



Contrast-enhanced US diagnostic algorithm of hepatocellular carcinoma in patients with occult hepatitis B

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Abstract

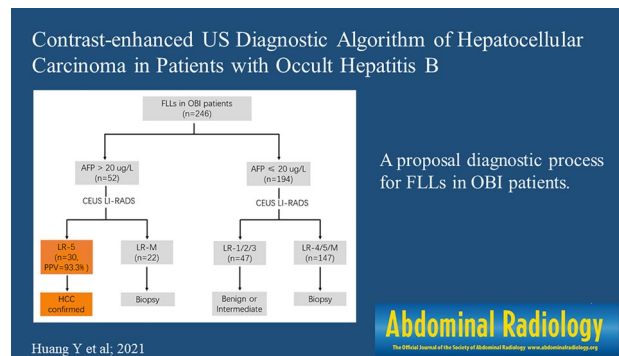
Purpose To assess the diagnostic performance of contrast-enhanced (CE) US Liver Imaging Reporting and Data System (LI-RADS) version 2017 and propose a diagnostic algorithm in diagnosing hepatocellular carcinoma (HCC) in patients with occult HBV infection (OBI).

Methods 251 OBI patients with 251 newly diagnosed focal liver lesions were retrospectively enrolled. Each nodule was evaluated according to CEUS LI-RADS. The subgroup analyses were also performed in patients with alpha-fetoprotein (AFP) more than 20ug/L or not. Diagnostic performance of CEUS LI-RADS for diagnosing HCC was validated via sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV), respectively.

Results There were 90 HCCs (90 of 251, 35.9%), of which 2 (2.0%), 53 (53.5%), and 35 (35.4%) were classified as LR-4, LR-5, and LR-M, respectively. The sensitivity, specificity, accuracy, PPV, and NPV of CEUS LR-5 for HCC diagnosis were 58.9%, 88.8%, 78.1%, 74.6%, and 79.4%, respectively. AFP increased in 50.6% (45/89) HCCs. Using a proposed diagnostic algorithm (for OBI patients with AFP more than 20 ug/L, LR-5 nodules were diagnosed as definitely HCC), the sensitivity, specificity, accuracy, PPV, and NPV were 62.2%, 71.4%, 63.5%, 93.3%, and 22.7%, respectively. Therefore, 12.2% (30 of 246) nodules could be confirmed as HCC by CEUS without biopsy.

Conclusion HCC diagnosis in patients with OBI is challenging. However, using LR-5 as a noninvasively diagnostic standard in OBI patients with AFP more than 20ug/L, HCC could be confirmed by CEUS without biopsy.

Graphic abstract



Keywords Hepatocellular carcinoma · Hepatitis B surface antigens · Contrast-enhanced US · Diagnostic techniques and procedures · Alpha-fetoprotein

Yang Huang and Wei Li have contributed equally to the study.

Extended author information available on the last page of the article

Abbreviations

AFP Alpha-fetoprotein
Anti-HCV Anti-hepatitis C virus antibody
APHE Arterial phase hyperenhancement

CEUS	Contrast-enhanced US
CHC	Combined hepatocellular-cholangiocarcinoma
CI	Confidence interval
FLL	Focal liver lesion
FNH	Focal nodular hyperplasia
HBcAb	Hepatitis B core antibody
HBsAg	Negative hepatitis B surface antigen
HCC	Hepatocellular carcinoma
ICC	Intrahepatic cholangiocarcinoma
LI-RADS	Liver Imaging Reporting and Data System
NPV	Negative predictive value
OBI	Occult HBV infection
OR	Odds ratio
PPV	Positive predictive value

Introduction

Chronic hepatitis B is a major cause of hepatocellular carcinoma (HCC), the second leading cause of cancer-related deaths globally [1]. However, because of the introduction of HBV vaccine into infant immunization schedules worldwide, the incidence of new HBV infection and HBV-related HCC have been dramatically decreasing [2]. Subsequently, within patients with chronic HBV infection, a population characterized by serum negative hepatitis B surface antigen (HBsAg) and positive antibodies to hepatitis B core antigen, with or without detectable antibodies to HBsAg, termed “occult HBV infection (OBI)”, has recently increased [3, 4]. Higher prevalence of OBI has been found in individuals with chronic liver disease than the general population and the prevalence may be as high as 40–75% in those with HBsAg-negative HCC [3]. However, several issues concerning the prevalence and diagnosis for HCC in OBI populations are still largely unknown.

OBI is an independent risk factor for hepatocarcinogenesis [4, 5]. A significantly increased risk of HCC in subjects with OBI in comparison with non-infected controls was shown in a meta-analysis study [6]. OBI is also an independent risk factor for intrahepatic cholangiocarcinoma (ICC) [7]. Besides, the correlations between other focal liver lesions (FLLs) and OBI are currently lacking. Therefore, the diagnosis of HCC in OBI patients may be more challenging.

For high-risk patients, including chronic HBV infection, imaging plays an essential role in the non-invasive detection and diagnosis of HCC. In 2017, the American College of Radiology releases the contrast-enhanced (CE) US Liver Imaging Reporting and Data System (LI-RADS), which standardizes technology, interpretation, reporting, and data collection for patients at risk [8–13]. There were several studies which confirmed that LR-5 is highly specific for HCC, enabling its use for a reliable non-invasive diagnosis

[14–17]. However, only cirrhosis and “overt” chronic hepatitis B patients are involved in these studies and the latter is characterized by the detection of HBsAg and viral genomic materials in the serum. There is no validation of whether CEUS LI-RADS could be useful for HCC diagnosis in OBI patients [18]. Based on the above issues, we designed this study to explore the diagnostic performance of CEUS LI-RADS and propose a diagnostic algorithm in diagnosing HCC in patients with OBI.

Materials and methods

Patient selection

This retrospective study protocol was approved by our institutional review board. The informed consent requirement was waived.

A search of our institutional database was performed for consecutive patients with newly diagnosed FLLs underwent diagnostic liver CEUS between January 2012 and December 2015. Clinical indications for CEUS of OBI patients were indeterminate FLLs detected at unenhanced CT/MRI performed for other clinical reasons or baseline ultrasound at health checkup.

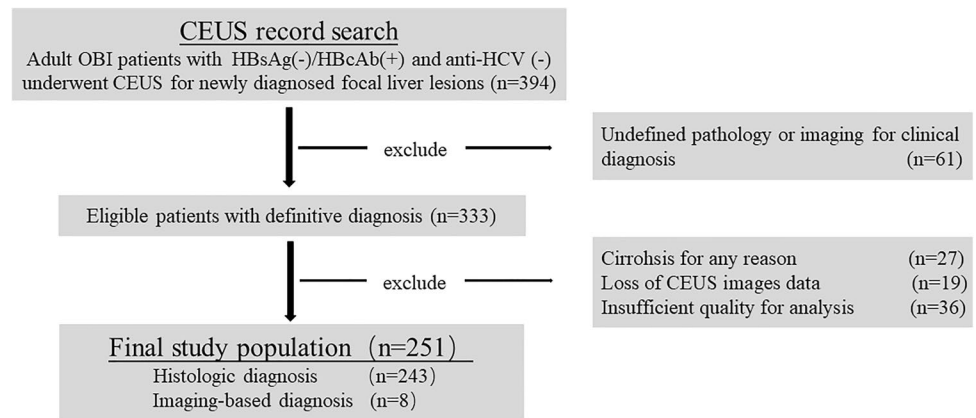
The inclusion criteria were as follows: (a) age of older than 18 years, (b) patients with OBI, based on negative-HBsAg with positive-hepatitis B core antibody (HBcAb) in the blood as a surrogate [3], (c) negative for anti-hepatitis C virus antibody (anti-HCV), (d) treatment-naïve liver nodules visible at baseline ultrasound, (e) availability of CEUS data, and (f) availability of diagnostic reference standards, either histological or imaging-based (history/imaging/follow-up).

The exclusion criteria were as follows: (a) liver cirrhosis due to any reason (viral, alcoholic, non-alcoholic fatty liver disease, hereditary, vascular, et al.), (b) poor image quality or missing CEUS data. Medical records and ultrasound reports were retrospectively reviewed. Patient information, including age, gender, HBV and HCV serum markers, and alpha-fetoprotein (AFP) values, were obtained. AFP values were documented within 6 months of the ultrasound examination. The study flowchart is shown in Fig. 1.

Diagnostic reference standard

Histological or imaging-based (history/imaging/follow-up) assessment were used as the diagnostic reference standards. The histological analysis was used as the only reference standard for diagnosing HCC [1, 19]. The imaging-based diagnostic standard for metastasis was characteristic features on images obtained with at least two contrast-enhanced imaging modalities and the growth of lesion seen on follow-up images, with known primary extrahepatic malignancies

Fig. 1 Flowchart illustrated the selection of observations included in this study. *CE* Contrast enhanced, *HBcAb* Hepatitis B core antibody, *HBsAg* Hepatitis B surface antigens, *anti-HCV* Anti-hepatitis C virus antibody



[20]. The imaging-based diagnosis standard of abscess was aspiration of pus or characteristic features on CT or MR imaging findings, with partial or complete resolution of the lesion at following up [21]. The imaging-based standard for cyst and hemangioma was characteristic feature on CT or MR imaging findings and with no change in size after more than 1-year follow-up period [22, 23]. Other malignancies and benign nodules were diagnosed with histological analysis.

CEUS examination

The conventional B-mode ultrasound and CEUS examinations were performed using three ultrasound devices (Toshiba Aplio 500, AlokaSSDa10 and SuperSonic Aixplorer). All patients underwent conventional B mode of the liver prior to CEUS. In cases with more than one lesion, only the lesion most visible and accessible FLL was chosen for CEUS. CEUS examinations were performed with low mechanical index. An antecubital vein bolus injection of 2.4 mL of SonoVue (Bracco, Milan, Italy) was administered, followed immediately by a 5 mL saline flush [24]. The timer was activated promptly from the beginning of contrast agent administration. Video clips of the examinations were recorded from the first arrival of detectable microbubbles at the target lesion until 2 min, with no change in the machine settings. After 2 min, intermittent scanning was administered and images recorded until 5 min. All B mode and CEUS images and cine clips were stored for further off-line analysis.

Image analysis

All CEUS images were anonymized. Two abdominal radiologists each with > 5 years of experience in hepatic CEUS imaging (Y. H. and W. L.) independently evaluated each patient's images and assessed all lesions using the LI-RADS 2017 CEUS algorithms. They were blinded to the final diagnosis and laboratory results, but they did have access

to patient age and sex. In case of disagreements between two readers, the third more experienced radiologists (L.D. C., with > 10 years of experience in hepatic CEUS imaging) reevaluated images to reach a consensus.

CEUS LI-RADS category was assigned to LR-1 to LR-5 or LR-M, based on features, including lesion size, arterial phase hyperenhancement (APHE), and washout pattern [8, 18]. APHE is defined as diffusely or partially (neither rim-like nor peripheral discontinuous) hyperenhancing in echogenicity than surrounding liver parenchyma in arterial phase. Rim APHE is defined as arterial phase enhancement is most pronounced in observation periphery. Washout is defined as temporal reduction in enhancement in whole or in part relative to liver beginning in or after the arterial phase and resulting in hypoenhancement. If washout occurred within 60 s after injection, it was defined as "early washout", otherwise, considered as "late washout". The degree of washout was also defined. Marked washout was defined as the degree of washout was marked within 2 min after contrast injection and observation appears black or punched out, otherwise defined as mild washout. The algorithm of CEUS LI-RADS category can be found on the official website of the American College of Radiology (<https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/CEUS-LI-RADS-v2017>).

Statistical analysis

Statistical analysis was performed using software (Medcalc, version 11.2; R Foundation for Statistical Computing, version 3.6.1, <http://www.r-project.org/>). Descriptive analysis is expressed as rates in absolute numbers and percentages. Continuous variables are reported as medians and ranges.

After the assignment of CEUS LI-RADS category, we validated the diagnostic performance of CEUS LI-RADS using LR-5 as the diagnostic criterion for HCC. Furthermore, considering the interference of non-HCCs, we performed the subgroup analyses with AFP more than 20ug/L or not. The overall diagnostic performance was assessed in

Table 1 Characteristics of patients and nodules

Characteristic	Value
Sex	
Male	152 (60.6)
Female	99 (39.4)
Mean age (y)*	55.7 ± 12.9
Nodule size	
<10 mm	8 (3.2)
10–19 mm	19 (7.6)
20–49 mm	65 (25.9)
≥50 mm	159 (63.3)
Tumor marker	
AFP > 20 ug/L	52 (21.1)
Histological examination	227 (90.4)
Diagnosis	
HCC	90 (35.9)
ICC	50 (19.9)
CHC	4 (1.6)
Metastases	25 (10.0)
Other malignancies	7 (2.8)
FNH	13 (5.2)
Hemangioma	25 (10.0)
Hepatic cyst	13 (5.2)
Inflammatory nodules	16 (6.4)
Other Benign nodules	8 (3.2)

AFP Alpha-fetoprotein, CHC Combined hepatocellular-cholangiocarcinoma, FNH Focal nodular hyperplasia, HCC Hepatocellular carcinoma, ICC Intrahepatic cholangiocarcinoma

Except where indicated, data are numbers of nodules and numbers in parentheses are percentages

*Data are mean ± standard deviation

terms of accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with corresponding 95% confidence interval (CI). The comparison of diagnostic performance of LR-5 for HCC between two subgroups was performed. The diagnostic odds ratio (OR) was also computed for LR-5. A *p* value less than 0.05 was considered significant.

Results

Patient characteristics

A total of 394 OBI patients with FLLs were searched from CEUS database. 61 patients were excluded because of undefined diagnosis, 27 were excluded because of cirrhosis, and 55 were excluded due to lack of availability of dynamic CEUS data. The final study cohort consisted of 251 nodules in 251 patients (Fig. 1). As shown in Table 1, the mean age of patients was 55.7 ± 12.9 years old and the proportion of men was 60.6% (152/251). AFP increased in 21.1% (52/251) patients. All nodules were confirmed by histological evaluation (*n* = 227) or imaging-based assessment (*n* = 24).

Of the 251 lesions, 176 (70.1%) were malignant and 75 (29.9%) were benign. The 176 malignancies consisted of 90 (35.9%) HCCs, 50 (19.9%) ICCs, 4 (1.6%) combined hepatocellular-cholangiocarcinomas (CHCs), 25 (10.0%) metastases, and seven (2.8%) other malignancies.

Table 2 Rates of different cellular types of 251 nodules by LI-RADS classes in OBI patients

Total nodules	LR-1	LR-2	LR-3	LR-4	LR-5	LR-M
<i>n</i> (%)	38(15.1)	0(0)	11(4.4)	16(6.4)	71(28.3)	115(45.8)
HCC	0	0	0	2(12.5)	53(74.6)	35(30.4)
ICC	0	0	4(36.4)	0	1(1.4)	45(39.1)
CHC	0	0	0	0	1(1.4)	3(2.6)
Metastases	0	0	2(18.2)	1(6.3)	2(2.8)	20(17.4)
Other malignancies	0	0	1(9.1)	0	4(5.6)	2(1.7)
FNH	0	0	2(18.2)	6(37.5)	5(7.0)	0
Hemangioma	23(60.5)	0	0	1(6.3)	0	1(0.9)
Hepatic cyst	13(34.2)	0	0	0	0	0
Inflammatory nodules	2(5.3)	0	2(18.2)	0	4(5.6)	8(7.0)
Other benign nodules	0	0	0	6(37.5)	1(1.4)	1(0.9)

CHC Combined hepatocellular-cholangiocarcinoma, FNH Focal nodular hyperplasia, HCC Hepatocellular carcinoma, ICC Intrahepatic cholangiocarcinoma, LI-RADS Liver Imaging Reporting and Data System, OBI Occult HBV infection

*Data in the first row are numbers of nodules in each LI-RADS category, and the numbers in parentheses are percentages equal to the proportion of each LI-RADS category in the whole group. Data in other places are numbers of nodules of different diseases in each LI-RADS category, and the numbers in parentheses are percentages equal to the proportion of different diseases in each LI-RADS category

CEUS LI-RADS category

Table 2 shows the FLLs assigned to each LI-RADS category. From LR-4, LR-5, to LR-M categories, the risk of HCC was 12.5% (2/16), 74.6% (53/71), and 30.4% (35/115), respectively. Except for 53 HCCs, 18 other cases were classified as LR-5 category, including 1 ICC, 1 CHC, 2 metastases, 4 other malignancies, and 10 benign nodules. 35 of 115 (30.4%) HCCs were designated as LR-M category. The majority of non-HCC LR-M cases were ICCs ($n=45$) and the remaining CHCs ($n=3$), metastases ($n=20$), and inflammatory nodules ($n=8$).

Imaging characteristics of HCC

Of 90 HCC nodules, 2 (2.0%), 53 (53.5%), and 35 (35.4%) were assigned to LR-4, LR-5, and LR-M, respectively. Only one HCC was smaller than 2 cm. The 2 HCCs classified as LR-4 displayed the hyper-hyper-hyper (1/2) / iso-hypo-hypo (1/2) pattern. The 53 HCCs assigned to LR-5 showed hyper-hypo-hypo (46/53, Figs. 2, 3) / hyper-iso-hypo (7/53) pattern. Of the 35 HCCs classified as LR-M, early (< 60 s) washout, marked washout, and both were displayed in 31, 1, and 3, respectively. Besides, 3 HCCs showed rim APHE.

Diagnostic performance of LR-5 in the prediction of HCC

Diagnostic performance of LI-RADS for HCC diagnosis is summarized in Table 3. Considering LR-5 for standard of HCC diagnosis, the sensitivity, specificity, accuracy, PPV, and NPV in OBI patients were 58.9% (95% CI: 48.7%, 69.1%), 88.8% (95% CI: 84.0%, 93.7%), 78.1% (95% CI: 78.0%, 78.2%), 74.6% (95% CI: 64.5%, 84.8%), and 79.4% (95% CI: 73.5%, 85.3%), respectively, with an OR of 11.24 (95% CI: 5.71, 23.00).

Proposal of a diagnostic algorithm

246 patients had the results of AFP, among whom 36.2% (89/246) had HCCs. AFP increased in 50.6% (45/89) patients with HCCs. Subset analysis was performed for patients according to AFP more than 20 ug/L or not. In the subgroup with elevated AFP, there were 52 cases, composed of 45 HCCs, 4 ICCs, 2 CHCs and 1 metastasis. Among them, 30 nodules were assigned to LR-5, including 28 HCCs, 1 ICC and 1 CHC. The other 22 nodules were all classified as LR-M. Considering LR-5 for standard of HCC diagnosis, the sensitivity, specificity, accuracy, PPV, and NPV in these patients were 62.2% (95% CI: 48.1%, 76.4%), 71.4% (95% CI: 38.0%, 105.0%), 63.5% (95% CI: 62.6%, 64.3%), 93.3% (95% CI: 84.4%, 102.0%), and 22.7% (95%

CI: 5.2%, 40.2%), respectively, with an OR of 4.00 (95% CI: 0.58, 46.48) (Table 3).

In the subgroup with normal AFP, there were 194 cases composed of 44 HCCs, 45 ICCs, 2 CHCs, 20 metastases, 10 other malignancies, and 73 benign nodules. Considering LR-5 for standard of HCC diagnosis, the sensitivity, specificity, accuracy, PPV, and NPV in these patients were 58.6% (95% CI: 42.2%, 71.5%), 89.3% (95% CI: 84.4%, 94.3%), 82.2% (95% CI: 81.8%, 82.1%), 61.0% (95% CI: 46.0%, 75.9%), and 87.6% (95% CI: 82.4%, 92.8%), respectively, with an OR of 10.82 (95% CI: 4.65, 26.60) (Table 3). The PPV of LR-5 for HCC was significantly higher in elevated AFP cases than normal AFP ones (93.3% vs 61.0%, $p=0.005$), with sensitivity (62.2% vs 58.6%, $p=0.60$) and specificity (71.4% vs 89.3%, $p=0.40$) showing no significant difference between two subgroups (Table 3).

Based on the above analysis, we proposed an HCC diagnostic algorithm in Fig. 4. For OBI patients with AFP more than 20 ug/L, using LR-5 as a diagnostic standard could achieve definite HCC diagnosis in 12.2% (30/246) cases with the high PPV (93.3%). In the 12.2% patients, HCC could be confirmed by CEUS without biopsy. Figure 2 shows a LR-5 case with elevated AFP. For OBI patients with normal AFP, 19.1% (47/246) cases were classified as LR-1/2/3. For these benign or immediate cases, biopsies were not required. For the remaining 68.7% (167/246) cases, including LR-M cases with elevated AFP and LR-4/5/M cases with normal AFP, biopsies were required for unsatisfactory PPV. Figure 3 shows a LR-5 case with normal AFP.

Discussion

It is reported that prior HBV infection (i.e., positive HBcAb with negative-HBsAg) can contribute to the development of HCC among patients with negative serum results for active HBV or HCV infection [4, 25]. However, few data regarding diagnosis of HCC in OBI patients are available in previous literatures. In this study, we firstly explored HCC diagnosis standard and applied the CEUS LI-RADS in OBI patients. We validated that the sensitivity (58.9%), specificity (88.8%), and PPV (74.6%) of LR-5 for diagnosing HCC were not high enough in OBI patients. However, in OBI patients with elevated AFP, the PPV (93.3%) of LR-5 for diagnosing HCC was satisfied. Besides, we firstly proposed a diagnostic algorithm in OBI patients, with 12.2% patients obtaining a noninvasively confirmed HCC diagnosis.

Our results demonstrated that the incidence rate of HCC in OBI patients was much lower than that in high-risk patients. According to the studies by Terzi et al. and Zheng et al. [14, 15], there were 75–81% HCC lesions in high-risk patients. In OBI patients, the prevalence of HCC in our institution was 35.9%. European Association for the Study

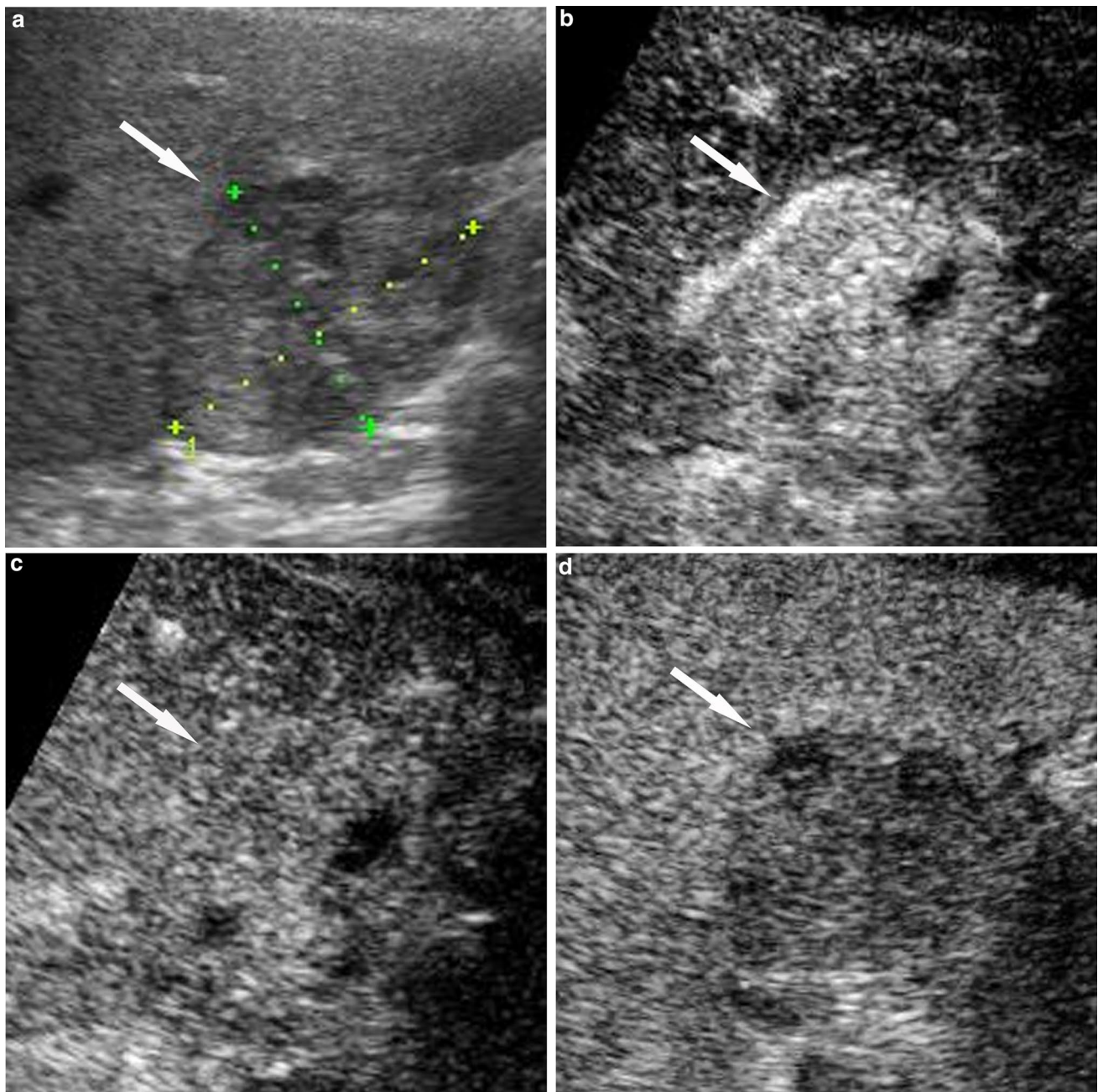


Fig. 2 Images obtained in a 71-year-old woman with occult HBV infection and surgically proved hepatocellular carcinoma (HCC), which classified as LR-5 according to Contrast-enhanced (CE) US Liver Imaging Reporting and Data System (LI-RADS) version 2017. Alpha-fetoprotein was 446.47 ug/L. **a** A 4.7 cm hypoechoic nodule (arrow) in the Segment V/VI of the liver was scanned in US. CEUS images were obtained. **b** Arterial phase (timer, 00:23) image showed

inhomogeneous hyperenhancement (not rim or peripheral discontinued globular enhancement) (arrow). Observation showed **c** iso-enhancement (timer, 01:11) (arrow). **d** Late onset and mild washout (>60 s; timer, 02:24) (arrow) were displayed. Defined diagnosis of HCC could be gained through CEUS LI-RADS according to the proposal diagnostic process

of the Liver Clinical Practice Guidelines on the management of HCC proposed the concept of intermediate risk for HCC, but the specific definition was not well defined [1]. Based on the practical prevalence of HCC in our institution, we considered OBI patients as intermediate risk. Except for

HCC, other malignancies accounted for a large proportion, including 19.9% ICCs, 1.6% CHCs, 10.0% metastases, and 2.8% other malignancies. Therefore, HCC detection was very difficult in OBI patients. With the increasing incidence

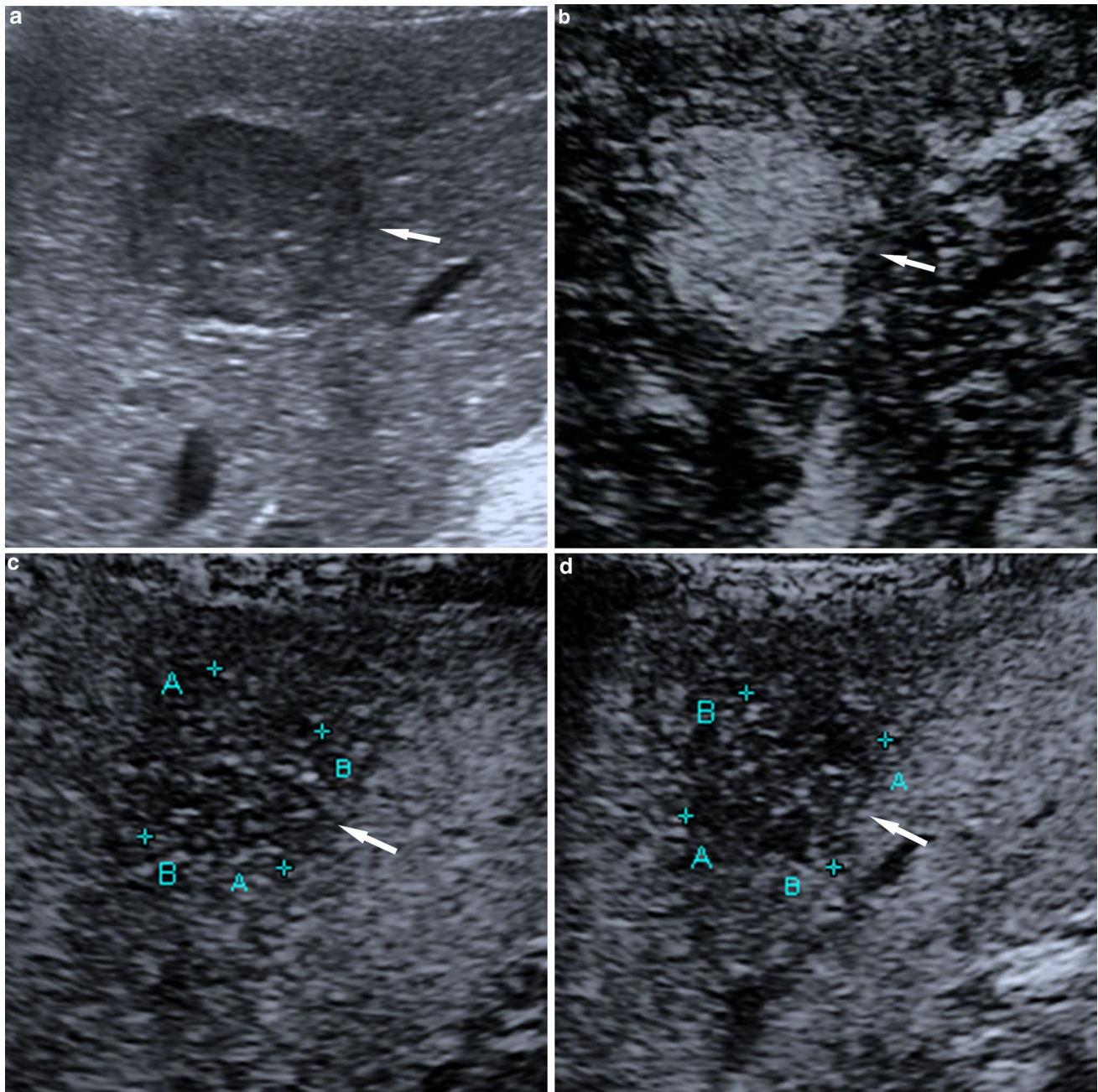


Fig. 3 Images obtained in a 42-year-old man with occult HBV infection and pathologically proved hepatocellular carcinoma, which satisfied LR-5 according to Contrast-enhanced (CE) US Liver Imaging Reporting and Data System version 2017. Alpha-fetoprotein was 1.14 ug/L. **a** A 2.6 cm hypoechoic nodule (arrow) in the Segment VI of the liver was scanned in US. CEUS images were obtained. **b** Arterial

phase (timer, 00:19) image showed homogeneous hyperenhancement (not rim or peripheral discontinued globular enhancement) (arrow). Observation showed **c** late onset (> 60 s; timer, 01:43) (arrow) and **d** mild washout (timer, 02:03) (arrow). Biopsy was required according to the proposal diagnostic process

of OBI, a diagnostic standard of HCC is crucial for patient management.

In our study, the percentage of LR-5 nodules in OBI patients was also lower than that in high-risk patients. Previous studies reported that the LR-5 nodules accounted for 51.6–57.4% in high-risk patients [14, 15]. However, in

our study, the nodules classified to LR-5 were not the most cases, which accounted for only 28.3%. The low prevalence of HCC in OBI patients might be the primary reason.

Among the LR-5 nodules of our study, the percentage of HCC (74.6%) was also lower than that of HCC in high-risk patients, a fairly high rate of 98–99% [14, 15]. Our results

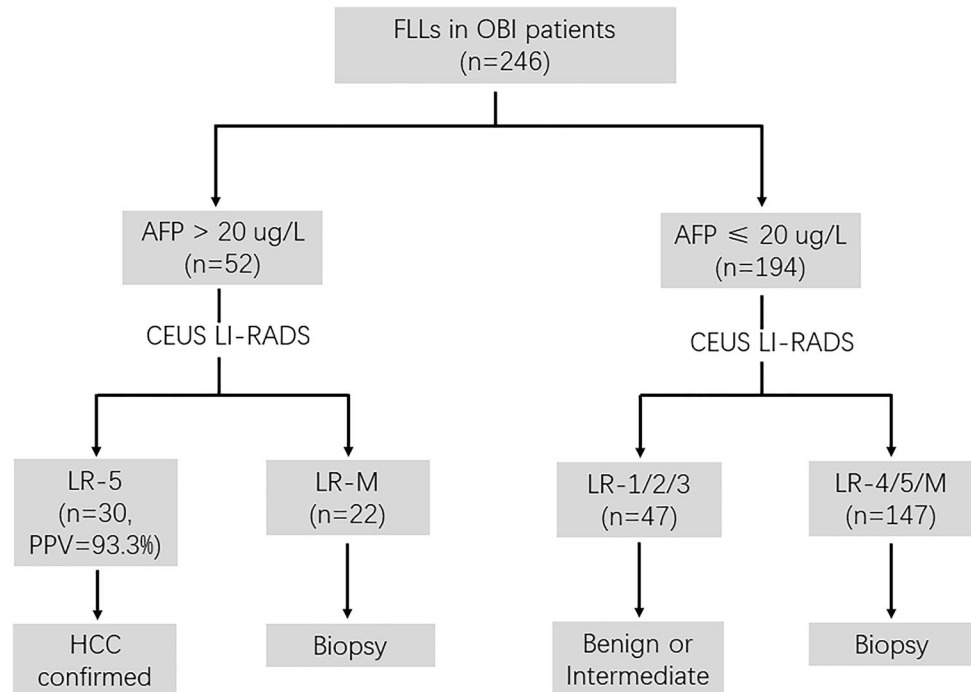
Table 3 Diagnostic performance of LI-RADS LR-5 category for Diagnosing HCC for occult HBV infection patients

Group	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)
Total	58.9 (48.7–69.1)	88.8 (84.0–93.7)	78.1 (78.0–78.2)	74.6 (64.5–84.8)	79.4 (73.5–85.3)
AFP > 20 (ug/L)	62.2 (48.1–76.4)	71.4 (38.0–1.05)	63.5 (62.6–64.3)	93.3 (84.4–1.02)	22.7 (5.2–40.2)
AFP ≤ 20 (ug/L)	58.6 (42.2–71.5)	89.3 (84.4–94.3)	82.2 (81.8–82.1)	61.0 (46.0–75.9)	87.6 (82.4–92.8)
<i>P</i>	0.60	0.40	0.004	0.005	<0.001

Data in parentheses are 95% confidence intervals. The *p* value indicates the comparisons between two subgroups

AFP Alpha-fetoprotein, LI-RADS Liver Imaging Reporting and Data System, HBV Hepatitis B viral, HCC Hepatocellular carcinoma

Fig. 4 A proposal diagnostic process for FLLs in OBI patients. AFP Alpha-fetoprotein, FLL Focal liver lesion, LI-RADS Liver Imaging Reporting and Data System, OBI Occult HBV infection, PPV Positive predictive value



showed that many non-HCC nodules manifested as APHE and late and mild washout in OBI patients. One of the reasons might be the high incidence of non-HCC malignancies, which showed typical malignant CEUS features of hyperenhancement followed by washout. Another reason might be due to more atypical benign nodules in OBI patients. We noted that several focal nodular hyperplasia and inflammatory nodules were assigned to LR-5, indicating that distinguishing HCCs from these atypical benign nodules in OBI patients was difficult. As a result, the specificity (88.8%) of using LR-5 for the diagnostic standard of HCC was not sufficiently high in OBI patients. Moreover, due to the overall low frequency rate (35.9%) of HCC, the PPV (74.6%) of LR-5 as predictor of HCC was low in OBI patients. It demonstrated that CEUS LI-RADS was challenging for the non-invasive diagnostic standard in the OBI population.

Serum AFP was still widely used as a screening test for HCC, particularly in Asia [1]. In our study, 50.6% of

patients with HCC have AFP more than 20 ug/L. Then, we determined whether the diagnostic performance of CEUS LI-RADS was improved in OBI patients with AFP more than 20ug/L. When performing HCC diagnosis under the condition of elevated AFP, most non-HCC malignancies and all benign nodules were eliminated. Then, applying the LR-5 category to diagnose HCC, the sensitivity had little increase (62.2% vs 58.9%) and the PPV showed obviously improvement (93.3% vs 74.6%). Based on the high PPV, we proposed that LR-5 might be definitive diagnosis of HCC in the subgroup of OBI population with AFP more than 20ug/L. This allowed 12.2% OBI patients suitable for non-invasive diagnosis of HCC. For other OBI patients suspicious of HCC, biopsies were needed.

Our study had limitations. First, its retrospective design might result in selection bias and affect generalizability. Not all FLLs detected on baseline US would receive further CEUS examinations. Many benign lesions like cyst and

hemangioma could be confirmed by baseline US. Therefore, the rates of different types of nodules in our study could not be reflective of its true morbidity in OBI patients. Second, the histological reference standard and follow-up information for some benign lesions were lacking, especially for the regenerative and dysplastic nodules, so their diagnosis could not be confirmed and they were not included in the analysis. This leads to variable distribution of LR category in different centers. Third, small nodules were much fewer in our study compared with previous reports. This might also be due to the absence of dysplastic nodules in our study which were usually smaller than 2 cm.

In conclusion, HCC diagnosis in patients with OBI is challenging. However, using LR-5 as a non-invasive diagnostic standard in OBI patients with AFP more than 20ug/L, HCC could be confirmed by CEUS without biopsy. The proposed diagnostic algorithm of HCC may be beneficial to the management for OBI patients in the clinic.

Author contributions W. W. and L.D. C. designed the study. Y. H., W. L., and L.D. C. reviewed the CEUS images. H.T. H. and S.M. R. collected the data. Y. H., W. L., H.T. H., S.M. R., and M.F. X. analyzed the data, edited the tables, and drew the figures. W. W., L.D. C., Y. H., W. L., X.Y. X., M.D. L., and M. K. edited the manuscript. All authors contributed to the article and approved the submitted version.

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Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Conflict of interest None.

Ethical approval Our institutional review board approved this retrospective study.

Informed consent It was waived.

Consent for publication Not applicable.

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