC of 0.95 (95% CI: 0.93–0.97). The correlation coefficient of the threshold-effect analysis was 0.13 (P>0.05). The results of the regression analysis showed that the country of publication (P=0.14) and the size of the lesion nodules (P=0.46) were not sources of heterogeneity.

Conclusions: Liver CEUS has an advantage in the early diagnosis of hepatocellular carcinoma, with high sensitivity and specificity, and has clinical application value.

Keywords: Contrast-enhanced ultrasound (CEUS); hepatocellular carcinoma; early stage; diagnosis; meta-analysis

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Introduction

Hepatocellular carcinoma is the sixth most common cancer worldwide and a common cause of cancer-related death (1,2). It has been reported that there are about 6.35 million new cases of malignant tumors in the world every year, among which, there are about 260,000 cases of primary hepatic carcinoma, which account for 4.1% of all tumors (3,4). The incidence of hepatocellular carcinoma is relatively high, especially in some developing countries, for which the incidence is 2–3 times that of western countries, and the incidence of hepatocellular carcinoma continues to increase (5). China has a high-incidence of hepatocellular carcinoma.

Because the symptoms of hepatocellular carcinoma are not obvious in the early stage of the disease, patients often have advanced hepatocellular carcinoma at the time of diagnosis. The disease is characterized by a relatively short course of disease and poor prognosis, and has a serious negative impact on public health (6,7). Early diagnosis is one of the important measures to prevent hepatocellular carcinoma and improve the survival rate of hepatocellular carcinoma patients. Thus, a simple, convenient, and rapid diagnosis method needs to be developed to enable the early prevention and treatment of hepatocellular carcinoma.

The occurrence of hepatocellular carcinoma is generally accompanied by changes in the hemodynamics of the lesion. During the transition from cirrhotic nodules to dysplastic nodules and small hepatocellular carcinomas, the blood supply of the nutrient arteries in the nodules gradually increases, while the blood supply of the original portal vein gradually decreases (5). Commonly used imaging examinations for hepatocellular carcinoma include ultrasound, computed tomography, and magnetic resonance imaging. Ultrasound is a safe, common and cost-effective screening test for hepatocellular carcinoma. However, due to differences in the manifestations of hepatocellular carcinoma, the accuracy of ultrasound diagnosis is only 53–77%, and the specificity of ultrasound is not high; thus, the use of ultrasound is limited (8).

Contrast-enhanced ultrasound (CEUS) refers to the addition of contrast-agent microbubbles to conventional ultrasound. The characteristics of the contrast agent can be used to better display the difference between the blood flow in the lesion and the adjacent tissue. Contrast-enhanced ultrasound combined with the characteristics of blood flow changes in hepatocellular carcinoma can better improve the accuracy of hepatocellular carcinoma diagnosis. There is a relatively large difference in blood perfusion between benign and malignant hepatocellular carcinoma, so CEUS can also provide a diagnostic basis for differentiating between benign and malignant hepatocellular carcinoma (9,10). CEUS can also be performed simultaneously with unenhanced ultrasound. Thus, it is feasible as a method for the rapid and early diagnosis of hepatocellular carcinoma.

However, the value of CEUS in the diagnosis of hepatocellular carcinoma is controversial. For example, CEUS has been reported to provide false positive diagnoses 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 computed tomography (CT), magnetic resonance imaging (MRI), and some biomarkers to improve the detection rate (12). However, some researchers have found that MRI has higher resolution and contrast enhancement function compared to ultrasound and CT, and it is recommended to be the preferred imaging method for hepatocellular carcinoma diagnosis (13). Therefore, in order to verify the application value of CEUS in early hepatocellular carcinoma diagnosis. Thus, in this study, we sought to explore the application value of CEUS in the early diagnosis of hepatocellular carcinoma by using a meta-analysis and provide evidence-based medical evidence for the early diagnosis of hepatocellular carcinoma. We present the following article in accordance with the PRISMA reporting checklist (available at https://jgo.amegroups.com/article/

Highlight box

Key findings

- This meta-analysis showed that contrast-enhanced ultrasound (CEUS) of the liver has certain advantages in the early diagnosis of hepatocellular carcinoma and has high sensitivity and specificity.

What is known and what is new?

- CEUS can be performed at the same time as unenhanced ultrasound; thus, it is feasible as a rapid examination for the early diagnosis of hepatocellular carcinoma. The value of CEUS in the diagnosis of hepatocellular carcinoma is still controversial.
- We conducted a meta-analysis to explore the application value of CEUS in the early diagnosis of hepatocellular carcinoma and provide medical evidence for its use in the early diagnosis of hepatocellular carcinoma.

What is the implication, and what should change now?

- CEUS of the liver has certain advantages in the early diagnosis of hepatocellular carcinoma and has clinical application value.

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Methods

Literature search

Articles about the use of CEUS for the early diagnosis of hepatocellular carcinoma were retrieved from the PubMed, Cochrane Library, Embase, Ovid Technologies (OVID), China National Knowledge Infrastructure (CNKI), Chongqing VIP Information (VIP), and Wanfang databases. The search was carried out by combining subject terms with free words. The Chinese and English keywords included contrast-enhanced ultrasound, early hepatocellular carcinoma, hepatocellular carcinoma, diagnosis, application, and value. The retrieval time was from the establishment of the databases to January 2023.

Article inclusion and exclusion criteria

Inclusion criteria

To be eligible for inclusion in this meta-analysis, the articles had to meet the following inclusion criteria: (I) include patients aged ≥18 years with liver nodules undergoing hepatocellular carcinoma screenings as the research objects; (II) use pathological diagnosis as the gold standard of diagnosis; (III) be an original Chinese- or English-language article; and (IV) indirectly or directly include primitive numbers, such as true positive numbers, false positive numbers, false negative numbers, and true negative numbers.

Exclusion criteria

Articles were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) the original data were missing, could not be extracted from the article or were not available; (II) the article concerned a review, master's or doctoral dissertation, conference, or other type of document; and/or (III) the intervention measures did not include CEUS or CEUS combined with other measures.

Article screening and data extraction

Two researchers independently screened the articles according to the inclusion and exclusion criteria. The data extracted included the general data and outcome data. The general data included the authors and publication year, country, number of cases, number of lesions, age of patients, and size of nodules. The outcome data included the number of true positives, false positives, false negatives, and true negatives of diagnosis.

Literature quality evaluation

The article quality evaluation was carried out using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) (14). The included articles were evaluated in Review Manager 5.3 (Cochrane collaboration network), which already included the evaluation tool. Each item was rated "Yes", "No", or "Unclear", and a document quality evaluation map was drawn. If all entries match, it is considered a low bias risk, some matches represent an unclear bias risk, and all non matches represent a high bias risk.

Statistical analysis

The statistical analysis was performed using Stata 17.0 (Computer Resource Center, USA). A bivariate mixed-effects model was fitted. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and the corresponding 95% confidence interval (CI) were calculated. A summary receiver operating characteristic curve was drawn, and the area under the curve (AUC) with the 95% CI was calculated (15). The publication bias of the included studies was assessed by Deek's funnel plot asymmetry test. If the P value was <0.05, there was an obvious publication bias in the article. The Q test and I^2 were used to determine heterogeneity. If the P value was <0.1 and the I^2 value was >50%, the heterogeneity was significant, and a meta-regression was used to explore the source of heterogeneity. A two-sided P value <0.05 was considered statistically significant.

Results

Literature search results

A total of 945 articles were retrieved from the databases, including 763 English-language articles and 182 Chinese-language articles. After removing the duplicate documents, 724 articles remained. After reading the titles and abstracts, 73 articles remained. After downloading the full text, 71 articles remained. Among these articles, 16 without a negative control group were excluded, 8 that did not

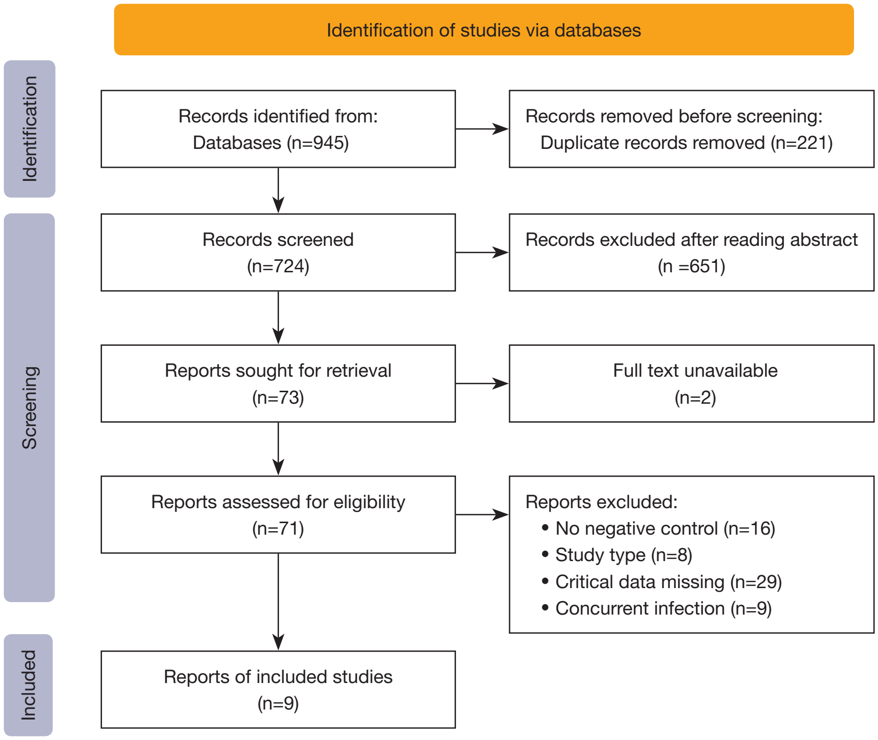

Figure 1 Article screening process and results.

match the research type were excluded, 29 with missing important data were excluded, and 9 that examined co-infections were excluded. Ultimately, 9 articles (5,6,16-22) were included in the meta-analysis. The screening process is shown in *Figure 1*.

Basic information of the included articles and quality evaluation of the literature

The general information of the included articles is detailed in *Table 1*. The quality evaluation results of QUADAS-2 are shown in *Figure 2*. Of the 9 articles, 3 did not clarify whether the case inclusion method was continuous or random (16,19,22). The experimental results of all the articles were interpretated based on the premise that the results of the gold standard method were known (5,6,16-22). However, 3 articles did not state whether the blind method was used in the judgment of results (16,19,21). Additionally, 3 articles had inappropriate exclusion of experimental group or control group cases (16,17,21). The time interval between the interpretation of the results of the experimental group and the gold standard method in the 4 articles was long (5,6,19,20). In summary, only 1 out of 9 articles has a low risk of bias, while the remaining 8 articles have an unclear risk of bias.

CEUS in the early diagnosis of hepatocellular carcinoma

The studies ultimately included in the meta-analysis were analyzed using a bivariate mixed-effects model. The CEUS had a pooled sensitivity of 0.92 (95% CI: 0.86–0.95), a pooled specificity of 0.93 (95% CI: 0.56–0.99), a pooled PLR of 13.47 (95% CI: 1.51–120.46), a pooled NLR of 0.09 (95% CI: 0.05–0.14), a combined DOR of 154.16 (95% CI: 15.93–1,492.02), a diagnostic score of 5.04 (95% CI: 0.277–7.31), and a pooled AUC of 0.95 (95% CI: 0.93–0.97). The heterogeneity test results showed that I^2>50% and P<0.1 (*Figures 3-6*).

Threshold effect

A Spearman correlation analysis was carried out using the logSENS and Log(1-SENS). The r correlation coefficient result was 0.13 (P>0.05). There was no threshold effect in this study. The source of heterogeneity was not the threshold effect.

Table 1 Basic information of the included articles

First author and year published	Country	Number of patients	Number of lesions	Age (years)	Sex ratio (male/female)	Nodule size (cm)
Chen 2005, (17)	China	75	180	59.2±6.8	39/36	0.7–3.1
Chen 2017, (16)	China	392	–	>55	–	<2
Dai 2008, (18)	China	35	–	–	–	<2
Gao 2017, (19)	China	215	236	57.6±10.6	136/79	<3
Hsiao 2019, (20)	China	66	–	63.3±9.3	45/21	1.6±0.7
Mei 2022, (5)	China	395	632	54.7±12.8	230/165	≤2
Palmieri 2015, (21)	Italy	124	148	46–97	96/28	≤2
Chen 2005, (22)	China	48	146	–	–	<3
Zhang 2022, (6)	China	84	–	≥18	54/30	<3

The age and nodule size in the table are represented by mean ± SD or range. SD, standard difference.

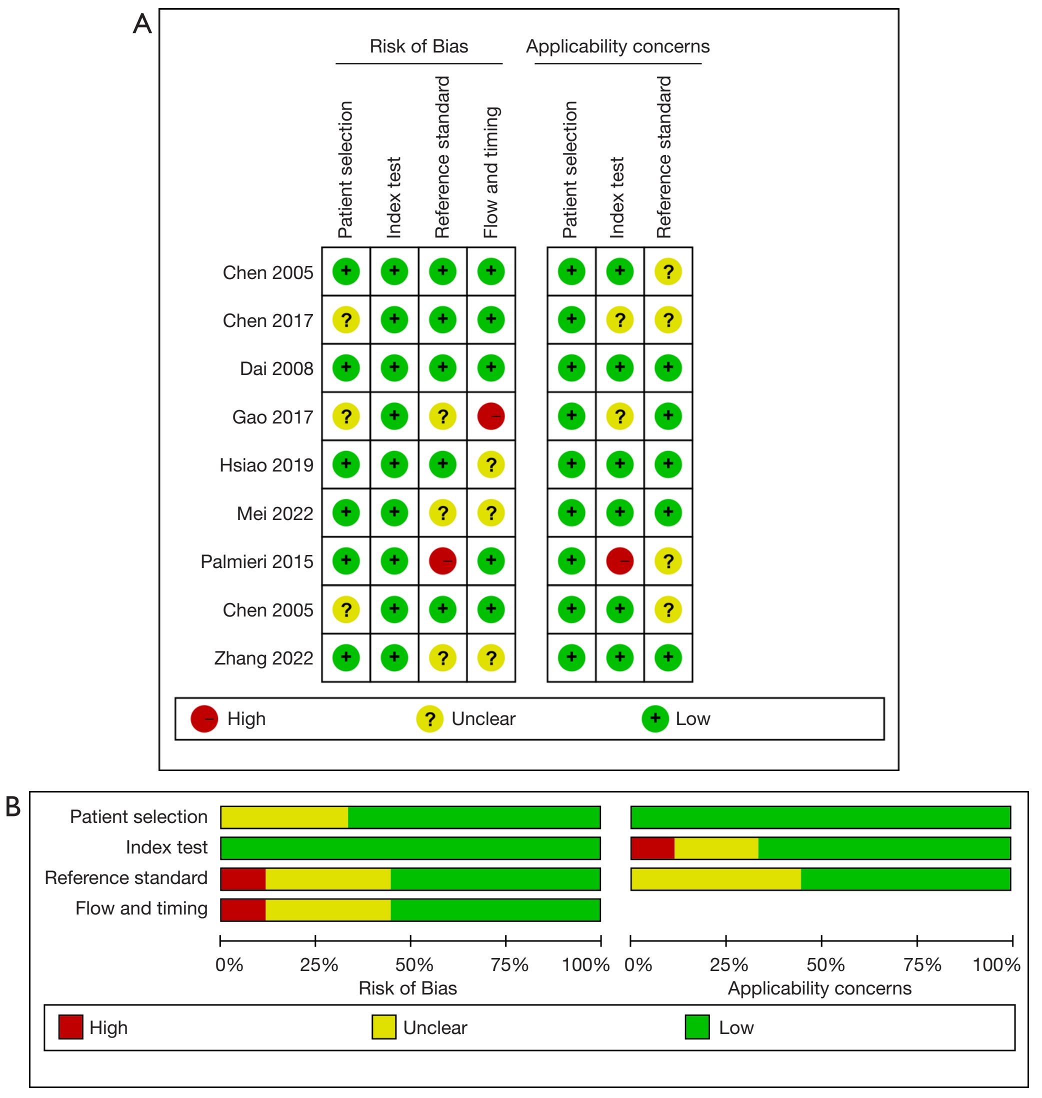

Figure 2 Literature quality assessment (QUADAS-2). QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2.

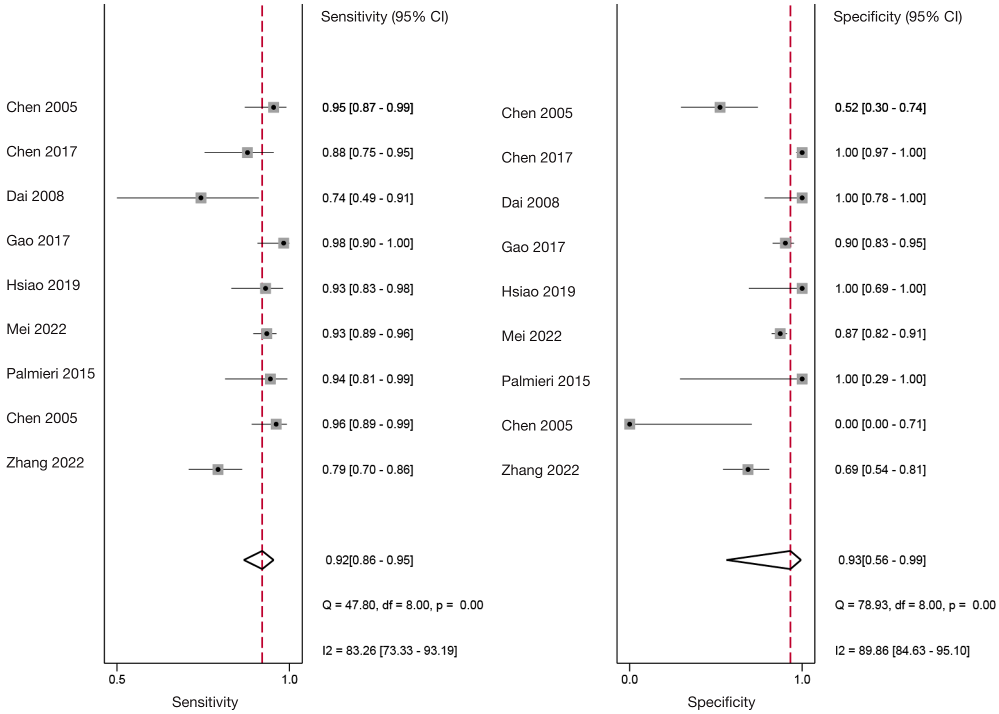

Figure 3 The forest plot of the combined sensitivity and specificity of contrast-enhanced ultrasound in the early diagnosis of hepatocellular carcinoma. CI, confidence interval.

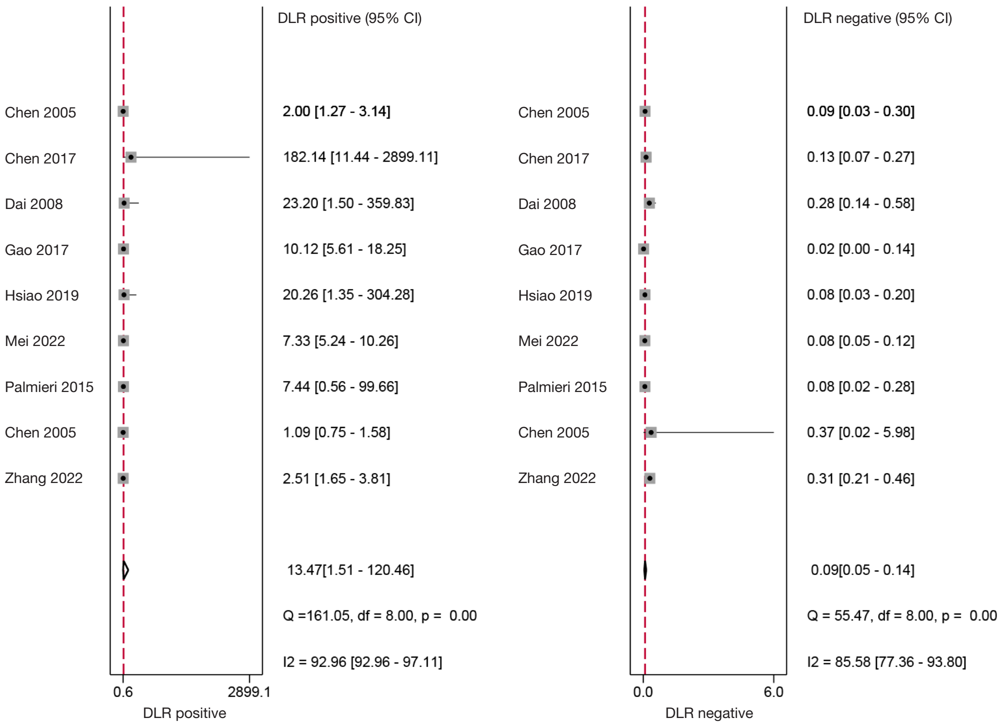

Figure 4 Forest plot of contrast-enhanced ultrasound in the early diagnosis of hepatocellular carcinoma with the positive likelihood ratio and negative likelihood ratio. DLR, diagnostic likelihood ratio; CI, confidence interval.

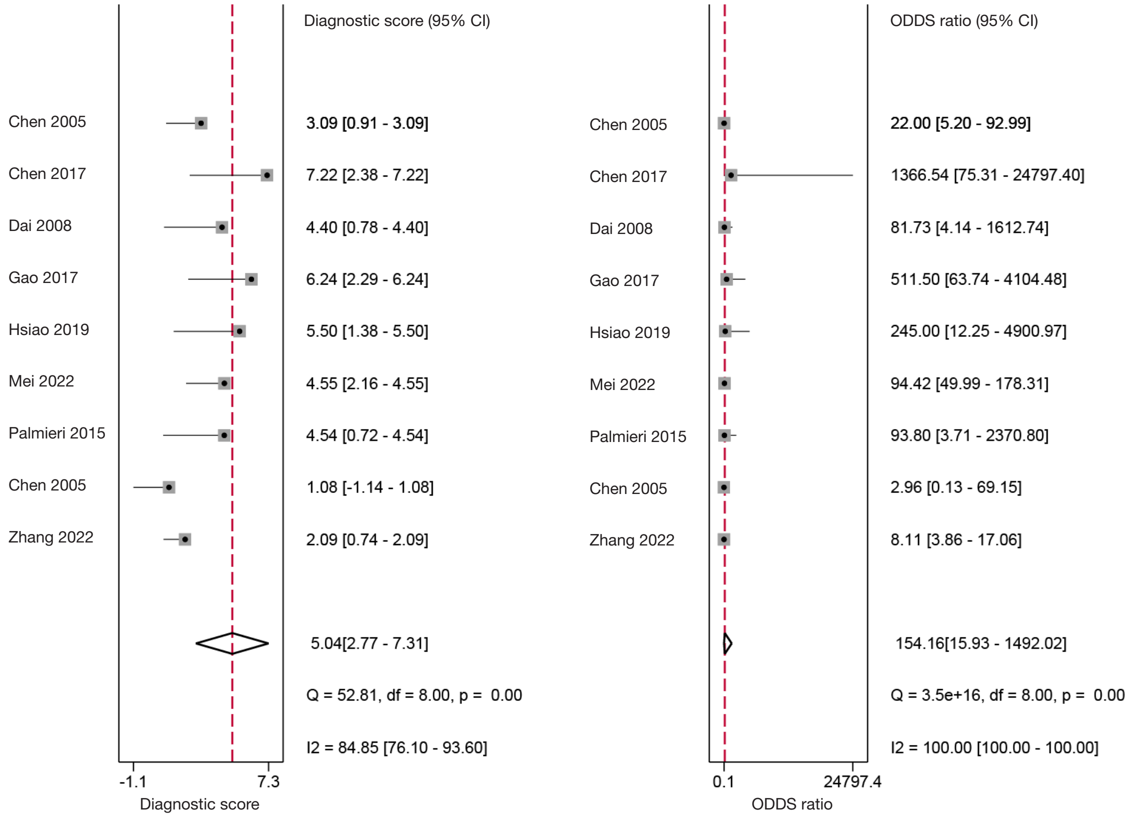

Figure 5 Forest plot of the combined diagnostic score and diagnostic odds ratio in the early diagnosis of hepatocellular carcinoma by contrast-enhanced ultrasound. CI, confidence interval.

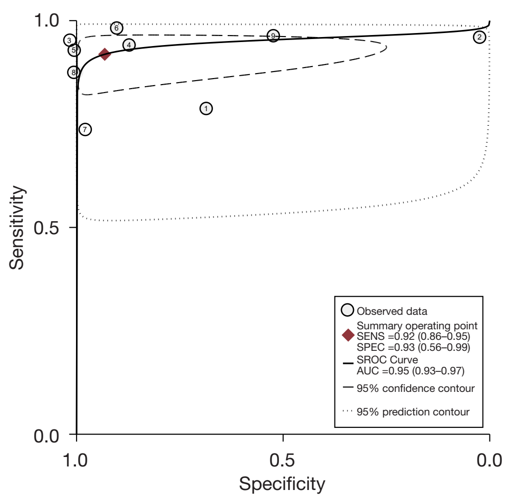

Figure 6 Summary receiver operating characteristic curve of contrast-enhanced ultrasound diagnosis of early hepatocellular carcinoma. Numbers 1–9 in the figure represent references (5,6,16-22). SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating characteristic curves; AUC, area under the curve.

Analysis of sources of heterogeneity

A meta-regression was used to find the source of heterogeneity of the included studies. The results showed that the country of publication (P=0.14) and the size of the lesions and nodules (P=0.46) were not sources of heterogeneity. Therefore, possible reasons can only be inferred from the literature. After re-analysis of the literature, we found that the heterogeneity of the analysis results may be caused by the differences in the detection instruments used by the medical units and the technical proficiency of the operators.

Publication bias

Deek's funnel plot asymmetry test was used to test the publication bias of the included articles. A P value of 0.74 was found, which indicated that there was no potential publication bias in the included articles (*Figure 7*).

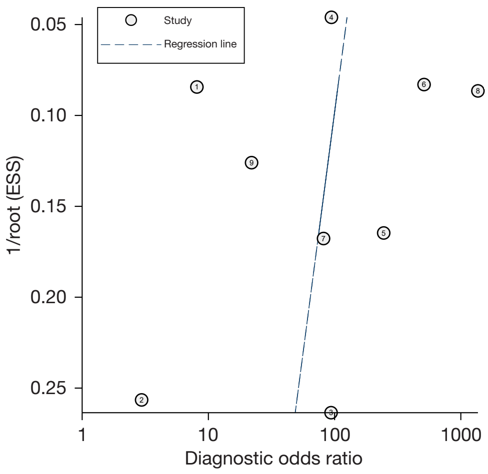

Figure 7 Deek's funnel plot asymmetry test results. Numbers 1–9 in the figure represent references (5,6,16-22). ESS, effective sample sizes.

Discussion

Hepatocellular carcinoma is a malignant tumor with high clinical mortality. According to epidemiological data, China has a high incidence of hepatocellular carcinoma. Thus, the current situation in relation to the prevention and treatment of hepatocellular carcinoma in China is still very serious. Hepatocellular carcinoma has gradually become a public health problem that threatens the health and quality of life of residents (6,23,24). A large number of studies have shown that the disease progression of hepatocellular carcinoma is faster than that of other malignant tumors (25-27). This is related to the dual blood supply to the liver by the hepatic artery and portal vein (25,27).

Surgery is the main means of radical cure for hepatocellular carcinoma. However, the onset of hepatocellular carcinoma is hidden, and the disease develops rapidly in the later stages. Some patients are already in the advanced stages of hepatocellular carcinoma when they develop symptoms. Surgical treatment is difficult for such patients, who may even miss the opportunity to undergo surgery (28,29). Thus, early diagnosis is of great significance if the success rates of surgery and prognosis are to be improved. Recent studies have reported that the early diagnosis of hepatocellular carcinoma and radical surgery for hepatocellular carcinoma significantly improves the 5-year survival rate of patients after surgery (7,30). However, the experience and abilities of different radiologists can lead to different outcomes even for the same lesion. Although standardized testing can minimize subjectivity, the impact of subjectivity is still inevitable due to the differences and complexity between individuals, and meta-analysis is a very applicable method for resolving controversial issues.

This study examined 9 articles on the use of CEUS in the early diagnosis of hepatocellular carcinoma. The meta-analysis results showed that the combined sensitivity and specificity of CEUS were 0.92 (95% CI: 0.86–0.95) and 0.93 (95% CI: 0.56–0.99), respectively. Thus, CEUS had high sensitivity and specificity in diagnosing early hepatocellular carcinoma. CEUS had an AUC of 0.95 (95% CI: 0.93–0.97), and a diagnostic score of 5.04 (95% CI: 0.277–7.31). This result indicates that CEUS is a highly specific diagnostic system and a better tool to avoid misdiagnosing non-HCC observations as HCC. However, it is not possible to reach 1, which means that there may still be missed diagnoses of HCC (31). The heterogeneity test results showed that there was heterogeneity in the included articles (I^2>50% and P<0.1), but the correlation coefficient of the threshold-effect analysis was 0.13 (P>0.05). Thus, the threshold effect was not the source of heterogeneity. A meta-regression was then used to analyze the sources of heterogeneity. However, the results showed that neither the country of publication (P=0.14) nor the size of lesions and nodules (P=0.46) were sources of heterogeneity. The above results also indicate that there are still many issues that have not been clarified in the field of early hepatocellular carcinoma diagnosis using liver ultrasound. Therefore, more research and analysis are needed for further exploration.

This meta-analysis had some limitations. First, many factors affect the accuracy of CEUS, such as differences in operators' technical proficiency, and differences in the use of instruments, which may have affected the heterogeneity of the included articles. Second, some of the 9 articles included in this analysis were missing the baseline data of patients. Thus, there were relatively few factors that could be analyzed in the meta-regression analysis, which had a certain effect on the heterogeneity analysis. Third, some of the results of the QUADAS-2 quality assessment were "unclear," which brings a risk of bias.

In summary, CEUS has certain advantages in the early diagnosis of hepatocellular carcinoma, and has high sensitivity and specificity. CEUS has clinical application value.

Conclusions

Hepatic CEUS has certain advantages in the diagnosis of early hepatocellular carcinoma due to its high sensitivity and specificity. However, considering some limitations in the analysis in this article, further research and analysis are needed to explore this conclusion.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-211/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-211/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-211/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of this work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

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