Abdominal Radiology (2024) 49:1432–1443
https://doi.org/10.1007/s00261-024-04250-7

HEPATOBILIARY

Intra-individual comparison of Sonazoid contrast-enhanced ultrasound and SonoVue contrast-enhanced ultrasound in diagnosing hepatocellular carcinoma

Danxia Guo[1] · Weijun Wan[1] · Xiumei Bai[1] · Rong Wen[1] · Jinbo Peng[1] · Peng Lin[1] · Wei Liao[1] · Weiche Huang[1] · Dun Liu[1] · Yuye Peng[1] · Tong Kang[1] · Hong Yang[1] · Yun He[1]

Received: 10 November 2023 / Revised: 10 February 2024 / Accepted: 13 February 2024 / Published online: 7 April 2024

Abstract

Purpose To assess whether the diagnostic performance of Sonazoid contrast-enhanced ultrasound (SZUS) is non-inferior to that of SonoVue contrast-enhanced ultrasound (SVUS) in diagnosing hepatocellular carcinoma (HCC) in individuals with high risk.

Materials and Methods This prospective study was conducted from October 2020 to May 2022 and included participants with a high risk of HCC who underwent SZUS and SVUS. All lesions were confirmed by clinical or pathological diagnosis. Each nodule was classified according to the Contrast-Enhanced Ultrasound Liver Imaging Reporting and Data System version 2017 (CEUS LI-RADS v2017) for SVUS and SZUS and the modified CEUS LI-RADS (using Kupffer phase defect instead of late and mild washout) for SZUS. The diagnostic performance of both two modalities for all observations was compared. Analysis of the vascular phase and Kupffer phase imaging characteristics of CEUS was performed.

Results One hundred and fifteen focal liver lesions from 113 patients (94 HCCs, 12 non-HCC malignancies, and 9 benign lesions) were analysed. According to CEUS LI-RADS (v2017), SVUS and SZUS showed similar sensitivity (71.3% vs. 72.3%) and specificity (85.7% vs. 81.0%) in HCC diagnosis. However, the modified CEUS LI-RADS did not significantly improve the diagnostic efficacy of Sonazoid compared to CEUS LI-RADS v2017, having equivalent sensitivity (73.4% vs. 72.3%) and specificity (81.0% vs. 81.0%). The agreement between SVUS and SZUS for all observations was 0.610 (95% CI 0.475, 0.745), while for HCCs it was 0.452 (95% CI 0.257, 0.647).

Conclusion Using LI-RADS v2017, SZUS and SVUS showed non-inferior efficacy in evaluating HCC lesions. In addition, adding Kupffer phase defects to SZUS does not notably improve its diagnostic efficacy.

Keywords Sonazoid · Kupffer phase · SonoVue · Hepatocellular carcinoma · CEUS LI-RADS

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths globally [1, 2]. Contrast-enhanced ultrasound (CEUS) has the ability to distinguish benign liver lesions from malignant ones with high diagnostic accuracy in high-risk populations [3–7]. To provide standardized classification and interpretation of focal liver lesions (FLLs) in high-risk patients, the American College of Radiology has developed the Contrast-Enhanced Ultrasound Liver Imaging Reporting and Data System 2017 version (CEUS LI-RADS v2017) [8, 9].

In clinical practice, there are two main types of contrast agents for CEUS, pure blood pool agents (PBA) and Kupffer-cell specific agent (KPA) [10–12]. However, CEUS LI-RADS v2017 only applies to CEUS that uses PBA such as sulphur hexafluoride microspheres (Lumason® [in the USA]/ SonoVue® [outside the USA]), perflutren lipid microsphere (Definity®/ Luminity®), and perflutren protein-type A microspheres (Optison®) [8, 13–15]. CEUS LI-RADS v2017 should not be applied

Danxia Guo and Weijun Wan contributed equally to this work.

✉ Yun He
heyun@stu.gxmu.edu.cn

[1] Department of Medical Ultrasound, First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Guangxi Zhuang Autonomous Region, Nanning 530021, China

for CEUS that uses KPA, such as perfluorobutane microspheres (Sonazoid®).

Sonazoid, enables not only vascular phase images but also unique Kupffer phase images (8 min after injection) [16–20], thereby providing more diagnostic information about FLLs [12, 21]. A prospective study compared the efficacy of Sonazoid CEUS (SZUS) and SonoVue CEUS (SVUS) in diagnosing high-risk HCC using CEUS LR-RADS v2017, and the results showed that SZUS had higher sensitivity, with both specificities being 100% [22]. To better utilize the imaging information provided by the Kupffer phase, Sugimoto et al. developed a modified CEUS LI-RADS (using Kupffer phase defect instead of late and mild washout) specifically for Sonazoid [23]. Several studies on high-risk patients involving the use of SZUS have shown that the modified CEUS LI-RADS has high sensitivity in diagnosing HCC (67.6–89.6%) [11, 23–26]. However, the imaging characteristics of SZUS and its diagnostic ability vis-à-vis HCC have not been thoroughly evaluated [27]. The diagnostic performance of the modified CEUS LI-RADS also needs further validation and comparison. Therefore, our aim in this study was to explore the different characteristics at different phases between SZUS and SVUS and to evaluate whether the diagnostic capability of SZUS is non-inferior to that of SVUS in high-risk patients with HCC.

Materials and methods

The study protocol was reviewed and approved by the Institutional Review Board (IRB No. 2022-KY-(067)), which meets the ethical standards for medical research involving human subjects as set out in the 1964 Declaration of Helsinki and its subsequent amendments. Participants provided written informed consent before participating in the study.

Participants

The prospective study recruited participants with FLLs (≥ 10 mm) who were treated at our centre between October 1, 2020 and May 1, 2022. The inclusion criteria were as follows: (1) aged ≥ 18 years; (2) the presence of risk factors for HCC [8, 28, 29]; (3) underwent both SVUS and SZUS within 2 weeks after study registration; and (4) planned to undergo hepatic surgery or percutaneous biopsy of the liver lesion or contrast-enhanced CT/MRI to diagnose HCC [30]. The exclusion criteria were as follows: (1) previous treatment for HCC; (2) diffuse liver cancer; (3) unclear or incomplete ultrasonic images; and (4) no pathologic results or contrast-enhanced CT/MRI diagnosed HCC.

CEUS examinations

Gray-scale ultrasound and CEUS examinations were performed by one of two radiologists (YH or PJB, both with more than 10 years of experience in liver CEUS). The examinations were conducted using either the LOGIQ E9 system (GE Healthcare, Milwaukee, WI, USA) or the Mindray Resona 7 system (Mindray, Shenzhen, China) with a low-frequency convex probe.

The contrast agents were prepared in accordance with the product guidelines. SVUS was performed first. After administering 1.2–2.4 ml of SonoVue (Bracco, Milan, Italy) suspension via a 21-gauge peripheral intravenous cannula in the antecubital fossa, a 5-ml normal saline bolus was used for flushing. SVUS was conducted using a low mechanical index (MI) of 0.08–0.14 in contrast pulse sequencing mode. The timer and video functions were started simultaneously. After intravenous injection, a cine loop was continuously recorded for approximately 60 s to capture the dynamic images. To evaluate washout patterns and time in the portal venous phase (PVP, lasts from about 30–45 s to 2 min after contrast injection) and the late phase (LP, lasts from the end of the PVP up to 4–6 min) [8], dynamic or static pictures were captured every 20–30 s for 5 min following the initial 60 s cine loop. To destroy the microbubbles, high-power pulses in brightness mode were applied after SVUS. Wait at least 30 min before SZUS [9, 22]. Sonazoid (GE Healthcare, Milwaukee, WI, USA) dosage is 0.12 μL/kg of body weight. And set MI to 0.19–0.22 for SZUS. Other steps remain the same. A minimum of 8 min after administration [16], dynamic or static imaging was performed during the Kupffer phase.

Image analysis

Two radiologists (PJB and WR) with 11 and 4 years of liver CEUS experience independently assessed the imaging features of liver lesions on the ultrasound and classified them in an LR category according to CEUS LI-RADS v2017 and the modified CEUS LI-RADS (using Kupffer phase defect instead of late and mild washout). They performed image analysis for each imaging modality (SonoVue and Sonazoid), regardless of pathology results, laboratory tests, or other imaging findings. However, they both realized that these individuals were at high risk for HCC. There was a 2-week interval between the blinded interpretations to reduce any learning bias.

The two reviewers characterized each nodule based on CEUS LI-RADS v2017 and the modified CEUS LI-RADS using the following diagnostic features: (1) arterial phase

enhancement and its pattern; (2) the presence and degree of washout within 5 min after injection; (3) the presence and degree of Kupffer phase defect (occurring after 8 min post-injection). Specifically, in the CEUS LI-RADS v2017 algorithm, nodules (≥ 10 mm) showing arterial phase hyperenhancement (APHE) that is neither rim nor peripherally discontinuous and demonstrating late (≥ 60 s) and mild washout are classified as LR-5. Lesions showing rim APHE or early (< 60 s) washout or marked washout are classified as LR-M. In the modified CEUS LI-RADS algorithm: (1) nodules (≥ 10 mm) showing APHE with Kupffer phase hypoechoic but no early washout are classified as LR-5; (2) lesions showing rim APHE or early washout or marked washout are classified as LR-M; (3) nodules ≥ 20 mm lacking APHE or early washout, but with Kupffer phase defect, or nodules ≥ 10 mm showing APHE but no early washout or Kupffer phase defect, are classed as LR-4; (4) nodules ≥ 20 mm without APHE or early washout or Kupffer phase defect, or nodules < 20 mm without APHE and no ealy washout, regardless of Kupffer phase appearance, are classified as LR-3; (5) nodules < 10 mm without APHE or early washout or Kupffer phase defect, are classified as LR-2; (6) if there is a definitely benign arterial phase pattern (such as hemangioma, cyst, focal fatty infiltration, or other definite benign findings), it is classified as LR-1 [23]. To minimize the impact of insufficient physician experience in interpretation, the results interpreted by the most senior physicians are considered the standard [31].

Reference standard

Pathologic diagnosis was made for 93.9% (108 of 115) of the FLLs, with 75 FLLs diagnosed by surgery and 33 diagnosed by biopsy. A total of 6.1% (7/115) of the FLLs were clinically diagnosed as HCC, as they were classified as LR-5 according to the contrast-enhanced CT/MRI LI-RADS Version 2018 criteria [30, 32]. Surgical excision or core biopsy histological evaluation was required to confirm benign findings.

Statistical analysis

The sensitivity, specificity and accuracy of each lesion based on CEUS LI-RADS v2017 criteria and modified CEUS LI-RADS criteria were compared using the McNemar test. The positive predictive value (PPV) and negative predictive value (NPV) were compared using a chi-square test or a Fisher's exact test [8]. The agreement of classification between two ultrasound imaging exams was evaluated using the weighted kappa coefficient (95% confidence interval [CI]). Statistical analysis was performed using IBM SPSS Statistics version 20.0 software. A significance level of 0.05 was used to determine statistical significance; *P* values below this threshold were considered statistically significant.

Results

Characteristics of patients

A total of 115 FLLs from 113 consecutive patients were ultimately selected for inclusion, with two patients each having two nodules (Fig. 1). The characteristics of the 113 patients are described in Table 1. The age of the patients enrolled in the study ranged from 27 to 79 years (mean, 52.2 ± 11.5 years), and 100 (88.5%) were male. The FLLs had a mean size of 4.6 ± 3.3 cm. Of the 115 FLLs, 81.7% (94/115) were diagnosed as HCCs, 10.4% (12/115) were diagnosed as non-HCC malignant tumours and 7.8% (9/115) were diagnosed as benign lesions. Of the 21 non-HCC FLLs, 8 were diagnosed as intrahepatic cholangiocarcinoma (ICC), 1 was diagnosed as combined HCC and cholangiocarcinoma (cHCC-CC), 2 were diagnosed as liver metastasis, 1 was diagnosed as hepatic hemangioendothelioma, 2 were diagnosed as dysplastic nodules, 3 were diagnosed as hemangiomas and 4 were diagnosed as focal nodular hyperplasias (FNH). All benign lesions were confirmed by pathology. Hepatitis B viral infection was the most frequent cause of liver disease, affecting 88.5% (100/113) of the patients. Cirrhosis was present in 93.0% (105/113) of the enrolled patients.

Important CEUS imaging characteristics

APHE

Table 2 shows there was no statistical difference in arterial phase features between SVUS and SZUS. Both SVUS and SZUS revealed nonrim APHE in 93.6% (88 of 94) of HCCs (Fig. 2). Rim APHE was seen in 1.0% (1 of 94) and 3.2% (3 of 94) of HCCs with SVUS and SZUS ($P = 0.500$). Nonrim APHE was observed in 58.3% (7 of 12) and 66.7% (8 of 12) of non-HCC malignancies with SVUS and SZUS ($P = 1.000$). Rim APHE was seen in 33.3% (4 of 12) and 25.0% (3 of 12) of HCCs with SVUS and SZUS ($P = 0.100$). Non-HCC malignancies that showed rim APHE on both ultrasound tests were pathologically confirmed as ICC (Fig. 3). The lesions that showed nonrim APHE in SZUS but rim APHE in SVUS were metastatic tumours. Both methods revealed that three hemangiomas exhibited peripheral globular and centripetal enhancement, while all focal nodular hyperplasias exhibited nonrim APHE.

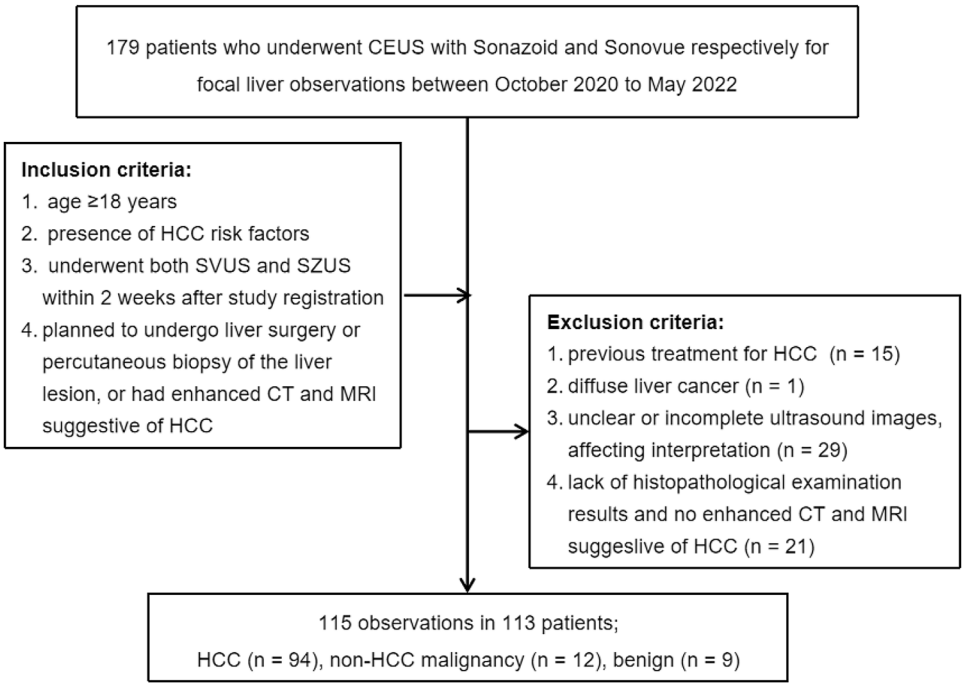

Fig. 1 Flow diagram of the study. CEUS = contrast-enhanced ultrasound, HCC = hepatocellular carcinoma

Washout

Table 3 lists the washout characteristics of hepatic observations. Washout was seen in 84.4% (97 of 115) and 89.6% (103 of 115) of all FLLs with SVUS and SZUS ($P = 0.146$). Combined late and mild washouts were seen in 72.3% (68 of 94) and 74.5% (70 of 94) of HCCs with SVUS and SZUS ($P = 0.831$). Early washout occurred in 15.9% (15 of 94) of HCCs with SVUS and 19.1% (18 of 94) with SZUS ($P = 0.581$). In addition, there were eight HCCs with early washout on SVUS but late washout on SZUS. One HCC presented a marked washout on SVUS but not on SZUS. Three non-HCC malignancies showed late and mild washouts on both SVUS and SZUS. There were two benign lesions with late and mild washout in SVUS, and three in SZUS. The washout pattern did not differ significantly between SVUS and SZUS. No washout was observed in 11.7% (11 of 94) and 6.4% (6 of 94) of non-HCC malignancies with SVUS and SZUS ($P = 0.180$).

Kupffer phase

Hypoenhancement was observed in 93.6% (88/94) of HCCs in the Kupffer phase, and 87 of these lesions also displayed washout in the SZUS portal or delayed phase. Additionally, all non-HCC malignancies showed washout in the Kupffer phase (Table 3). One of the six HCCs that did not wash out during the vascular phase of SZUS showed hypoenhancement during the Kupffer phase, while the other five remained isoenhanced. Two hemangiomas and one FNH showed hypoenhancement during the Kupffer phase.

Imaging features of HCC based on pathological differentiation and tumor size

Table 4 summarizes the CEUS characteristics of SVUS and SZUS across different pathological differentiations and tumor sizes. The early washout rate for moderately differentiated HCC was 23.1% with SVUS and 26.9% with SZUS. For poorly differentiated HCC, the rates were 25% with SVUS and 37.5% with SZUS. Among well-differentiated HCC cases, only one showed early washout with SZUS. Additionally, three cases of well-differentiated HCC did not show washout with SVUS, while only one case did not show washout with SZUS.**LI-RADS Categorisation.**

Table 5 presents the distribution of CEUS LI-RADS categories for CEUS. Under the premise of using the CEUS LI-RADS v2017 algorithm, of 11 observations assessed as LR-4 by SVUS, 6 were assessed as LR-5 by SZUS, all of which were HCC (Fig. 4). Of 7 observations assessed as LR-4 by SZUS, 2 were assessed as LR-5 by SVUS, all of which were HCC. Of 25 observations assessed as LR-M by SVUS, 6 were assessed as LR-5 by SZUS, 5 of which were HCC. Of 28 observations assessed as LR-M by SZUS, 9 were assessed as LR-5 by SVUS, all of which were HCC. The reviewer achieved concordance in the CEUS LI-RADS category for 79.1% (91/115) of the observations using SVUS and SZUS. The agreement between SVUS and SZUS for all

Table 1 Clinical-Pathologic Characteristics of 113 Participants with 115 Observations

Characteristic	Value
Age (y)*	52.2 ± 11.5
Sex†	
Male	100 (88.5%)
Female	13 (11.5%)
Aetiology of chronic liver disease†	
Hepatitis B virus	100 (88.5%)
Hepatitis C virus	2 (1.8%)
Hepatitis B&C virus	1 (0.9%)
Others	10 (8.7%)
Known cirrhosis†	105 (93.0%)
AFP level (ng/ mL) †	
8.78–400 ng/mL	84 (73.7%)
400 ng/mL	29 (26.3%)
Lesion size (mm)†	
≤ 2 cm	16 (17.0%)
> 2 cm	78 (83.0%)
Standard reference of diagnosis†	
Pathologic diagnosis	108 (93.9%)
By surgery	75 (65.2%)
By biopsy	33 (28.7%)
Typical image features at least two imaging modalities	7 (6.1%)
Diagnosis of the hepatic observation†	
HCC	94 (81.7%)
Well-differentiated	9
Moderately-differentiated	26
Poorly- differentiated	8
No differentiation result for HCC	51
Non-HCC malignancy	12 (10.4%)
cHCC-CC	1
ICC	8
Metastatic tumor	2
Hepatic hemangioendothelioma	1
Benign	9 (7.8%)
Dysplastic nodule	2
Hemangioma	3
Focal nodular hyperplasia	4

AFP = a-fetoprotein, cHCC-CC = combined HCC and cholangiocarcinoma, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma

*Data are mean ± standard deviation

†Data are numbers of patients or observations, and data in parentheses are percentages

observations was 0.610 (95% CI 0.475, 0.745), while for HCCs it was 0.452 (95% CI 0.257, 0.647).

In the interpretation of Sulfur hexafluoride images, two radiologists disagreed on 4 HCC lesions: P.J.B. classified 3 as LR-M and 1 as LR-4, while W.R. labeled all as LR-5. For Perfluorobutane images, there were 7 HCC lesions with differing assessments: P.J.B. rated 6 as LR-5 and 1 as LR-4, while W.R. assessed 3 as LR-M, 2 as LR-4, and 1 as LR-3.

Diagnostic performance of HCC

Table 6 presents the diagnostic performance of the CEUS LI-RADS v2017 LR-5 category using SVUS and SZUS and the modified CEUS LI-RADS criteria with Sonazoid for HCC diagnosis in terms of sensitivity, specificity, accuracy, PPV and NPV. The diagnosis of HCC using SVUS and SZUS with CEUS LI-RADS v2017 showed no significant difference. The sensitivity for SVUS was 71.3% (95% CI 60.9%, 79.9%) and for SZUS was 72.3% (95% CI 62.0%, 80.9%), with a P-value of 1.000, and the specificity was 85.7% (95% CI 62.6%, 96.2%) and 81.0% (95% CI 57.4%, 93.7%), with a P-value of 1.000. The application of the modified CEUS LI-RADS did not significantly enhance the diagnostic effectiveness of Sonazoid. This is evident from the sensitivity rates, which were 73.4% (95% CI 63.1%, 81.7%) for the modified version and 72.3% (95% CI 62.0%, 80.9%) for the CEUS LI-RADS v2017, with no significant difference (P = 1.000). Additionally, both versions demonstrated the same specificity of 81.0% (95% CI 57.4%, 93.7%).

Discussion

In this prospective study with 115 lesions, we compared the individual diagnostic performance of SZUS and SVUS in a population with a high risk for HCC in the high-prevalence region of South China. Our study findings revealed that the sensitivities of SVUS and SZUS in diagnosing HCC were 71.3 and 72.3% with $P > 0.05$ when utilizing the CEUS LI-RADS v2017 algorithm. The specificities were 85.7 and 81.0% with $P > 0.05$, and both techniques exhibited an accuracy of 73.9%. Similar results were found in a prospective phase 3 multicentre study [33]. We discovered that when employing the CEUS LI-RADS v2017 criteria, SZUS demonstrated diagnostic efficacy comparable to SVUS in identifying HCC among populations with high risk.

This is inconsistent with previous research findings [22], where Kang et al. demonstrated that in comparing SZUS and SVUS, SZUS provided higher sensitivity (79% vs. 54%) and accuracy (90% vs. 80%) for HCC diagnosis in 59 high-risk patients. The findings of Kang et al.'s investigation were attributed to the differences in the incidence of contrast agent washout between the two imaging modalities, with a rate that was substantially lower for SVUS than for SZUS. Kang et al. believe that perfluorobutane is more stable under high acoustic pressure than sulphur hexafluoride. The existence and appropriate timing of washout play a crucial role in distinguishing between benign and malignant lesions [27].

Table 2 Comparison of arterial phase features based on CEUS modality

	No APHE		Nonrim APHE		Rim APHE		Peripheral Globular Enhancement	
Variable	SVUS	SZUS	SVUS	SZUS	SVUS	SZUS	SVUS	SZUS
HCC (n = 94)	5 (5.3%)	3(3.2%)	88 (93.6%)	88(93.6%)	1 (1.0%)	3(3.2%)	0 (0)	0 (0)
Non-HCC malignancy (n = 12)	1 (8.3%)	1 (8.3%)	7 (58.3%)	8(66.7%)	4 (33.3%)	3(25.0%)	0 (0)	0 (0)
Other benign lesions (n = 9)	1 (11.1%)	2 (22.2%)	4 (44.4%)	4 (44.4%)	0 (0)	0 (0)	4 (44.4%)	3 (33.3%)

CEUS = contrast-enhanced ultrasound, APHE = arterial phase hyperenhancement, HCC = hepatocellular carcinoma, SVUS = SonoVue-enhanced ultrasound, SZUS = Sonazoid-enhanced ultrasound

The data represent the number of observations, with percentages indicated in parentheses

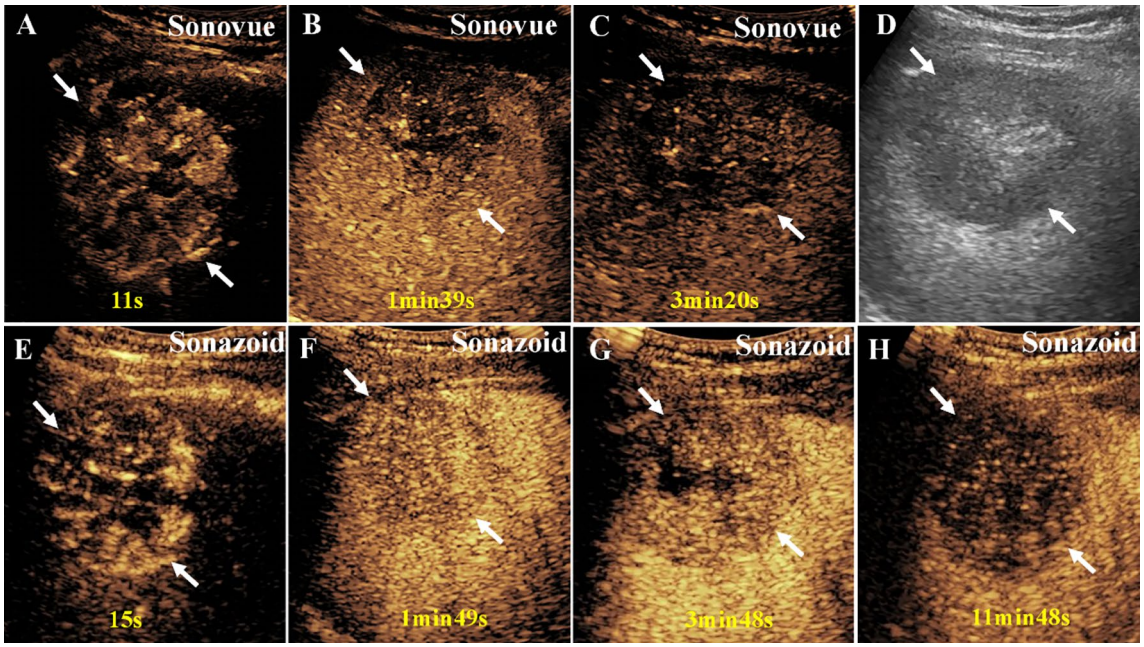

Fig. 2 A 53-year-old male underwent both of the contrast-enhanced ultrasound examinations, and hepatocellular carcinoma was subsequently diagnosed by pathology. **A** The arterial phase image shows heterogeneous arterial hyperenhancement (APHE) of the lesion (arrow) after injection of SonoVue. **B–C** A mild washout (arrow) was detected in the delayed phase after injection of SonoVue. **D** Conventional ultrasound demonstrated a 54 mm focal lesion in the right lobe of the liver (arrow). **E** APHE (arrow) was also detected at 15 s after injection of Sonazoid. **F–G** A mild washout (arrow) was noted in the delayed phase at 1 min 49 s after injection of Sonazoid. **H** During the Kupffer phase, a persistent hypoenhancement (arrow) was observed at 11 min and 48 s after injection of Sonazoid. It was categorized as LR-5 according to two contrast agents, and it was pathologically confrmed as HCC

However, the washout rates across the SVUS and SZUS in our investigation were found to be comparable (84.4% vs. 89.6%, $P = 0.146$), which is in accordance with the findings of the latest head-to-head comparison experiments with the two agents [9]. In a separate study by the same team conducted by Kang [34], which included a larger sample size of 105 participants, it was observed that the effectiveness of SZUS in diagnosing HCC in high-risk patients was comparable to that of SVUS.

Previous studies have reported that differentiation serves as a significant biological feature of HCC, correlating with imaging characteristics of CEUS, particularly washout [15, 35, 36]. Korosh Khalili et al. demonstrated that the adhesion and/or phagocytosis of contrast agents by the reticuloendothelial system is crucial for the late-phase enhancement of lesions during CEUS [15]. In the present study, moderately and poorly differentiated HCCs exhibited a higher rate of early washout compared to

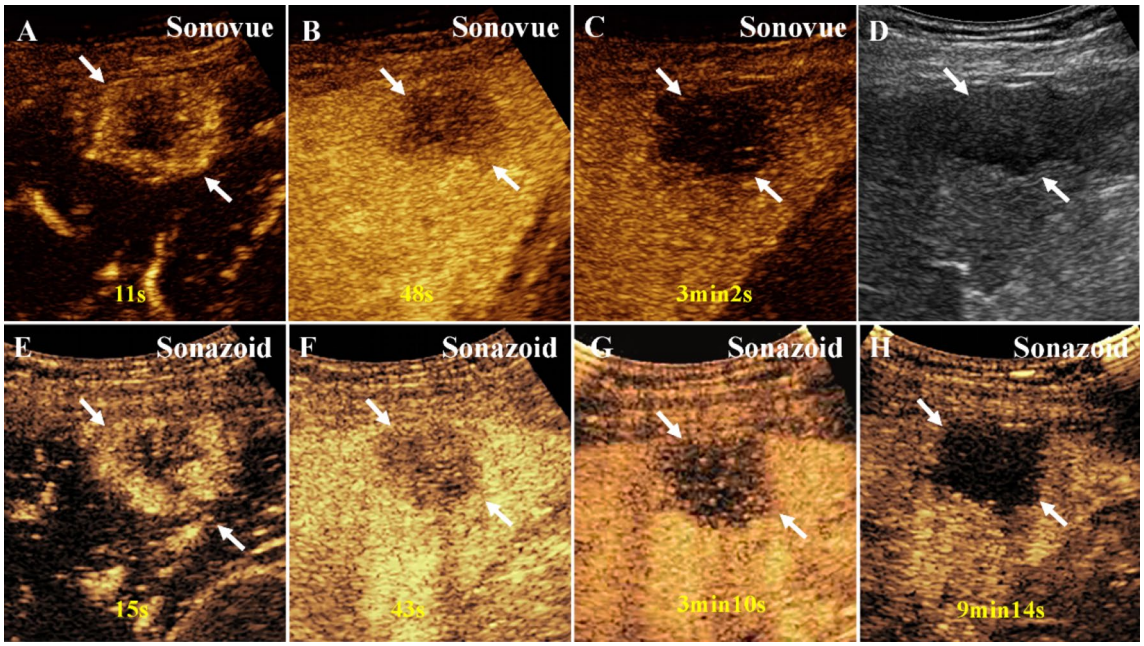

Fig. 3 A 55-year-old male was diagnosed with intrahepatic cholangiocarcinoma by pathology. **A** Rim APHE was observed in the arterial phase after the injection of SonoVue. **B** A relatively early washout was observed at 48 s in SonoVue CEUS. **C** A marked washout was noted 3 min 2 s in SonoVue CEUS. **D** Conventional ultrasound demonstrated a 33 mm focal lesion in the right lobe of the liver (arrow). **E** After injection of Sonazoid, a similar rim-APHE was detected at 15 s. **F** Early washout (arrow) was noted at 43 s in Sonazoid CEUS. **G** mild hypoenhancement was noted at 3 min 10 s in Sonazoid CEUS. **H** During the Kupffer phase, more marked washout was observed. It was categorized as LR-M according to two contrast agents

Table 3 Comparison of washout and Kupffer phase characteristics according to contrast agent used

	No Washout		Late (≥ 60 s) and Mild Washout		Early Washout		Marked Washout		Kupffer-Phase Defect
Variable	SVUS	SZUS	SVUS	SZUS	SVUS	SZUS	SVUS	SZUS	SZUS
HCC (n = 94)	11(11.7%)	6(6.4%)	68(72.3%)	70(74.5%)	15(15.9%)	18(19.1%)	1(1.1%)	0(0)	88(93.6%)
Non-HCC malignancy (n = 12)	0(0)	0(0)	3(25.0%)	3(25.0%)	9(75.0%)	9(75.0%)	3(25.0%)	1(8.3%)	12(100%)
Other benign lesions (n = 9)	7(77.8%)	6(66.7%)	2(22.2%)	3(33.3%)	0(0)	0(0)	0(0)	0(0)	3(33.3%)

CEUS = contrast-enhanced ultrasound, APHE = arterial phase hyperenhancement, HCC = hepatocellular carcinoma, SVUS = SonoVue-enhanced ultrasound, SZUS = Sonazoid-enhanced ultrasound. Washout evaluation was performed with the exclusion of rim APHE or peripheral globular-enhancing observations

The data represent the number of observations, with percentages indicated in parentheses

well-differentiated HCCs. Conversely, well-differentiated HCCs were more likely to display late washout or even no washout [35, 37, 38]. This could be attributed to a decrease in reticuloendothelial system activity in moderately and poorly differentiated tumors [39], while the activity of the reticuloendothelial system in well-differentiated HCC is comparable to that of normal liver tissue [40].

The CEUS LI-RADS v2017 was specifically developed for pure blood ultrasound contrast agents [8]. Investigations into whether the scope of CEUS LI-RADS can be broadened to incorporate Kupffer-cell specific agent have been carried out [9, 11, 22, 34, 41, 42]. Our study found that 93.6% of HCCs showed nonrim APHE in both SVUS and SZUS. Late and mild washouts were noted in 72.3% (SVUS) and 74.5%

Table 4 Comparison of CEUS features of HCC across different pathological grades and tumor sizes depending on the contrast agent utilized

Variable	No APHE		Nonrim APHE		Rim APHE		No Washout		Late (≥ 60 s) and Mild Washou		Early Washout (< 60 s)		Kupffer Phase Defect
	SVUS	SZUS	SVUS	SZUS	SVUS	SZUS	SVUS	SZUS	SVUS	SZUS	SVUS	SZUS	SZUS
Differentiation degree (n = 43)													
Well-differentiated (n = 9)	1(11.1)	1(11.1)	8(88.9)	8(88.9)	0	0	3(33.3)	1(11.1)	6(66.7)	7(77.8)	0	1(11.1)	8(88.9)
Moderately-differentiated (n = 26)	2(7.7)	1(3.8)	24(92.3)	25(96.2)	0	0	0	0	20(76.9)	19(73.1)	6(23.1)	7(26.9)	26(100)
Poorly- differentiated (n = 8)	0	0	8(100)	8(100)	0	0	1(12.5)	0	5(62.5)	5(62.5)	2(25)	3(37.5)	7(87.5)
Tumor size (n = 94)													
≤ 2 cm (n = 16)	1(6.5)	1(6.5)	15(94.6)	15(94.6)	0	0	5(31.3)	2(12.5)	10(62.5)	13(81.3)	1(6.5)	1(6.5)	13(81.3)
> 2 cm (n = 78)	4(5.1)	2(2.6)	73(93.6)	73(93.6)	1(1.3)	3(3.4)	6(7.7)	4(5.1)	58(74.1)	57(73.1)	14(17.9)	17(21.8)	75(96.2)

CEUS = contrast-enhanced ultrasound, APHE = arterial phase hyperenhancement, HCC = hepatocellular carcinoma, SVUS = SonoVue-enhanced ultrasound, SZUS = Sonazoid-enhanced ultrasound

The data represent the number of observations, with percentages indicated in parentheses

(SZUS) of HCCs, with early washout seen in 15.9% (SVUS) and 19.1% (SZUS) of HCCs (P = 0.831, 0.581, respectively). Previous research indicates that SVUS washout relies on portal blood supply differences in liver lesions, whereas SZUS is further affected by Kupffer cell uptake, explaining the inconsistent patterns between the two contrast agents [9, 43]. However, the above research results indicate that HCC has similar arterial enhancement and washout patterns with both contrast agents. Our study found that the agreement between SVUS and SZUS for all observations was measured at 0.610, whereas for HCCs specifically, the agreement was found to be 0.452. Moreover, the diagnostic performance of SVUS and SZUS is comparable when diagnosing HCC using the CEUS LI-RADS v2017 algorithm [9, 34]. Therefore, we suggest that it would be feasible to apply CEUS LI-RADS v2017 to SZUS for non-invasive HCC diagnosis.

Most SZUS and SVUS evaluations agree on lesion classification, albeit with some discrepancies. Under CEUS LI-RADS v2017, SZUS upgraded 6 of 11 LR-4 observations and 6 of 25 LR-M observations from SVUS to LR-5, all 6 from the former and 5 from the latter being HCC. This aligns with previous studies [22, 44]. Conversely, SVUS upgraded 2 of 7 LR-4 observations and 9 of 28 LR-M observations by SZUS to LR-5, all being HCC. These findings suggest that SVUS and SZUS may complement each other in diagnosing HCC [44]. However, given the small sample size in this study, further research with larger samples is needed for both contrast agents.

It has been observed that some HCCs do not show washout in PVP and LP but only show washout in the Kupffer stage, and some previous studies suggest that SZUS improves the sensitivity of HCC diagnosis by evaluating Kupffer defects [2, 11, 45]. However, this phenomenon was not observed in our study. In our study, 93.6% (88/94) of HCC lesions showed washout in the Kupffer phase, 87 of which lesions also showed washout in the SZUS portal or delayed phase. This result suggests that the feature of the Kupffer phase does not exhibit additional diagnostic efficacy relative to the LP in diagnosing HCC [9, 27]. At the same time, it suggests that the performance of the Kupffer phase may not be required when incorporating perfluorobutane into CEUS LI-RADS v2017. However, there are also studies that suggest potential advantages for Sonazoid in screening settings, allowing assessment of wash out related findings during the late phase for a longer period of time [12, 16, 46].

During the Kupffer phase, washout occurred in three benign lesions, including two hemangiomas. Huang et al. warned of potential misdiagnosis of atypical hemangiomas as HCC using contrast-enhanced ultrasound [9]. Hence, in diagnosing focal liver lesions, we must consider both arterial phase and gray scale ultrasound findings alongside the Kupffer phase imaging [47].

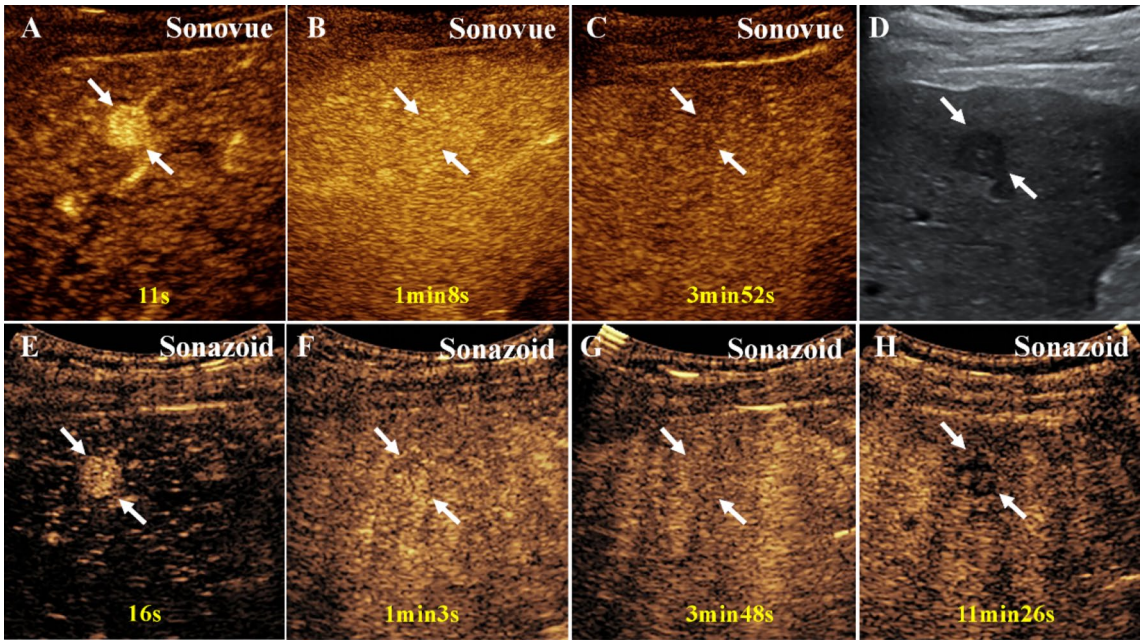

Fig. 4 A 63-year-old male was pathologically diagnosed with hepatocellular carcinoma. The lesion was classified as LR-4 using SonoVue CEUS (LI-RADS v2017), but was reclassified as LR-5 with Sonazoid CEUS (modified LI-RADS criteria). **A** A relatively homogeneous APHE was observed at 11 s after injection of SonoVue. **B**–**C** No washout was detected in either the portal or delayed phase after injection of SonoVue. **D** Conventional ultrasound demonstrated a 16 mm focal lesion in segment 5/6 of the liver (arrow). **E** After injection of Sonazoid, APHE was also detected at 16 s. **F**–**G** Similarly, there was no washout detected either in the portal or the delayed phase after injection of Sonazoid. **H** Particularly interesting is that mild washout was observed in the Kupffer phase, so this lesion is classified as LR-5

Table 5 Distribution of CEUS LI-RADS v2017 categories in both CEUS examinations

		SZUS									
		All (n = 115)					HCC (n = 94)				
		LR-5	LR-4	LR-3	LR-1/2	LR-M	LR-5	LR-4	LR-3	LR-1/2	LR-M
SVUS	LR-5	59(51.3%)	2	0	0	9	56(59.6%)	2	0	0	9
	LR-4	6	5(4.3%)	0	0	0	6	3(3.2%)	0	0	0
	LR-3	1	0	3(2.6%)	0	0	1	0	2(2.1%)	0	0
	LR-1/2	0	0	1	4(3.5%)	0	0	0	0	0(0)	0
	LR-M	6	0	0	0	19(16.5%)	5	0	0	0	10(10.6%)
K value (95% CI)		0.610 (0.475, 0.745)					0.452 (0.257, 0.647)				

CEUS = contrast-enhanced ultrasound, HCC = hepatocellular carcinoma, SVUS = SonoVue-enhanced ultrasound, SZUS = Sonazoid-enhanced ultrasound

The data represent the number of observations, with percentages indicated in parentheses

Our study presents several limitations. Firstly, the data was sourced from a single center, potentially introducing bias. Multicenter studies with larger sample sizes would enhance the reliability of our findings. Secondly, the non-randomized administration of two contrast agents may have led to additional bias. However, independent and randomized assessments of ultrasonic imaging features of liver lesions by radiologists helped to mitigate this [33]. In addition, despite adhering to recommended parameters, individual and equipment variations necessitate future exploration of optimal contrast settings for improved washout visualization. Lastly, the application of CEUS-LIRADS v2017 in HCC diagnosis by radiologists inherently involves subjective interpretation. Future studies will aim to incorporate quantitative analysis to minimize subjective evaluation [48].

In conclusion, the diagnostic efficacy of both SZUS and SVUS, in conjunction with LI-RADS v2017, in evaluating HCC lesions is found to be comparable. Furthermore, the incorporation of Kupffer phase defects in SZUS does not significantly enhance its diagnostic efficacy.

Table 6 Diagnostic performance of different criteria for HCC diagnosis based on CEUS modality

Criteria	Sensitivity	Specificity	Accuracy	PPV	NPV
(1) SVUS with CEUS LI-RADS v2017	71.3% [67/94] (60.9%, 79.9%)	85.7% [18/21] (62.6%, 96.2%)	73.9% [85/115] (64.7%, 81.5%)	95.7% [67/70] (87.2%, 98.9%)	40.0% [18/45] (26.1%, 55.6%)
(2) SZUS with CEUS LI-RADS v2017	72.3% [68/94] (62.0%, 80.9%)	81.0% [17/21] (57.4%, 93.7%)	73.9% [85/115] (64.7%, 81.5%)	94.4% [68/72] (85.7%, 98.2%)	39.5% [17/43] (25.4%, 55.5%)
(3) SZUS with modified CEUS LI-RADS (using Kupffer-phase defect instead of late and mild washout)	73.4% [69/94] (63.1%, 81.7%)	81.0% [17/21] (57.4%, 93.7%)	74.8% [86/115] (66.1%, 81.8%)	94.5% [69/73] (85.8%, 98.2%)	40.5% [17/42] (26.0%, 56.7%)
P Value (1 vs 2)	1.000	1.000	1.000	-	-
P Value (2 vs 3)	1.000	1.000	1.000	-	-
P Value (1 vs 3)	0. 832	1.000	1.000	-	-

CEUS LI-RADS = Contrast Enhanced Ultrasound Liver Imaging Reporting and Data System, HCC = hepatocellular carcinoma, SVUS = Sono-Vue-enhanced ultrasound, SZUS = Sonazoid-enhanced ultrasound, PPV = positive predictive value, NPV = negative predictive value

Data in parentheses are 95% confidence intervals

Acknowledgements We thank the Laboratory of Guangxi Zhuang Autonomous Region Engineering Research Center for Artificial Intelligence Analysis of Multimodal Tumor Images, Key Laboratory of Ultrasonic Molecular Imaging and Artificial Intelligence, Guangxi Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor, Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor (Guangxi Medical University) and the Ministry of Education for supporting the study.

Funding This study was funded by the Clinical Research Climbing Project of The First Affiliated Hospital of Guangxi Medical University (no. YYZS2020024), the Key Research and Development Project of Qingxiu District, Guangxi Nanning (no. 2020045), and the National Natural Science Foundation of Guangxi (2020GXNSFDA238005 and 2023GXNSFDA026013).

Declarations

Conflict of interests The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, et al (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians 71:209–249. https://doi.org/https://doi.org/10.3322/caac.21660
2. Li L, Zheng W, Wang J, et al (2022) Contrast-Enhanced Ultrasound Using Perfluorobutane: Impact of Proposed Modified LI-RADS Criteria on Hepatocellular Carcinoma Detection. American Journal of Roentgenology 219:434–443. https://doi.org/https://doi.org/10.2214/AJR.22.27521
3. Schellhaas B, Wildner D, Pfeifer L, et al (2016) LI-RADS-CEUS - Proposal for a Contrast-Enhanced Ultrasound Algorithm for the Diagnosis of Hepatocellular Carcinoma in High-Risk Populations. Ultraschall in Der Medizin (Stuttgart, Germany: 1980) 37:627–634. https://doi.org/https://doi.org/10.1055/s-0042-112221
4. Schellhaas B, Strobel D (2019) Tips and Tricks in Contrast-Enhanced Ultrasound (CEUS) for the Characterization and Detection of Liver Malignancies. Ultraschall in Der Medizin (Stuttgart, Germany: 1980) 40:404–424. https://doi.org/https://doi.org/10.1055/a-0900-3962
5. Terzi E, Iavarone M, Pompili M, et al (2018) Contrast ultrasound LI-RADS LR-5 identifies hepatocellular carcinoma in cirrhosis in a multicenter restropective study of 1,006 nodules. J Hepatol 68:485–492. https://doi.org/https://doi.org/10.1016/j.jhep.2017.11.007
6. Sporea I, Badea R, Popescu A, et al (2014) Contrast-Enhanced Ultrasound (CEUS) For The Evaluation Of Focal Liver Lesions – A Prospective Multicenter Study Of Its Usefulness In Clinical Practice. Ultraschall in der Medizin - European Journal of Ultrasound 35:259–266. https://doi.org/https://doi.org/10.1055/s-0033-1355728
7. Bernatik T, Seitz K, Blank W, et al (2010) Unclear focal liver lesions in contrast-enhanced ultrasonography--lessons to be learned from the DEGUM multicenter study for the characterization of liver tumors. Ultraschall in Der Medizin (Stuttgart, Germany: 1980) 31:577–581. https://doi.org/https://doi.org/10.1055/s-0029-1245649
8. Kono Y, Lyshchik A, Cosgrove D, et al (2017) Contrast Enhanced Ultrasound (CEUS) Liver Imaging Reporting and Data System (LI-RADS®): the official version by the American College of Radiology (ACR). Ultraschall in der Medizin - European Journal of Ultrasound 38:85–86. https://doi.org/https://doi.org/10.1055/s-0042-124369
9. Huang J, Gao L, Li J, et al (2023) Head-to-head comparison of Sonazoid and SonoVue in the diagnosis of hepatocellular carcinoma for patients at high risk. Front Oncol 13:1140277. https://doi.org/https://doi.org/10.3389/fonc.2023.1140277
10. Sun L, Yin S, Xing B, et al (2023) Contrast-Enhanced Ultrasound With SonoVue and Sonazoid for the Diagnosis of Colorectal Liver Metastasis After Chemotherapy. J of Ultrasound Medicine 42:355–362. https://doi.org/https://doi.org/10.1002/jum.16042
11. Hwang JA, Jeong WK, Kang H-J, et al (2022) Perfluorobutane-enhanced ultrasonography with a Kupffer phase: improved diagnostic sensitivity for hepatocellular carcinoma. Eur Radiol 32:8507–8517. https://doi.org/https://doi.org/10.1007/s00330-022-08900-6
12. Zhai H, Liang P, Yu J, et al (2019) Comparison of Sonazoid and SonoVue in the Diagnosis of Focal Liver Lesions: A Preliminary Study: Ultrasound Contrast Agent in Focal Liver Lesions. J

Ultrasound Med 38:2417–2425. https://doi.org/https://doi.org/10.1002/jum.14940
13. Domenech E, de Dios Berná-Serna J, Polo L, et al (2011) Effect of SonoVue on the Synovial Membrane in Rabbit Knees. Journal of Ultrasound in Medicine 30:1241–1246. https://doi.org/https://doi.org/10.7863/jum.2011.30.9.1241
14. Chung YE, Kim KW (2015) Contrast-enhanced ultrasonography: advance and current status in abdominal imaging. Ultrasonography (Seoul, Korea) 34:3–18. https://doi.org/https://doi.org/10.14366/usg.14034
15. Khalili K, Atri M, Kim TK, Jang H-J (2021) Recognizing the Role of the Reticuloendothelial System in the Late Phase of US Contrast Agents. Radiology 298:287–291. https://doi.org/https://doi.org/10.1148/radiol.2020203245
16. Dietrich CF, Nolsøe CP, Barr RG, et al (2020) Guidelines and Good Clinical Practice Recommendations for Contrast-Enhanced Ultrasound (CEUS) in the Liver-Update 2020 WFUMB in Cooperation with EFSUMB, AFSUMB, AIUM, and FLAUS. Ultrasound Med Biol 46:2579–2604. https://doi.org/https://doi.org/10.1016/j.ultrasmedbio.2020.04.030
17. Yanagisawa K, Moriyasu F, Miyahara T, et al (2007) Phagocytosis of ultrasound contrast agent microbubbles by Kupffer cells. Ultrasound in Medicine & Biology 33:318–325. https://doi.org/https://doi.org/10.1016/j.ultrasmedbio.2006.08.008
18. Park HS, Kim YJ, Yu MH, et al (2015) Real-time Contrast-Enhanced Sonographically Guided Biopsy or Radiofrequency Ablation of Focal Liver Lesions Using Perflurobutane Microbubbles (Sonazoid): Value of Kupffer-Phase Imaging. Journal of Ultrasound in Medicine 34:411–421. https://doi.org/https://doi.org/10.7863/ultra.34.3.411
19. Liu G, Moriyasu F, Hirokawa T, et al (2008) Optical microscopic findings of the behavior of perflubutane microbubbles outside and inside Kupffer cells during diagnostic ultrasound examination. Invest Radiol 43:829–836. https://doi.org/https://doi.org/10.1097/RLI.0b013e3181852719
20. Iijima H, Moriyasu F, Miyahara T, Yanagisawa K (2006) Ultrasound contrast agent, Levovist microbubbles are phagocytosed by Kupffer cells-In vitro and in vivo studies. Hepatology Research: The Official Journal of the Japan Society of Hepatology 35:235–237. https://doi.org/https://doi.org/10.1016/j.hepres.2006.04.016
21. Goto E, Masuzaki R, Tateishi R, et al (2012) Value of post-vascular phase (Kupffer imaging) by contrast-enhanced ultrasonography using Sonazoid in the detection of hepatocellular carcinoma. J Gastroenterol 47:477–485. https://doi.org/https://doi.org/10.1007/s00535-011-0512-9
22. Kang H-J, Lee JM, Yoon JH, et al (2020) Contrast-enhanced US with Sulfur Hexafluoride and Perfluorobutane for the Diagnosis of Hepatocellular Carcinoma in Individuals with High Risk. Radiology 297:108–116. https://doi.org/https://doi.org/10.1148/radiol.2020200115
23. Sugimoto K, Kakegawa T, Takahashi H, et al (2020) Usefulness of Modified CEUS LI-RADS for the Diagnosis of Hepatocellular Carcinoma Using Sonazoid. Diagnostics (Basel, Switzerland) 10:828. https://doi.org/https://doi.org/10.3390/diagnostics10100828
24. Sugimoto K, Saito K, Shirota N, et al (2022) Comparison of modified CEUS LI-RADS with sonazoid and CT/MRI LI-RADS for diagnosis of hepatocellular carcinoma. Hepatology Research 52:730–738. https://doi.org/https://doi.org/10.1111/hepr.13793
25. Hwang JA, Jeong WK, Min JH, et al (2021) Sonazoid-enhanced ultrasonography: comparison with CT/MRI Liver Imaging Reporting and Data System in patients with suspected hepatocellular carcinoma. Ultrasonography 40:486–498. https://doi.org/https://doi.org/10.14366/usg.20120
26. Liao W, Que Q, Wen R, et al (2023) Comparison of the Feasibility and Diagnostic Performance of ACR CEUS LI-RADS and a Modified CEUS LI-RADS for HCC in Examinations Using Sonazoid. J of Ultrasound Medicine jum.16282. https://doi.org/https://doi.org/10.1002/jum.16282
27. Barr RG, Huang P, Luo Y, et al (2020) Contrast-enhanced ultrasound imaging of the liver: a review of the clinical evidence for SonoVue and Sonazoid. Abdominal Radiology 45:3779–3788. https://doi.org/https://doi.org/10.1007/s00261-020-02573-9
28. Galle PR, Forner A, Llovet JM, et al (2018) EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 69:182–236. https://doi.org/https://doi.org/10.1016/j.jhep.2018.03.019
29. Marrero JA, Kulik LM, Sirlin CB, et al (2018) Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology (Baltimore, Md) 68:723–750. https://doi.org/https://doi.org/10.1002/hep.29913
30. Chernyak V, Fowler KJ, Kamaya A, et al (2018) Liver Imaging Reporting and Data System (LI-RADS) Version 2018: Imaging of Hepatocellular Carcinoma in At-Risk Patients. Radiology 289:816–830. https://doi.org/https://doi.org/10.1148/radiol.2018181494
31. Wen R, Lin P, Gao R, et al (2022) Diagnostic performance and interreader agreement of CEUS LI-RADS in ≤ 30 mm liver nodules with different experienced radiologists. Abdom Radiol (NY) 47:1798–1805. https://doi.org/https://doi.org/10.1007/s00261-022-03468-7
32. Heimbach JK, Kulik LM, Finn RS, et al (2018) AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology (Baltimore, Md) 67:358–380. https://doi.org/https://doi.org/10.1002/hep.29086
33. Lv K, Zhai H, Jiang Y, et al (2021) Prospective assessment of diagnostic efficacy and safety of SonazoidTM and SonoVue® ultrasound contrast agents in patients with focal liver lesions. Abdominal Radiology (New York) 46:4647–4659. https://doi.org/https://doi.org/10.1007/s00261-021-03010-1
34. Kang H-J, Lee JM, Yoon JH, et al (2022) Sonazoid™ versus SonoVue® for Diagnosing Hepatocellular Carcinoma Using Contrast-Enhanced Ultrasound in At-Risk Individuals: A Prospective, Single-Center, Intraindividual, Noninferiority Study. Korean J Radiol 23:1067–1077. https://doi.org/https://doi.org/10.3348/kjr.2022.0388
35. Yang D, Li R, Zhang X-H, et al (2018) Perfusion Characteristics of Hepatocellular Carcinoma at Contrast-enhanced Ultrasound: Influence of the Cellular differentiation, the Tumor Size and the Underlying Hepatic Condition. Sci Rep 8:4713. https://doi.org/https://doi.org/10.1038/s41598-018-23007-z
36. Fan PL, Ding H, Mao F, et al (2020) Enhancement patterns of small hepatocellular carcinoma (≤ 30 mm) on contrast-enhanced ultrasound: Correlation with clinicopathologic characteristics. Eur J Radiol 132:109341. https://doi.org/https://doi.org/10.1016/j.ejrad.2020.109341
37. Feng Y, Qin X-C, Luo Y, et al (2015) Efficacy of contrast-enhanced ultrasound washout rate in predicting hepatocellular carcinoma differentiation. Ultrasound Med Biol 41:1553–1560. https://doi.org/https://doi.org/10.1016/j.ultrasmedbio.2015.01.026
38. Cai W-J, Ying M, Zheng R-Q, et al (2023) Contrast-Enhanced Ultrasound Liver Imaging Reporting and Data System in Hepatocellular Carcinoma ≤5 cm: Biological Characteristics and Patient Outcomes. Liver Cancer 12:356–371. https://doi.org/https://doi.org/10.1159/000527498
39. Tanaka M, Nakashima O, Wada Y, et al (1996) Pathomorphological study of Kupffer cells in hepatocellular carcinoma and hyperplastic nodular lesions in the liver. Hepatology 24:807–812. https://doi.org/https://doi.org/10.1053/jhep.1996.v24.pm0008855180

40. Liu K (2003) Pathomorphological study on location and distribution of Kupffer cells in hepatocellular carcinoma. World J Gastroenterol 9:1946. https://doi.org/https://doi.org/10.3748/wjg.v9.i9.1946
41. Kang H-J, Kim JH, Yoo J, Han JK (2022) Diagnostic criteria of perfluorobutane-enhanced ultrasonography for diagnosing hepatocellular carcinoma in high-risk individuals: how is late washout determined? Ultrasonography 41:530–542. https://doi.org/https://doi.org/10.14366/usg.21172
42. Li L, Mao S, Wang J, et al (2023) Intraindividual Comparison of Contrast-Enhanced Ultrasound Using Perfluorobutane With Modified Criteria Versus CT/MRI LI-RADS Version 2018 for Diagnosing HCC in High-Risk Patients. American Journal of Roentgenology 220:682–691. https://doi.org/https://doi.org/10.2214/AJR.22.28420
43. Yang HK, Burns PN, Jang H-J, et al (2019) Contrast-enhanced ultrasound approach to the diagnosis of focal liver lesions: the importance of washout. Ultrasonography (Seoul, Korea) 38:289–301. https://doi.org/https://doi.org/10.14366/usg.19006
44. Li L, Zou X, Zheng W, et al (2023) Contrast-enhanced US with Sulfur Hexafluoride and Perfluorobutane: LI-RADS for Diagnosing Hepatocellular Carcinoma. Radiology 308:e230150. https://doi.org/https://doi.org/10.1148/radiol.230150
45. Takahashi H, Sugimoto K, Kamiyama N, et al (2022) Noninvasive Diagnosis of Hepatocellular Carcinoma on Sonazoid-Enhanced US: Value of the Kupffer Phase. Diagnostics 12:141. https://doi.org/https://doi.org/10.3390/diagnostics12010141
46. Lee JY, Minami Y, Choi BI, et al (2020) The AFSUMB Consensus Statements and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound using Sonazoid. Ultrasonography 39:191–220. https://doi.org/https://doi.org/10.14366/usg.20057
47. Hu J, Burrowes DP, Caine BA, et al (2023) Nodules Identified on Surveillance Ultrasound for HCC: CEUS or MRI as the Initial Test? J Ultrasound Med 42:1181–1190. https://doi.org/https://doi.org/10.1002/jum.16183
48. Krolak C, Dighe M, Clark A, et al (2023) Quantification of Hepatocellular Carcinoma Vascular Dynamics With Contrast-Enhanced Ultrasound for LI-RADS Implementation. Invest Radiol. https://doi.org/https://doi.org/10.1097/RLI.0000000000001022