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Diagnostic Accuracy of CEUS LI-RADS for the Characterization of Liver Nodules 20 mm or Smaller in Patients at Risk for Hepatocellular Carcinoma

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Conflicts of interest are listed at the end of this article.

See also the editorial by Crocetti in this issue.

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Background: American College of Radiology contrast agent–enhanced US Liver Imaging Reporting and Data System (CEUS LI-RADS) was developed to improve the accuracy of hepatocellular carcinoma (HCC) diagnosis at contrast agent–enhanced US. However, to the knowledge of the authors, the diagnostic accuracy of the system in characterization of liver nodules 20 mm or smaller has not been fully evaluated.

Purpose: To evaluate the diagnostic accuracy of CEUS LI-RADS in diagnosing HCC in liver nodules 20 mm or smaller in patients at risk for HCC.

Materials and Methods: Between January 2015 and February 2018, consecutive patients at risk for HCC presenting with untreated liver nodules 20 mm or less were enrolled in this retrospective double-reader study. Each nodule was categorized according to the CEUS LI-RADS and World Federation for Ultrasound in Medicine and Biology (WFUMB)–European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) criteria. Diagnostic performance of CEUS LI-RADS and WFUMB-EFSUMB characterization was evaluated by using tissue histologic analysis, multiphase contrast-enhanced CT and MRI, and imaging follow-up as reference standard and compared by using McNemar test.

Results: The study included 175 nodules (mean diameter, 16.1 mm ± 3.4) in 172 patients (mean age, 51.8 years ± 10.6; 136 men). The sensitivity of CEUS LR-5 versus WFUMB-EFSUMB criteria in diagnosing HCC was 73.3% (95% confidence interval [CI]: 63.8%, 81.5%) versus 88.6% (95% CI: 80.9%, 94%), respectively ($P < .001$). The specificity of CEUS LR-5 versus WFUMB-EFSUMB criteria was 97.1% (95% CI: 90.1%, 99.7%) versus 87.1% (95% CI: 77%, 94%), respectively ($P = .02$). No malignant lesions were found in CEUS LR-1 and LR-2 categories. Only two nodules (of 41; 5%, both HCC) were malignant in CEUS LR-3 category. The incidences of HCC in CEUS LR-4, LR-5, and LR-M were 48% (11 of 23), 98% (77 of 79), and 75% (15 of 20), respectively. Two of 175 (1.1%) histologic analysis–confirmed intrahepatic cholangiocarcinomas were categorized as CEUS LR-M by CEUS LI-RADS and misdiagnosed as HCC by WFUMB-EFSUMB criteria.

Conclusion: The contrast-enhanced US Liver Imaging Reporting and Data System (CEUS LI-RADS) algorithm was an effective tool for characterization of small (≤ 20 mm) liver nodules in patients at risk for hepatocellular carcinoma (HCC). Compared with World Federation for Ultrasound in Medicine and Biology–European Federation of Societies for Ultrasound in Medicine and Biology criteria, CEUS LR-5 demonstrated higher specificity for diagnosing small HCCs with lower sensitivity.

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Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and ranked second for deaths caused by cancer (1,2). Noninvasive imaging plays an important role in the diagnosis of HCC, which is essential for appropriate patient treatment (3,4). Imaging of small HCC is challenging because of the complexity of dual blood supply to the liver, multistage hepatic carcinogenesis, overlapping of microvascular perfusion of regenerative and dysplastic nodules, and different histologic grades for HCC. Over the years, real-time low mechanical index contrast agent–enhanced US has been used in Europe and Asia as a first-line diagnostic modality for HCC and is recommended by several national and international professional societies (3,5–9).

Despite reported high sensitivity and positive predictive value of contrast-enhanced US for the diagnosis of HCC in cirrhosis, the diagnosis of small HCC, especially those smaller than 2 cm, remains a challenge despite advances in US and harmonic imaging techniques (3,10–12). Only recently was contrast-enhanced US for liver indication approved in the United States (13). To improve the diagnostic accuracy of HCC and facilitate communication among radiologists and between radiologists and physicians, the American College of Radiology developed the contrast-enhanced US Liver Imaging Reporting and Data System (CEUS LI-RADS) as a standardized reporting system for liver nodules in patients at risk for HCC (14,15). However, the diagnostic accuracy

Abbreviations

CEUS LI-RADS = contrast agent–enhanced US Liver Imaging Reporting and Data System, CI = confidence interval, EFSUMB = European Federation of Societies for Ultrasound in Medicine and Biology, HCC = hepatocellular carcinoma, WFUMB = World Federation for Ultrasound in Medicine and Biology

Summary

The American College of Radiology contrast agent–enhanced US Liver Imaging Reporting and Data System effectively categorized liver nodules 20 mm or smaller in patients at risk for hepatocellular carcinoma. Nodules categorized as CEUS LR-5 demonstrated high specificity, positive predictive value, and positive likelihood ratio in diagnosing small hepatocellular carcinoma.

Key Results

- By using the American College of Radiology contrast agent–enhanced US Liver Imaging Reporting and Data System (CEUS LI-RADS), nodules categorized as CEUS LR-5 demonstrated sensitivity and specificity of 73% and 97%, respectively, for the diagnosis of hepatocellular carcinoma (HCC) 20 mm or less in patients at risk for HCC.
- By using World Federation for Ultrasound in Medicine and Biology (WFUMB)–European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) criteria for the same patients, the sensitivity and specificity were 89% and 87%, respectively ($P < .001$ for comparison with CEUS LI-RADS).
- No malignancy was found in nodules categorized as CEUS LR-1 and LR-2. Five percent of CEUS LR-3 nodules were malignant; the incidences of HCC in CEUS LR-4, LR-5, and LR-M categories were 48%, 97%, and 75%, respectively.
- Two of 175 (1.1%) nodules diagnosed at pathologic analysis as intrahepatic cholangiocarcinomas were categorized as CEUS LR-M by CEUS LI-RADS and misdiagnosed as HCC by WFUMB-EFSUMB criteria.

of CEUS LI-RADS in its characterization of small liver nodules (≤ 20 mm), to our knowledge, has not been fully evaluated.

Until recently, World Federation for Ultrasound in Medicine and Biology (WFUMB)–European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) 2012 guidelines were widely accepted as the criteria for diagnosis of HCC. They were intended to create a standard protocol for the use of contrast agent at US in liver application on an international basis and improve the treatment of patients worldwide. The key contrast-enhanced US features for the diagnosis of HCC in liver cirrhosis by WFUMB-EFSUMB criteria are arterial phase hyperenhancement followed by washout in the late phase (5).

CEUS LI-RADS was initially introduced in 2016 and has different diagnostic features and characterization algorithm compared with WFUMB-EFSUMB criteria. The size of a lesion, the type and degree of arterial phase enhancement, the presence of washout, and the timing and degree of washout are the major features used for categorization (16).

The aim of our study was to evaluate the diagnostic accuracy of the American College of Radiology CEUS LI-RADS and WFUMB-EFSUMB criteria for diagnosing HCCs in liver nodules 20 mm or smaller in patients at risk for HCC.

Materials and Methods

Our retrospective study was approved by the institutional ethics committee and written informed consent was waived.

Patient Selection

Between January 2015 and February 2018, consecutive hepatic contrast-enhanced US examinations performed in a West China tertiary academic medical center hospital were retrospectively evaluated. Patients with risk factors for HCC who presented with untreated liver nodules with maximal diameter of 20 mm or smaller at initial imaging (screening or diagnostic US, or contrast-enhanced CT or MRI performed as a part of standard clinical care) were included. All nodules were visible at baseline US. Risk factors for HCC were defined in accordance to American Association for the Study of Liver Diseases guidelines, which include cirrhosis of any cause and/or chronic hepatitis B (3).

Clinical indications for contrast-enhanced US were as follows: a US screening examination positive for liver nodule in patients at risk for HCC per current clinical standards of practice, the WFUMB-EFSUMB and CEUS LI-RADS guidelines; focal liver observation at single-phase CT or unenhanced MRI performed for other clinical reasons; indeterminate focal liver observation at multiphase contrast-enhanced CT or MRI; and definite HCC on CT or MRI images in preparation for or during tissue sampling, surgical resection, or percutaneous ablation treatment. Patients with definitely benign findings at contrast-enhanced US returned to standard surveillance. Patients with findings that were indeterminate or suspicious for HCC at contrast-enhanced US or multiphase CT or MRI were referred to a multidisciplinary discussion and further management (ie, follow-up imaging, tissue sampling, or treatment).

US Examination

Conventional precontrast gray-scale and contrast-enhanced US examinations were performed by using a US system (IU22; Philips Medical Solutions, Mountain View, Calif) with a C5–1 MHz convex or L9–3 MHz linear probe. Pulse inversion harmonic imaging and mechanical index of less than 0.1 were used for contrast-enhanced US examinations with technical recommendations by following the WFUMB-EFSUMB and CEUS LI-RADS guidelines (5,16). The image focus was placed below the region of interest and a dual screen format was used for all the contrast-enhanced US examinations showing a gray-scale image alongside the contrast-specific image. A bolus injection of 1.2–2.4 mL sulfur hexafluoride–filled microbubble contrast agent (SonoVue; Bracco, Milan, Italy) was administered via a 20-gauge catheter line placed in the antecubital vein. A 5-mL flush of 0.9% sodium chloride solution was followed after the injection of the contrast agent (SonoVue; Bracco). The imaging timer was started simultaneously with the completion of the contrast agent injection (SonoVue; Bracco). The region of interest, including target lesion and surrounding liver parenchyma, was imaged continuously for the first 60 seconds and intermittently afterward until washout was confidently observed or liver parenchymal enhancement faded, typically 5 minutes or longer (17). The set of contrast-enhanced US imaging was stored on the hard drive of the US system and copied to portable hard drive for later evaluation.

Table 1: Rating Criteria of WFUMB-EFSUMB and CEUS LI-RADS

Rating Criteria with Nodule Size	Arterial Phase	Portal or Late Phase
WFUMB-EFSUMB		
Nodule size not required	Hyperenhancement	Washout
CEUS LI-RADS		
LR-5		
≥1 cm	Not rim, not peripheral discontinuous globular hyperenhancement	Late mild washout
LR-M		
Nodule size not required	Rim hyperenhancement	Washout
Nodule size not required	Not rim, not peripheral discontinuous globular hyperenhancement	Early washout (<60 sec) or marked out at 120 seconds
LR-4		
≥2 cm	No hyperenhancement	Late and mild washout
≥1 cm	Not rim, not peripheral discontinuous globular hyperenhancement	No washout
<1 cm	Not rim, not peripheral discontinuous globular hyperenhancement	Late and mild washout
LR-3		
<2 cm	No hyperenhancement	No washout or late and mild washout
≥2 cm	No hyperenhancement	No washout
<1 cm	Not rim, not peripheral discontinuous globular hyperenhancement	No washout
LR-2		
<1 cm	Isoenhancement	No washout
LR-1		
Nodule size not required	Definitely benign arterial phase pattern (cyst, hemangioma, focal fatty deposition/sparing or other definitely benign observation)	No washout

Note.—CEUS LI-RADS = contrast-enhanced US Liver Imaging Reporting and Data System, EFSUMB = European Federation of Societies for Ultrasound in Medicine and Biology, WFUMB = World Federation for Ultrasound in Medicine and Biology.

Reference Standard

A composite reference standard was used. All observations with LR-1 classification at contrast-enhanced CT or MRI were considered benign. All lesions with LR-5 classification at contrast-enhanced CT or MRI were considered to be HCC. In patients with lesions classified as CEUS LR-1, contrast-enhanced CT or MRI was used as reference standard. In patients with lesions classified as CEUS LR-2, LR-3, and LR-4, imaging follow-up or tissue sampling was performed per multidisciplinary discussion recommendations. Lesions with a size increase less than 50% in 12 months and without progression to a higher CEUS LI-RADS category at follow-up imaging were classified as benign. Observations with a size increase greater than 50% at follow-up imaging, additional contrast-enhanced CT or MRI, or tissue sampling was performed per multidisciplinary discussion recommendations. Indeterminate findings that progressed to LR-5 at follow-up imaging were considered to be HCC. In patients with CEUS LR-M observations, histologic tissue analysis was used as reference standard. Patients with CEUS LR-3 and LR-4 observations without histologic diagnosis that remained indeterminate at follow-up imaging were removed from the analysis because of lack of a reference standard.

Tissue Sampling

Tissue sample of the lesion was obtained by surgical resection or US-guided biopsy. Biopsy was performed by using an

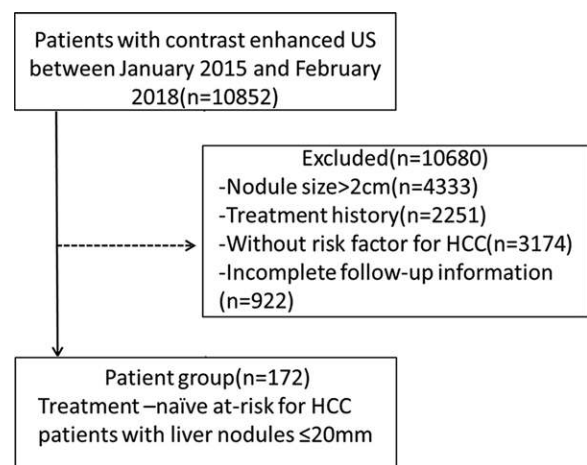


Figure 1: Study population flowchart. HCC = hepatocellular carcinoma.

18-gauge core needle with a 15- or 22-mm throw (Bard-Magnum Biopsy Instrument MN1816; Bard Medical, Covington, Ga) with real-time US guidance. The liver background of the surgical or biopsied specimen was evaluated at pathologic analysis and staged by using Scheuer fibrosis staging.

Contrast-enhanced US Imaging Analysis

Two certified radiologists (Q.L. and J.W.L., with more than 10 years and 5 years of experience in liver contrast-enhanced US, respectively) who were blinded to reference standard

Table 2: Clinical and Pathologic Information

Characteristic	Result
Mean age (y)*	51.8 ± 10.6 (21–78)
Sex	
Men	136 (79)
Women	36 (21)
Mean nodule size (mm)*	16.1 ± 3.4 (8–20)
Liver disease etiologic cause	
HBV	158 (91.9)
HCV	6 (3.5)
HBV and HCV	1 (0.6)
PBC	1 (0.6)
Alcohol	1 (0.6)
Unknown etiology	5 (2.9)
Fibrosis stage	
S1	2 (1.2)
S2	10 (5.8)
S3	17 (9.9)
S4	84 (48.8)
NA	59 (34.3)
Pathologic Analysis	
HCC	104 (59.4)
Well differentiated	1
Moderately differentiated	78
Poorly differentiated	25
DN/RN	11 (6.3)
FNH	1 (0.6)
Hemangioma	3 (1.7)
Intrahepatic cholangiocarcinoma	2 (1.1)
Reactive lymphoid hyperplasia	1 (0.6)
Biliary adenoma	1 (0.6)
NEN	1 (0.6)
No pathologic analysis	
Contrast-enhanced CT or MRI	
Hemangioma	12 (6.9)
Follow-up	39 (22.3)
<50% size increase in 12 months	38 (21.7)
≥50% size increase in 12 months	1 (0.6)

Note.—Unless otherwise indicated, data are liver nodules ($n = 175$) or patients ($n = 172$) and data in parentheses are percentages. Mean data are \pm standard deviation. DN = dysplastic nodule, FNH = focal nodular hyperplasia, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, RN = regenerative nodule, NA = not available, NEN = neuroendocrine neoplasm, PBC = primary biliary cirrhosis.

* Data in parentheses are range.

results and other imaging test results reviewed the contrast-enhanced US examinations in the liver nodules independently and assigned a category according to CEUS LI-RADS (2017 version) and WFUMB-EFSUMB criteria (Table 1). If no consensus was reached, arbitration from a blinded expert radiologist (A.L., with >20 years of experience) was performed. The following diagnostic features were used to characterize each nodule on the basis of CEUS LI-RADS: nodule size; arterial phase enhancement and its pattern; presence, timing, and degree of washout; mosaic and nodule-in-nodule architec-

ture; and tumor in vein, size change at follow-up imaging (16). For characterization of the lesion on the basis of WFUMB-EFSUMB criteria, presence of arterial phase hyperenhancement and washout were documented (5). To better understand why small HCC nodules could manifest with different enhancing patterns, correlation between histologic HCC tumor grading and CEUS LI-RADS classification was performed.

Treatment Options

All patients with focal liver observations requiring treatment were reviewed at the multidisciplinary discussion. After that, all treatment options including liver resection, radiofrequency ablation, and embolization were discussed with the patients in detail. The final decision on treatment approach was on the basis of the patient preference.

Statistical Analysis

Qualitative data are presented as numbers and percentage. Quantitative data are presented as mean \pm standard deviation. Comparison of the rate of poorly differentiated HCCs in LR-5 and LR-M was performed by using the χ^2 test. Characteristics of each liver nodule at contrast-enhanced US were registered separately and were processed blindly for statistical evaluation. The unit of analysis was each liver nodule rather than each patient. For category CEUS LR-5 and WFUMB-EFSUMB characterization, the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for HCC were calculated by using standard procedures (18). Estimated values of sensitivity, specificity, and accuracy of LR-5 and WFUMB-EFSUMB criteria in diagnosing HCC were compared by using the McNemar test. Weighted κ value was calculated to measure interobserver agreement of CEUS LI-RADS classifications of the nodules. The strength of agreement was interpreted according to the classification for κ as follows: 0–0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement. Significance was indicated by a P value less than .05. Statistical analyses were performed by using commercially available statistical software (MedCalc10.4.7.0; MedCalc Software, Ostend, Belgium).

Results

Patients and Liver Nodule Characteristics

On the basis of the selection criteria, a total of 175 nodules in 172 patients were included (Fig 1). Three patients had two nodules each. The mean size of liver nodules was 16.1 mm \pm 3.4. Clinical characteristics of patients including age, sex, cause of liver disease, nodule size, fibrosis stage, and tumor histopathologic results are in Table 2.

Of the 172 patients (mean age, 51.8 years \pm 10.6), 136 (79.1%) were men. Histopathologic tissue analysis of 124 of 175 nodules (70.9%) was obtained, including 114 surgical specimens and 10 US-guided core biopsies. The fibrosis staging and etiologic causes are listed in Table 2.

Overall, the numbers of nodules proved by reference standard were 124 by pathologic analysis, 12 by initial contrast-enhanced

Table 3: Nodules in CEUS LI-RADS Categories and WFUMB-EFSUMB Criteria

Category	No. of Nodules (<i>n</i> = 175)*	Incidence of HCC (%)	Incidence of Malignancy (%)	Reference Standard (No. of Nodules)		
				Pathologic Analysis	Contrast-enhanced CT or MRI	Follow-up
CEUS LI-RADS						
LR-1	10 (5.7)	0	0	1	9	0
LR-2	2 (1.1)	0	0	0	0	2
LR-3	41 (23.4)	5 (2/41)	5 (2/41)	2	3	36
LR-4	23 (13.1)	48 (11/23)	52 (12/23)	22	0	1
LR-5	79 (45.1)	98 (77/79)	98 (77/79)	79	0	0
LR-M	20 (11.4)	75 (15/20)	85 (17/20)	20	0	0
WFUMB-EFSUMB criteria	102 (58.3)	91.2 (93/102)	93.1 (95/102)	102	0	0

Note.—Unless otherwise indicated, data in parentheses are numerators/denominators. CEUS LI-RADS = contrast-enhanced US Liver Imaging Reporting and Data System, EFSUMB = European Federation of Societies for Ultrasound in Medicine and Biology, HCC = hepatocellular carcinoma, WFUMB = World Federation for Ultrasound in Medicine and Biology.

* Data in parentheses are percentages.

Table 4: Imaging Characteristics of Different Types of Small Liver Nodules

Image Features	Malignant Lesions (<i>n</i> = 108)				Benign Lesions (<i>n</i> = 67)				Total
	HCC (<i>n</i> = 105)	ICC (<i>n</i> = 2)	NEN (<i>n</i> = 1)	RN/DN (<i>n</i> = 49)	Hemangioma (<i>n</i> = 15)	FNH (<i>n</i> = 1)	Biliary Adenoma (<i>n</i> = 1)	RLH (<i>n</i> = 1)	
Gray-scale echogenicity									
Hyperechoic	21	15	14	50
Hypoechoic	84	2	1	34	1	1	1	1	125
Arterial phase									
Hyperenhancement									
Homogeneous	97	2	1	9	1	1	1	1	113
Inhomogenous	4	2	6
Rim	1	1	2
Peripheral nodular	10	10
Isoenhancement									
Isoenhancement	1	12	13
Hypoenhancement									
Hypoenhancement	2	28	1	31
Late phase enhancements									
Isoenhancement									
Isoenhancement	11	...	1	37	1	50
Hypoenhancement									
Hypoenhancement	94	2	...	12	4	1	1	1	115
Hyperenhancement									
Hyperenhancement	10	10
Washout									
<60 seconds									
<60 seconds	14	2	1	1	18
Marked, ≤120 seconds									
Marked, ≤120 seconds	2	1	1	4

Note.—Data are numbers of nodules. DN = dysplastic nodule, FNH = focal nodular hyperplasia, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, NEN = neuroendocrine neoplasm, RLH = reactive lymphoid hyperplasia, RN = regenerative nodule.

CT or contrast-enhanced MRI, and 39 by follow-up (Table 3). The time interval between contrast-enhanced US and biopsy or operation was 13 days \pm 7.

Interobserver Agreement in CEUS LI-RADS Classification

The rating of liver nodules according to CEUS LI-RADS by readers with different level of experience in contrast-enhanced US study of the liver had excellent interobserver agreement with κ value of 0.84.

Distribution of CEUS LI-RADS Categories

Frequencies of CEUS LI-RADS categories and incidences of HCC and malignancy of each category are in Table 3.

US characteristics of 175 enrolled liver nodules are listed in Table 4. Nondiscontinuous peripheral nodular arterial phase hyperenhancement was seen in 121 lesions, including 113 lesions with homogeneous hyperenhancement, six lesions with inhomogeneous hyperenhancement, and two lesions with rim hyperenhancement.

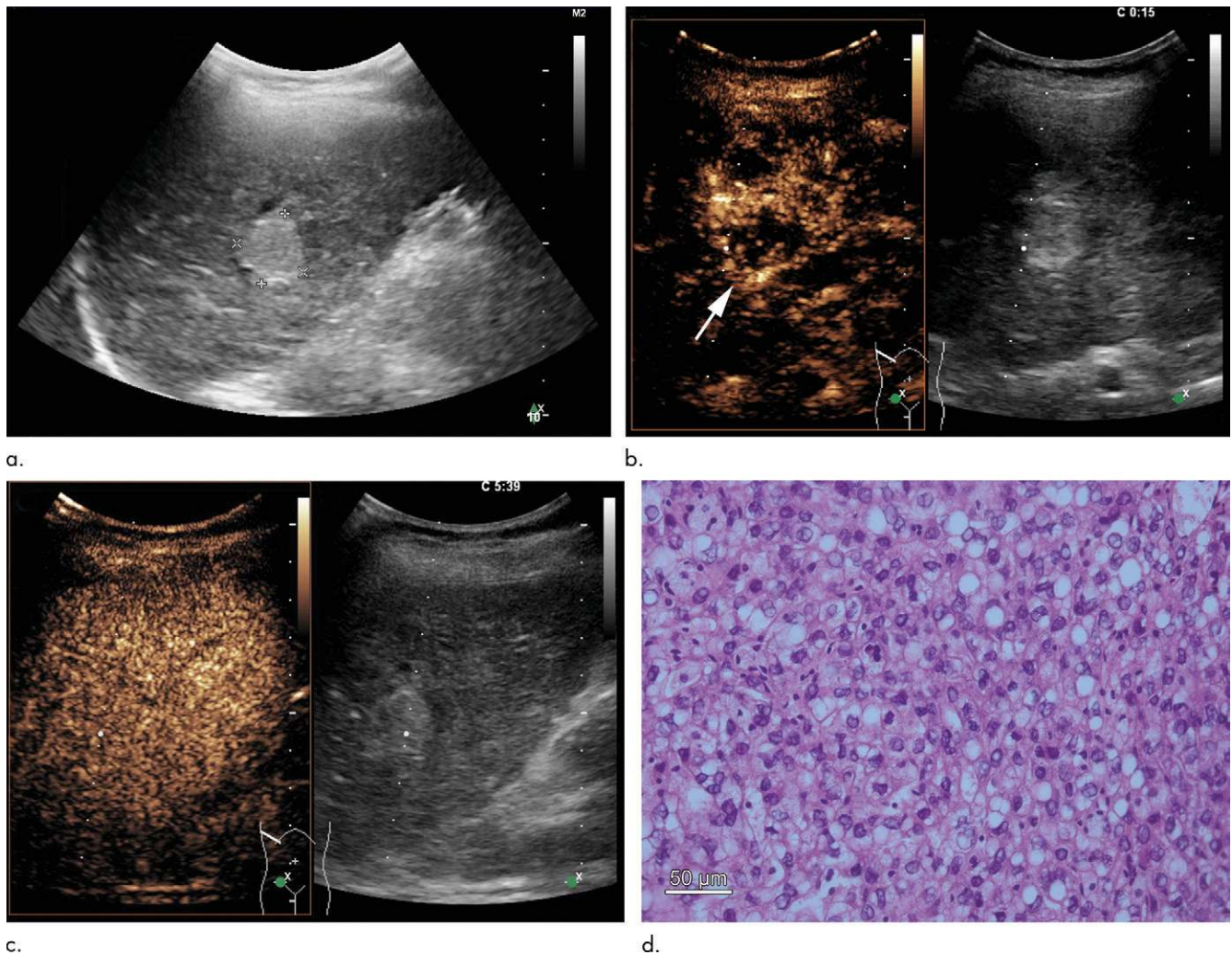


Figure 2: Images show a nodule categorized as LR-3 in a 44-year-old woman with chronic hepatitis B. **(a)** A 2-cm hyperechoic nodule (caliper) was demonstrated at conventional gray-scale US in the right lobe of the liver. **(b)** Arterial phase hypoechoic enhancement (arrow) was shown at contrast-enhanced US. **(c)** The lesion showed isoechoic enhancement compared with the surrounding liver parenchyma in the portal and late phase. **(d)** The patient underwent US-guided biopsy because of markedly elevated α -fetoprotein (729 ng/mL) and the lesion was proved to be moderately differentiated hepatocellular carcinoma at pathologic analysis; image shows hematoxylin-eosin staining (magnification, $\times 400$).

Washout was observed in 115 of 175 liver nodules (65.7%). Early washout with onset time less than 60 seconds was seen in 18 nodules, of which 14 nodules (78%) were proved to be HCC at histopathologic analysis. Early washout (<60 seconds) was observed in both intrahepatic cholangiocarcinomas in our series. Five nodules demonstrated marked washout within 120 seconds including two HCCs, two intrahepatic cholangiocarcinomas, and one hemangioma. No malignant nodules were found in the CEUS LR-1 and LR-2 categories. Only two nodules (of 41; 5%; both HCC) were malignant in the CEUS LR-3 category (Fig 2), and they were diagnosed at histopathologic analysis and at follow-up contrast-enhanced CT.

According to WFUMB-EFSUMB criteria, the typical contrast-enhanced US pattern for HCC was hyperenhancement in the arterial phase followed by washout in the portal-venous phases (5). This pattern was displayed in 102 nodules in our series, which included 79 LR-5, three LR-4, and 20 LR-M nodules if they were categorized by CEUS LI-RADS.

Diagnostic Accuracy of CEUS LI-RADS and WFUMB-EFSUMB Criteria

Overall, 79 of 175 nodules (45.1%) were categorized as CEUS LR-5 (Fig 3). The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and disease prevalence of CEUS LR-5 for diagnosing HCC were 73.3% (95% confidence interval [CI]: 63.8%, 81.5%), 97.1% (95% CI: 90.1%, 99.7%), 97.5% (95% CI: 90.7%, 99.3%), 70.8% (95% CI: 63.8%, 77%), 25.7 (95% CI: 6.5, 101.1), 0.3 (95% CI: 0.2, 0.4), and 60%, respectively (Table 5). Two high-grade dysplastic nodules were categorized as LR-5.

Twenty-three nodules (of 175; 13.1%) were categorized as CEUS LR-4, which corresponded to 11 HCCs (48%), nine regenerative or dysplastic nodules (39%) (Fig 4), one focal nodular hyperplasia, one neuroendocrine tumor, and one hemangioma.

Twenty nodules (of 175; 11.4%) were categorized as CEUS LR-M, which corresponded to 15 HCCs (75%) (Fig 5), two

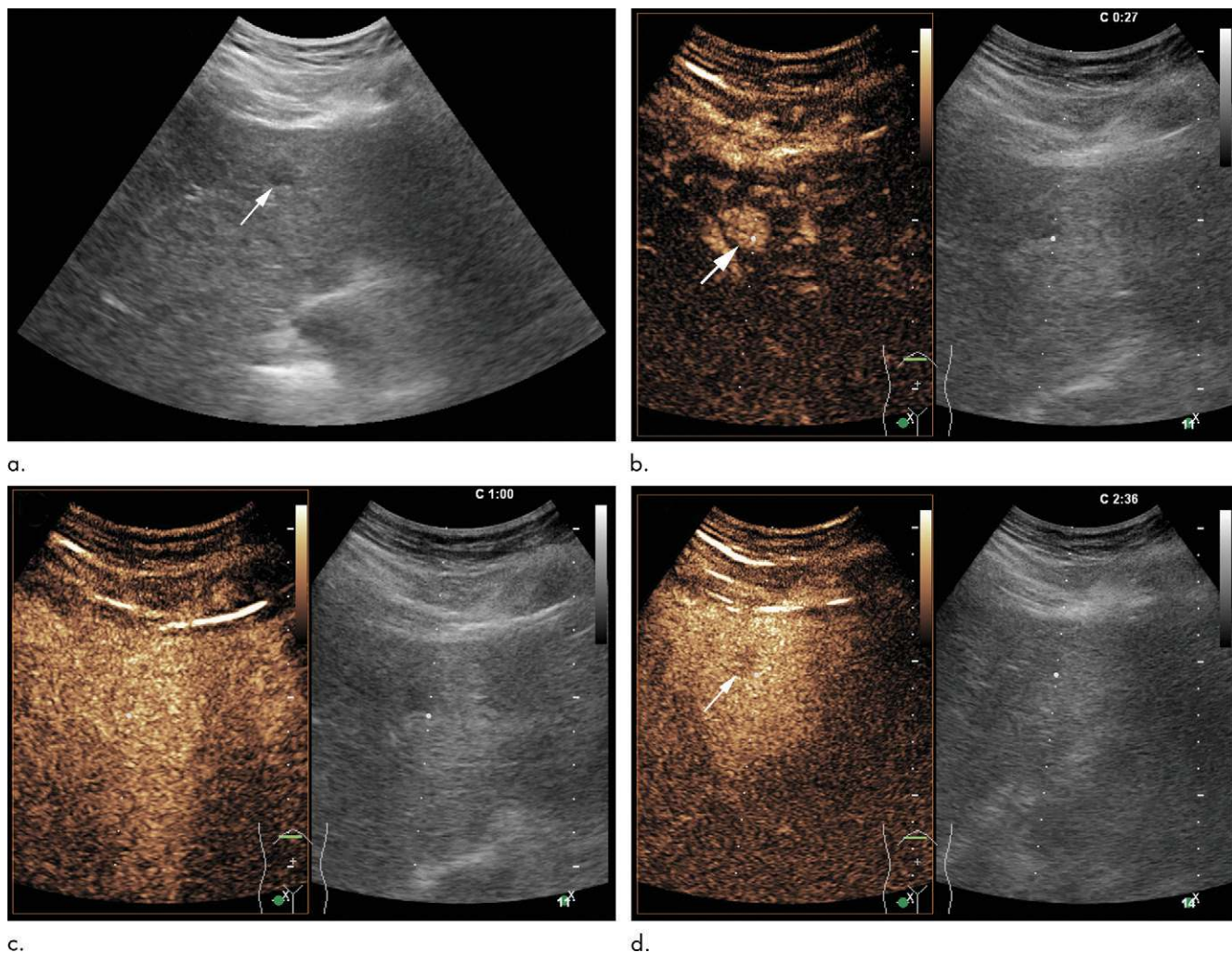


Figure 3: LR-5 nodule in a 45-year-old man with chronic hepatitis B. **(a)** A 1.3-cm hypoechoic nodule (arrow) in the left lateral segment of the liver was shown at conventional gray-scale US. **(b)** Homogeneous hyperenhancement (arrow) in the arterial phase was shown at contrast-enhanced US. **(c)** The lesion was seen at isoenhancement at 60 seconds after contrast agent (SonoVue; Bracco) injection. **(d)** Mild washout (arrow) in the late phase was shown. The lesion was classified as LR-5 according to the findings of contrast-enhanced US. Moderately differentiated hepatocellular carcinoma and cirrhosis (S4) was confirmed at histopathologic analysis.

Table 5: Diagnostic Performance of CEUS LI-RADS and WFUMB-EFSUMB Criteria

Criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)
CEUS LR-5	73.3 (77/105) [63.8, 81.5]	97.1 (68/70) [90.1, 99.7]	82.9 (145/175) [76.4, 88.1]
WFUMB-EFSUMB	88.6 (93/105) [80.9, 94]	87.1 (61/70) [77, 94]	88 (154/175) [82.2, 92.4]
<i>P</i> value of CEUS LR-5 vs WFUMB-EFSUMB	<.001	.02	.09

Note.—Data in parentheses are numerator/denominator and data in brackets are 95% confidence intervals. CEUS LI-RADS = contrast-enhanced US Liver Imaging Reporting and Data System, EFSUMB = European Federation of Societies for Ultrasound in Medicine and Biology, WFUMB = World Federation for Ultrasound in Medicine and Biology.

intrahepatic cholangiocarcinomas (Fig 6), one reactive lymphoid hyperplasia, one cholangioadenoma, and one hemangioma, respectively.

The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and disease prevalence of WFUMB-EFSUMB criteria for the diagnosis of HCCs were 88.6% (95% CI: 80.9%, 94%), 87.1% (95% CI: 77%, 94%), 91.2% (95% CI: 84.8%, 95%), 83.6% (95% CI: 74.8%, 89.7%), 6.9 (95% CI: 3.7,

12.7), 0.1 (95% CI: 0.1, 0.2), and 60%, respectively (Table 5). There were differences in sensitivity and specificity between CEUS LR-5 and WFUMB-EFSUMB criteria ($P < .001$ and $P = .02$, respectively).

CEUS LI-RADS Category and HCC Grading

In 104 pathologic analysis–proven HCCs, there was one well-differentiated tumor, 78 moderately differentiated tumors, and 25 poorly differentiated tumors.

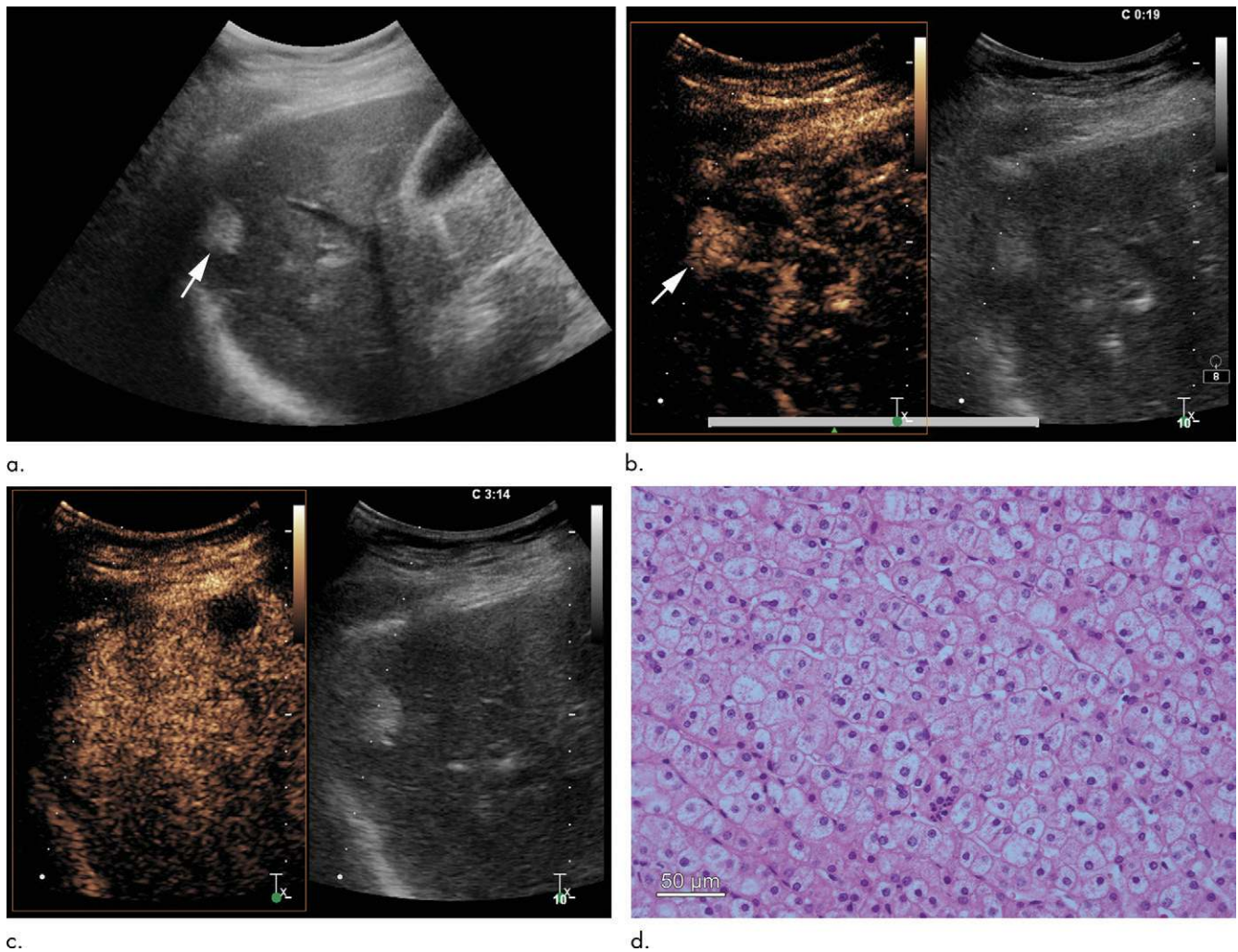


Figure 4: LR-4 nodule in a 60-year-old man with chronic hepatitis B. **(a)** A 2-cm hyperechoic nodule (arrow) was shown in the right lobe of the liver at conventional gray-scale US. **(b)** Homogeneous hyperenhancement (arrow) in the arterial phase was shown at contrast-enhanced US. **(c)** The enhancement persisted in the late phase without definite washout. **(d)** The lesion was assigned to LR-4 and dysplastic nodule was confirmed at histopathologic analysis; hematoxylin-eosin staining (magnification, $\times 400$).

Correlation between CEUS LI-RADS classification and HCC differentiation is in Table 6. Among the 15 HCCs classified as CEUS LR-M, six (40%) were poorly differentiated HCC. The rate of poorly differentiated HCCs classified as CEUS LR-5 was only 23% (18 of 77). However, there was no difference in the rates of poorly differentiated HCCs between CEUS LR-M and CEUS LR-5 ($P > .05$).

Discussion

American College of Radiology contrast-enhanced US Liver Imaging Reporting and Data System (CEUS LI-RADS) was developed as a standardized reporting system for liver nodules in patients at risk for hepatocellular carcinoma (HCC) (14,16,19). However, the efficacy of CEUS LI-RADS in the diagnosis of HCC has not been widely validated, especially in small liver nodules. Only liver nodules 20 mm or smaller were included in this study, of which 105 of 175 nodules (60.0%) were HCCs. Compared with World Federation for Ultrasound in Medicine and Biology (WFUMB)–European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) criteria, LR-5

demonstrated higher specificity for diagnosing small HCC in patients at risk for HCC with lower sensitivity (97.1% vs 87.1% [$P = .02$] and 73.3% vs 88.6% [$P < .001$], respectively). In CEUS LI-RADS, CEUS LR-5 aims for high specificity and positive predictive value close to 100% in diagnosing HCC in patients at risk for HCCs. The positive predictive value of LR-5 reported by Terzi et al (20) was 98.5% with an HCC prevalence rate of 81.5% (820 of 1006), similar to our study results. Two dysplastic nodules in our study were classified as LR-5 compared with three high-grade dysplastic nodules in Terzi et al. The development of HCC is thought to occur through a multistep pathway (21–23). Moreover, high-grade dysplastic nodule was regarded as an HCC precursor with a reported rate of HCC transformation close to 99% (20). The hemodynamics of the contrast agent may overlap between high-grade dysplastic nodule and well-differentiated HCC (24,25). Therefore, dysplastic nodule may manifest with a similar enhancing pattern as that in well-differentiated small HCC.

CEUS LR-4 was designed to classify those lesions that are probably but not definitely HCC. Terzi et al reported a rate of

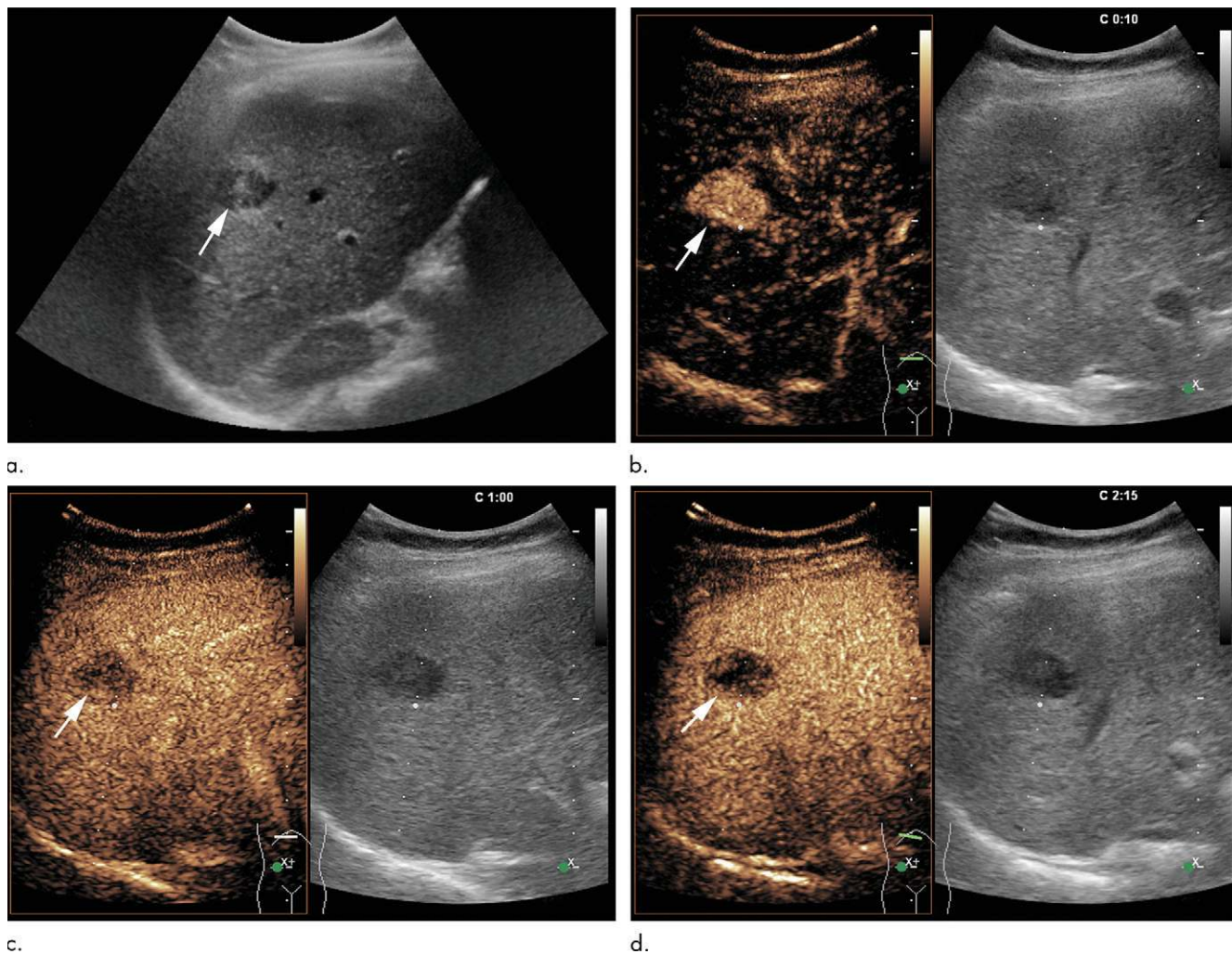


Figure 5: LR-M nodule in a 60-year-old woman with chronic hepatitis B. **(a)** A 1.9-cm hypoechoic nodule (arrow) was shown in segment VII at gray-scale US. **(b)** Homogeneous hyperenhancement of the nodule (arrow) in the arterial phase was shown at contrast-enhanced US. **(c)** Early washout of the contrast agent (<60 seconds) was observed (arrow) in the portal phase. **(d)** Mild washout of the nodule (arrow) in the late phase was observed. This lesion was assigned to LR-M according to its contrast-enhanced US findings. Poorly differentiated hepatocellular carcinoma and cirrhosis (stage 4) of surrounding liver were confirmed at histopathologic analysis.

HCC of 85.6% in LR-4 (20). However, we reported a relatively low HCC rate (11 of 23; 48%) in LR-4, possibly because of differences in the examined study sample (European vs Asian ethnicity) and/or underlying liver disease (over 90% chronic hepatitis B in our study sample). The limited number of LR-4 nodules and higher rate of regenerative or dysplastic nodules (eight of 23; 35%) may also contribute to this discrepancy.

Among 105 HCCs, washout onset within 60 seconds was observed in 14 nodules (13.3%). Those nodules were therefore classified as LR-M. Moreover, six of these nodules (42.9%) were poorly differentiated tumors. Early washout (<60 seconds) has been reported (5,26,27) to occur in poorly differentiated HCCs or to suggest a nonhepatocellular malignancy, which is in concordance with our findings. Interestingly, although the rate of poorly differentiated HCCs in LR-M is nearly twofold to that in LR-5 (18 of 77; 23%), no significant difference between the rates was found, which is likely because of the small sample size of our study.

Two pathologic analysis–proven intrahepatic cholangiocarcinomas were included in our study sample and were classified

as LR-M with nonrim arterial phase hyperenhancement, with marked washout in one nodule and early marked washout in the other nodule. Both nodules were regarded as HCC by WFUMB-EFSUMB criteria. Vilana et al (28) concluded that contrast-enhanced US could not help to differentiate HCC from intrahepatic cholangiocarcinoma. However, their diagnostic criteria did not include timing of washout onset time or washout intensity. Because the LR-M classification indicates malignancy not specific for HCC that requires tissue sampling, if intrahepatic cholangiocarcinoma can be accurately categorized as LR-M, then CEUS LI-RADS has considerable diagnostic value.

There were several limitations to our study. First, because the topic was focused on small liver nodules, our study sample was relatively small, especially in the subgroup of LR-2, which was partly because patients with nodules smaller than 1 cm seldom underwent contrast-enhanced US in daily clinical practice. Second, pathologic results were not available for all the nodules, especially for the LR-1, LR-2, and LR-3 subgroups, which could make more nodules eligible for inclusion but also compromise

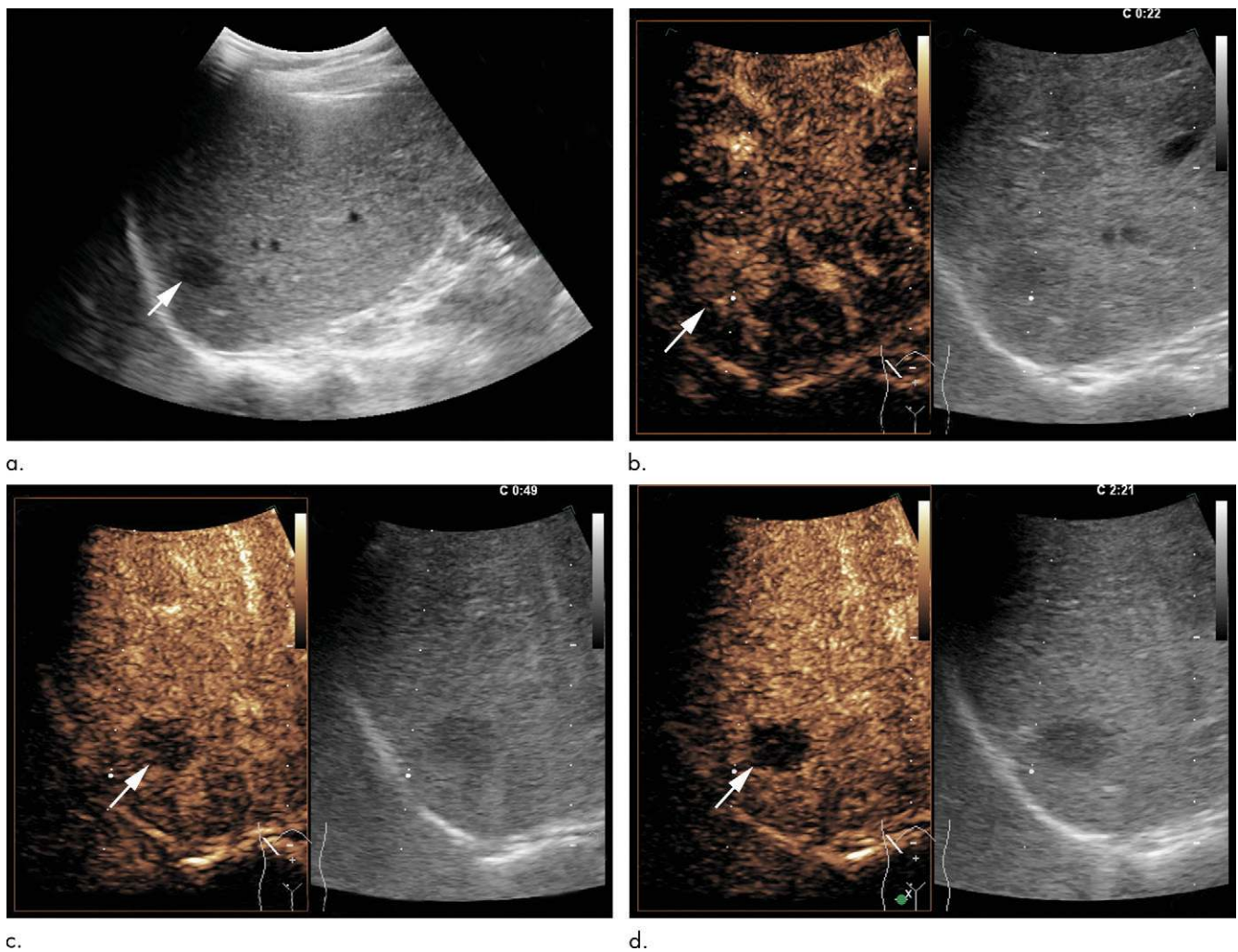


Figure 6: LR-M nodule in a 46-year-old woman with chronic hepatitis B. **(a)** A 1.7-cm hypoechoic nodule (arrow) in the right liver lobe was shown at conventional gray-scale US. **(b)** The lesion was homogeneously hyperenhanced (arrow) in the arterial phase at contrast-enhanced US. **(c)** Early washout of the contrast agent (washout onset time, 49 seconds) was observed (arrow). **(d)** Marked washout (arrow) in the late phase was shown at contrast-enhanced US. The lesion was assigned to LR-M. Intrahepatic cholangiocarcinoma and septal fibrosis (stage 2) of the surrounding liver were confirmed at histopathologic analysis.

Table 6: Correlation between CEUS LI-RADS Classification and Hepatocellular Carcinoma Differentiation

CEUS LI-RADS Classification	Well-differentiated HCC	Moderately Differentiated HCC	Poorly Differentiated HCC
LR-3	NA	1 (1)	NA
LR-4	NA	10 (13)	1 (4)
LR-5	1 (100)	58 (74)	18 (72)
LR-M	NA	9 (12)	6 (24)
Total	1	78	25

Note.—Data are numbers of nodules; data in parentheses are percentages. CEUS LI-RADS = contrast-enhanced US Liver Imaging Reporting and Data System, HCC = hepatocellular carcinoma, NA = not available.

the reference standard strength. Third, no prospective validation of the findings was performed. Finally, our study sample was mainly composed of patients with chronic hepatitis B. Therefore, our results may not be reproducible in patients with other etiologic causes.

A multicenter prospective study with a larger study sample is needed to validate the findings, such as the hypothesis that poorly differentiated HCC is more likely to be categorized

as LR-M. A useful area of CEUS LI-RADS application is radiomics. CEUS LI-RADS creates easily extractable imaging parameters (radiomic data) for contrast-enhanced US examinations, thus providing help for future diagnostic explorations by simplifying extraction of imaging features, automation of image analysis, and improving mining of data to develop a model to predict clinical outcomes and improve management of the patients with indeterminate liver nodules.

In conclusion, American College of Radiology contrast-enhanced US Liver Imaging Reporting and Data System classification of small liver nodules is reproducible in well-trained hands. Compared with World Federation for Ultrasound in Medicine and Biology—European Federation of Societies for Ultrasound in Medicine and Biology criteria, CEUS LR-5 demonstrated higher specificity for diagnosing hepatocellular carcinomas (HCCs). LR-4 and LR-M classifications are highly suspicious for malignancy, but not specific enough for HCC, and therefore tissue sampling is recommended in this group. Our study also confirmed that LR-3 was more likely to be benign. Meanwhile, no lesion in LR-1 and LR-2 was malignant.

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