Diagnostic role of contrast-enhanced ultrasonography versus conventional B-mode ultrasonography in cirrhotic patients with early hepatocellular carcinoma: a retrospective study

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Background: Early diagnosis of hepatocellular carcinoma (HCC) is very important for the prognosis of patients. However, there are very few studies that compared the diagnostic accuracy of contrast-enhanced ultrasonography (CEUS) and B-mode ultrasonography for early HCC in cirrhotic patients.

Methods: This retrospective study included cirrhotic patients, who were suspected of early HCC between January 2020 and June 2021. The diagnosis of patients was based on the pathology results of surgery or biopsy. Demographic and clinical characteristics of included patients were recorded. The diagnoses of suspected lesions using both types of ultrasonography were recorded, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of early HCC in cirrhotic patients were calculated.

Results: Eventually, 137 patients with solitary lesions in the liver were included in this study, including 89 patients diagnosed with HCC and 48 patients diagnosed with non-HCC. The median diameter of suspected lesions was 26 mm, and the median level of alpha fetoprotein (AFP) was 37.2 ng/mL. When comparing the demographic and clinical characteristics of cirrhotic patients with HCC and non-HCC, it was found that patients with HCC had significantly higher levels of AFP than those with non-HCC (P=0.03). The sensitivity, specificity, PPV, NPV, and accuracy of CEUS in early HCC were 73%, 93.8%, 95.6%, 65.2% and 80.3%, respectively. In CEUS, all of these parameters were much higher than those in B-mode ultrasonography, i.e., 64%, 75%, 82.6%, 52.9%, and 67.9%. It was also found that the diagnostic accuracy of CEUS was much higher than that of B-mode ultrasonography especially regarding lesions <20 mm. To further improve the sensitivity of CEUS in early HCC, AFP was combined with CEUS for the diagnosis of early HCC. As a result, the sensitivity, specificity, PPV, NPV, and accuracy of CEUS combined with AFP level were 83.1%, 87.5%, 92.5%, 73.7%, and 84.7%, respectively.

Conclusions: Our study confirmed that CEUS' diagnostic accuracy for early HCC in cirrhotic patients was significantly higher than that of B-mode ultrasonography. However, the sensitivity of CEUS needs to be improved further, and the combination of CEUS and AFP level may be a potential solution.

Keywords: Contrast-enhanced ultrasonography (CEUS); B-mode ultrasonography; alpha fetoprotein (AFP); diagnostic accuracy; early hepatocellular carcinoma (early HCC)

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies of the digestive tract, and liver cirrhosis, caused by viral hepatitis or alcoholic liver disease, is one of the most important risk factors for HCC (1-3). The incidence rate of HCC is high all over the world and has been increasing by 2% to 3% annually since 2007 (4). It has been reported that the cases of, and deaths from, HCC in China account for about half of cases worldwide (5). Surgical treatment is the most effective treatment for HCC, but it is limited to early-stage HCC. Local treatment can also alleviate the progress of the disease to a certain extent. However, once the invasion of surrounding organs and distant metastasis in HCC occurs in patients, drug treatment, including chemotherapy drugs, targeted drugs, and immune checkpoint inhibitors must be administered. Therefore, early diagnosis of HCC is very important for the prognosis of patients.

The advantages of B-mode ultrasonography are its low cost, short amount of time taken to complete the procedure, and high sensitivity to detect large tumors. Hence, it is the most commonly used abdominal examination tool. At present, all HCC guidelines also recommend B-mode ultrasonography as an initial screening tool for early HCC in patients with liver cirrhosis (6). Previous studies have demonstrated that B-ultrasonography has good specificity and overall accuracy in the diagnosis of liver tumors (7). However, the morphological structure and echo characteristics of cirrhotic livers are abnormal, and imaging does not always identify early HCC, which leads to low sensitivity of B-mode ultrasonography in the diagnosis of early HCC and a tendency to missed diagnoses (8). To make up for this shortcoming, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are often used for further examination of HCC after initial screening using B-mode ultrasonography. Previous studies have shown that contrast-enhanced CT and MRI have higher sensitivity and specificity in the diagnosis of early HCC compared with B-mode ultrasonography (9,10). However, contrast-enhanced CT and MRI are expensive and time-consuming compared with B-mode ultrasonography. In addition, some patients may be allergic to the contrast agents used for contrast-enhanced CT and MRI. These factors limit the application of contrast-enhanced CT and MRI in the diagnosis of early HCC. Meanwhile, the advantages of contrast-enhanced ultrasonography (CEUS) mean that it is more widely used in the diagnosis of early

HCC. Also, CEUS uses intravenous injection of contrast agent and conventional ultrasonography, which can detect blood perfusion and microvascular distribution of organs and tumors and has almost no side-effects (11-13). It has been reported that CEUS acts as an effective examination tool for early HCC, and that the specificity of CEUS is higher than that of contrast-enhanced CT and MRI (4,9). In a randomized controlled trial, Kudo *et al.* demonstrated that CEUS had significantly higher sensitivity and overall accuracy than B-mode ultrasonography in the diagnosis of early HCC (14). However, there were few patients with HCC in this study, which limits the clinical applicability of the results. However, there are no other similar studies, which compared the diagnostic accuracy of CEUS and B-mode ultrasonography in the diagnosis of HCC.

Our study was performed to compare the diagnostic role of CEUS and B-mode ultrasonography in early HCC by retrospectively collecting the characteristics and diagnoses of cirrhotic patients admitted to our hospital during a 1.5-year period. To remove the heterogeneity between included patients, we only included cirrhotic patients receiving both CEUS and B-mode ultrasonography. The aim of our study was to further verify the superiority of CEUS compared with B-mode ultrasonography in the diagnosis of early HCC. We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/jgo-21-611).

Methods

Patient recruitment

Our study was approved by the ethics committee of the Affiliated Hospital of Jiangnan University (No. 2021-066) and then performed according to the principles of the Helsinki Declaration [2013]. Cirrhotic patients who were suspected of early HCC between January 2020 and June 2021 were included in this study. The diagnosis of patients was based on the pathological results (the gold standard) once surgery or biopsy had been performed. Patients with the following patient characteristics were excluded from this study: younger than 18 years old, did not have liver cirrhosis, received only one examination of CEUS and B-mode ultrasonography, did not undergo surgery or biopsy for definite diagnosis, was eventually diagnosed as having multiple lesions of HCC or a solitary lesion of HCC with a diameter exceeding 5 cm, and could not provide their comprehensive characteristics. Due to the retrospective

design, written informed consents were not obtained in this study. All included patients were followed up at least until pathological results were obtained. Some demographic and clinical characteristics of included patients were extracted from their medical records, including age, gender, body mass index (BMI), etiology of cirrhosis [hepatitis B virus (HBV) related cirrhosis, hepatitis C virus (HCV) related cirrhosis, alcohol-related cirrhosis or other cirrhosis], Child-Pugh classification (A, B or C), lesion location (major branch or segmental branch), lesion size, and level of alpha fetoprotein (AFP).

B-mode ultrasonography and CEUS

Both B-mode ultrasonography and CEUS were performed by skilled radiologists using a medical ultrasound system (EPIQ 5, Bothell, WA, USA) with a 1–5 MHz convex transducer. First, B-mode ultrasonography was performed using gray-scale ultrasound. According to the suspected lesions detected by B-mode ultrasonography, CEUS was performed using contrast-enhanced imaging after the injection of 1–2 mL contrast medium of sulfur hexafluoride (SonoVue, Bracco, Italy) into the location of the lesion followed by 5–10 mL of normal saline. The contrast medium was administered a second time if necessary. The suspected lesion and nearby liver parenchyma were detected for about one minute, then whole liver parenchyma and the suspected lesion were detected until washout took place. The diagnosis of suspected lesions in this study was based on the judgement of one to three skilled radiologists, who did not have access to demographic and clinical characteristics of included patients.

Statistical analysis

Statistical analysis in this study was performed using SPSS 18.0 (IBM Corp., New York City, NY, USA). Continuous variables are reported as medians and quartiles and compared using Mann-Whitney U tests. Categorical variables are reported as frequencies and percentages and compared using chi square tests. A two-tailed P value <0.05 was considered as indicating a statistically significant difference. The diagnoses of suspected lesions using both examinations were recorded, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of both examinations of early HCC in cirrhotic patients were calculated. Also, the diagnostic role of the AFP level in early HCC was measured, and then the

diagnostic role of CEUS was combined with the AFP level measured to determine whether AFP level could further improve the sensitivity and overall accuracy of CEUS in the diagnosis of early HCC in cirrhotic patients.

Results

More than 30,000 patients were admitted to our hospital for abdominal B-mode ultrasonography between January 2020 and June 2021, of whom 469 patients also received examination of CEUS. In all, 332 patients were excluded from this study according to the exclusion criteria. Eventually, 137 patients with solitary lesions in the liver were included in this study (*Figure 1*). According to the pathological results of surgery or biopsy, 89 patients were diagnosed as HCC, and 48 patients were diagnosed as non-HCC.

Demographic and clinical characteristics of cirrhotic patients are shown in *Table 1*. Median age was 56 years, 99 patients (72.3%) were male, and the median BMI was 23.1. In about three quarters of included patients the cirrhosis was caused by HBV. More than 90% patients were diagnosed as Child-Pugh classification A. Also, about three quarters of suspected lesions were located at a major branch. The median diameter of suspected lesions was 26 mm, and the median level of AFP was 37.2 ng/mL. Eighty-nine lesions (65.0%) were eventually diagnosed as HCC (*Table 2*). Nineteen of the remaining lesions were non-HCC malignancies, including 12 intrahepatic cholangiocarcinomas (ICCs), one HCC combined with ICC, and six metastatic lesions. Twenty-nine lesions were benign, including 12 dysplastic nodules, 10 regenerative nodules, three hemangioma, two focal nodular hyperplasias, and two inflammatory pseudotumors. Comparing demographic and clinical characteristics of cirrhotic patients with HCC or non-HCC in this study, it was found that patients with HCC had significantly higher levels of AFP than those with non-HCC patients (*Table 3*). No additional differences were found between them.

Two representative patients with early HCC of diameters of 20 mm are shown in *Figure 2*. It was found that a small HCC was hypoechoic in B-mode ultrasonography, but that it was not easy to distinguish it from other lesions. In addition, a small HCC in CEUS showed hyperenhancement in the arterial phase and hypoenhancement in the portal and delayed phase, which can be distinguished from other lesions. The diagnostic roles of CEUS and B-mode ultrasonography are listed in *Table 4*. The sensitivity,
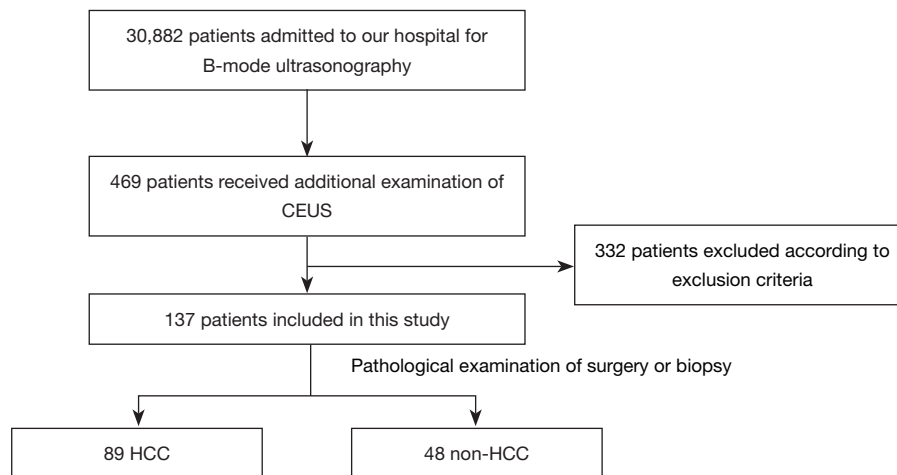
Figure 1 Flow chart. CEUS, contrast-enhanced ultrasonography; HCC, hepatocellular carcinoma.

Table 1 Demographic and clinical characteristics of cirrhotic patients

Characteristics	Data
Number	137
Age, year	56 (49.0–63.0)
Gender	
Male	99 (72.3%)
Female	38 (27.7%)
BMI	23.1 (21.6–24.5)
Etiology of cirrhosis	
HBV related	101 (73.7%)
HCV related	8 (5.8%)
Alcohol related	22 (16.1%)
Other	6 (4.4%)
Child-Pugh classification	
A	125 (91.2%)
B	12 (8.8%)
Lesion location	
Major branch	100 (73.0%)
Segmental branch	37 (27.0%)
Lesion size, mm	26 (18.0–42.0)
Level of AFP, ng/mL	37.2 (8.6–655)

BMI, body mass index; AFP, alpha fetoprotein; HBV, hepatitis B virus; HCV, hepatitis B virus.

Table 2 Diagnosis of liver lesion

Final diagnosis	Data
HCC	89 (65.0%)
Non-HCC malignancy	19 (13.9%)
ICC	12 (8.8%)
Combined HCC and ICC	1 (0.7%)
Metastasis	6 (4.4%)
Benign lesions	29 (21.2%)
Dysplastic nodule	12 (8.8%)
Regenerative nodule	10 (7.3%)
Hemangioma	3 (2.2%)
Focal nodular hyperplasia	2 (1.5%)
Inflammatory pseudotumor	2 (1.5%)

HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

specificity, PPV, NPV, and accuracy of CEUS in early HCC were 73%, 93.8%, 95.6%, 65.2%, and 80.3%, respectively. All of these parameters in CEUS were much higher than those in B-mode ultrasonography, i.e., 64%, 75%, 82.6%, 52.9%, and 67.9%. Then, these lesions were divided into large lesions (≥20 mm) and small lesions (<20 mm), and diagnostic roles of CEUS and B-mode ultrasonography in suspected HCCs with different diameters were determined (*Table 5*). It was found that diagnostic accuracy of CEUS was much higher than that of B-mode ultrasonography

Table 3 Comparisons of demographic and clinical characteristics of cirrhotic patients with hepatocellular carcinoma (HCC) or non-HCC

Characteristics	HCC	Non-HCC	P value
Number	89	48	
Age, year	59 (46.0–65.0)	57 (49.0–64.0)	0.98
Gender			0.60
Male	63 (70.8%)	36 (75.0%)	
Female	26 (29.2%)	12 (25.0%)	
BMI	23.1 (21.4–24.5)	22.9 (21.6–24.1)	0.55
Etiology of cirrhosis			0.15
HBV related	60 (67.4%)	41 (85.4%)	
HCV related	6 (6.7%)	2 (4.2%)	
Alcohol related	18 (20.2%)	4 (8.3%)	
Other	5 (5.6%)	1 (2.1%)	
Child-Pugh classification			0.61
A	82 (92.1%)	43 (89.6%)	
B	7 (7.9%)	5 (10.4%)	
Lesion location			0.11
Major branch	61 (68.5%)	39 (81.3%)	
Segmental branch	28 (31.5%)	9 (18.7%)	
Lesion size, mm	26 (20.0–42.0)	26 (19.0–39.0)	0.83
Level of AFP, ng/mL	58.0 (14.9–1,366)	22.5 (9.3–219)	0.03

HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; BMI, body mass index; AFP, alpha fetoprotein; HBV, hepatitis B virus; HCV, hepatitis B virus.

especially in lesions <20 mm. To further improve the sensitivity of CEUS in early HCC, AFP was chosen as an auxiliary diagnostic tool of CEUS, because in this study the levels of AFP in HCC were much higher than those in non-HCC. As a result, the sensitivity, specificity, PPV, NPV, and accuracy of CEUS combined with AFP levels achieved were up to 83.1%, 87.5%, 92.5%, 73.7%, and 84.7%, respectively (*Table 6*). This significantly improved the sensitivity of CEUS in early HCC without reducing the specificity of CEUS too significantly.

Discussion

Our study included more cirrhotic patients with HCC than previous studies and demonstrated higher sensitivity of CEUS compared to B-mode ultrasonography in the diagnosis of early HCC. The results showed that with the use of contrast medium, CEUS assessed the vascular distribution and blood supply of liver lesions more effectively and thus diagnosed HCC more accurately than B-mode ultrasonography, regardless of whether tumors had a diameter greater or less than 2 cm. However, in general, the sensitivity of CEUS in the diagnosis of HCC was still not particularly high. Therefore, this study attempted to combine AFP levels and CEUS in the diagnosis of early HCC. The results showed that combined AFP levels and CEUS had higher sensitivity and diagnostic accuracy than AFP level or CEUS alone. The results of this study demonstrate that there are several options for the diagnosis of early HCC.

B-mode ultrasonography is the most commonly used abdominal examination tool, and it is mainly used in hepatobiliary pancreatic diseases and gynecological diseases. However, in recent years few studies have focused on the diagnosis of cirrhotic patients with early HCC using B-mode ultrasonography. Previous studies have pointed out that the
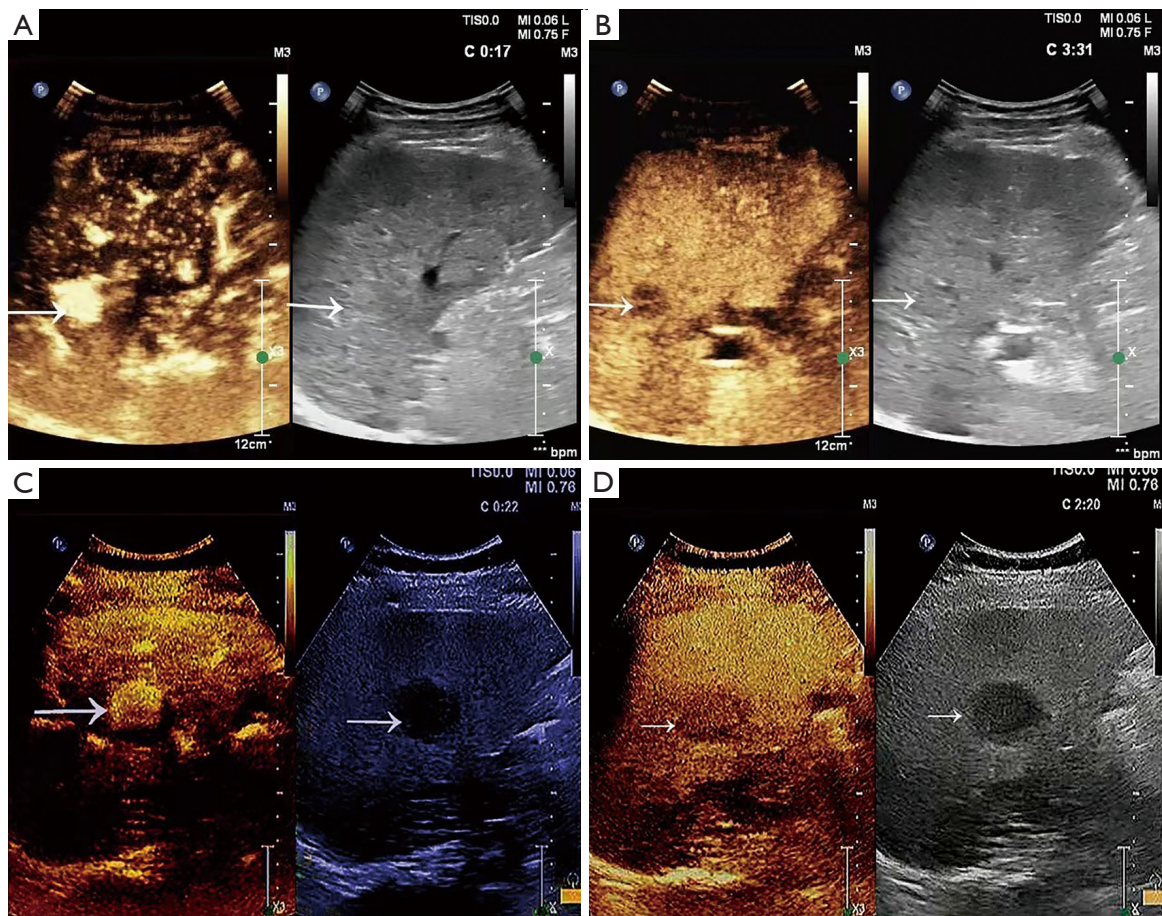
Figure 2 Representative imaging of two cirrhotic patients with early similar HCC using CEUS (left) and B-mode ultrasonography (right). Patient 1 with early HCC with a diameter of 16 mm × 15 mm (A: arterial phase, B: portal and delayed phases) and Patient 2 with early HCC with a diameter of 18 mm × 16 mm (C: arterial phase, D: portal and delayed phases). Early HCC in both patients showing hyperenhancement in the arterial phase and hypoenhancement in the portal and delayed phase. The arrows refer to the location of HCC. HCC, hepatocellular carcinoma; CEUS, contrast-enhanced ultrasonography.

Table 4 Diagnostic roles of contrast-enhanced ultrasonography and B-mode ultrasonography in cirrhotic patients suspected of hepatocellular carcinoma

Variable	CEUS	B-mode ultrasonography
Sensitivity	73	64
Specificity	93.8	75
PPV	95.6	82.6
NPV	65.2	52.9
Accuracy	80.3	67.9

PPV, positive predictive value; NPV, negative predictive value; CEUS, contrast-enhanced ultrasonography.

sensitivity and specificity of B-mode ultrasonography in the diagnosis of HCC are 50–60% and 70–80%, respectively (14-16), which is similar to our results. It should also be noted that the overall accuracy in the diagnosis of early HCC was relatively low. Therefore, further assessments are needed to diagnose suspected HCC after ultrasonography, such as CT and MRI. However, the two examinations are expensive and time-consuming, which can easily lead to the delay of the disease. Contrast-enhanced ultrasonography is an advanced B-ultrasonography examination tool. In China, the contrast agent used is SonoVue, a type of sulfur hexafluoride, which rarely leads to serious allergic reactions and adverse reactions and allows clearer imaging and more

Table 5 Diagnostic roles of contrast-enhanced ultrasonography and B-mode ultrasonography in cirrhotic patients suspected of hepatocellular carcinoma with different diameters

Variable	CEUS-lesion <20 mm	B-mode ultrasonography-lesion <20 mm	CEUS-lesion ≥20 mm	B-mode ultrasonography-lesion ≥20 mm
Sensitivity	69	51.7	75	70
Specificity	86.7	66.7	97	78.8
PPV	90.9	75	97.8	85.7
NPV	59.1	41.2	68.1	59.1
Accuracy	75	56.8	82.8	73.1

PPV, positive predictive value; NPV, negative predictive value; CEUS, contrast-enhanced ultrasonography.

Table 6 Diagnostic role of contrast-enhanced ultrasonography combined with alpha fetoprotein level in cirrhotic patients suspected of hepatocellular carcinoma

Variable	CEUS combined with AFP level
Sensitivity	83.1
Specificity	87.5
PPV	92.5
NPV	73.7
Accuracy	84.7

PPV, positive predictive value; NPV, negative predictive value; CEUS, contrast-enhanced ultrasonography; AFP, alpha fetoprotein.

accurate diagnosis (17-19). Previous studies mostly showed that CEUS achieved about 70–90% sensitivity and about 80–100% specificity in the diagnosis of HCC (14,20-22). In our study, the sensitivity of CEUS in the diagnosis of early liver cancer was 73.0%, while the sensitivity was 93.8%, which was significantly superior to the 64.0% sensitivity and 75.0% specificity of B-mode ultrasonography. This provides a theoretical basis for CEUS to replace B-mode ultrasonography as a novel screening tool of early HCC, but the premise is to further reduce the cost of the contrast medium.

We also found that the sensitivity of CEUS in the diagnosis of early HCC in cirrhotic patients was still not high. Therefore, we also sought to identify an auxiliary examination tool to improve the sensitivity of CEUS in early HCC diagnosis. AFP is one of the most commonly used serum markers for the diagnosis of HCC. In our study, most patients underwent measurement of AFP level after identifying a liver lesion. AFP was then chosen as the auxiliary diagnostic tool of CEUS, and CEUS was combined with AFP level to diagnose early HCC in cirrhotic patients. When selecting the diagnostic cut-off point of AFP, we referred to previous studies. A higher cut-off point will lead to higher specificity and lower sensitivity, while a lower cut-off point will slightly reduce the specificity and significantly improve the sensitivity (23-25). We therefore chose the lower AFP cut-off point, 10 ng/mL, and early HCC was diagnosed when the patient met any of the diagnostic criteria of CEUS or AFP level. This led to the sensitivity of combined diagnostic criteria achieving 83.1% with the specificity dropping to 87.5%, which meant that the specificity and sensitivity reached a relatively satisfactory level.

This study has some limitations. First, the patients included in this study were first screened using B-mode ultrasonography. Only those patients who were confirmed using B-mode ultrasonography to have a solitary liver lesion were further examined using CEUS. Tumors too small in diameter or too difficult to distinguish on B-mode ultrasonography were not included in the study. This may have led to a certain degree of selection bias in this study, which was mainly due to the retrospective design of the study, a shortcoming that needs to be addressed in future prospective studies. Second, the patients included in this study were all patients with liver cirrhosis, but there were some differences in the etiology of liver cirrhosis, including cirrhosis caused by HBV, HCV, and alcohol, which may have led to the difference in the phenotypes of HCC and the surrounding liver parenchyma. When the sample size is adequate, the diagnosis of HCC in patients with liver cirrhosis caused by a single cause may be able to demonstrate the accuracy of CEUS and B-ultrasonography. Third, this study was a retrospective study, und thus the

selection of serum markers was relatively limited, and only the more commonly used serum markers in the clinical setting were selected for analysis. AFP is the most commonly used serum marker for suspected HCC in China, but other new markers may have higher diagnostic accuracy. More in-depth future research should be carried out.

Conclusions

Few studies on the accuracy of CEUS and B-mode ultrasonography in the diagnosis of HCC are available. This study included cirrhotic patients suspected of HCC, and the results showed that CEUS had a higher diagnostic accuracy than B-mode ultrasonography for HCCs with both large and small diameters. However, the sensitivity of CEUS in the diagnosis of HCC was still low. This study attempted to combine AFP levels and CEUS in the diagnosis of HCC. It was found that the sensitivity and accuracy of the combined diagnostic criteria for HCC were significantly improved. Contrast-enhanced ultrasonography and AFP are commonly used imaging examination tools and serum markers, respectively, and the combination of the two has significant clinical significance and provides a new approach to the diagnosis of early HCC.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://dx.doi.org/10.21037/jgo-21-611

Data Sharing Statement: Available at https://dx.doi.org/10.21037/jgo-21-611

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jgo-21-611). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Our study was approved by the ethics committee of the Affiliated Hospital of Jiangnan University (No. 2021-066) and then performed according to the principles of the Helsinki Declaration [2013]. Due to the retrospective design, written informed consents were not obtained in this study.

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(English Language Editor: B. Meiser)