Original Article

The efficacy of modified contrast-enhanced ultrasound Liver Imaging Reporting and Data System (CEUS LI-RADS) using Sonazoid in diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis

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Background: The contrast-enhanced ultrasound Liver Imaging Reporting and Data System (CEUS LI-RADS) is an algorithm for the diagnosis of hepatocellular carcinoma (HCC) in high-risk populations. Previous studies have shown the algorithm to have high specificity and moderate sensitivity. Nevertheless, it is designated for utilization solely with blood pool contrast agents. Sonazoid, a contrast agent that combines blood pools and Kupffer cells properties, has recently gained approval for marketing in an increased number of countries. Enhanced sensitivity in diagnosing HCC may be achieved through the distinctive Kupffer phase (KP) exhibited by Sonazoid. Certain academics have suggested the modified CEUS LI-RADS using Sonazoid. The main criteria of mild and late (≥60 seconds) washout in CEUS LI-RADS LR-5 were replaced by KP (>10 minutes) defects as the primary criteria. The purpose of this research was to evaluate the effectiveness of the modified CEUS LI-RADS using Sonazoid in diagnosing HCC.

Methods: Original studies on Sonazoid and CEUS LI-RADS were searched in the PubMed, Embase, Cochrane Library, and Web of Science databases until 13 July 2023, with no restrictions on language. We enrolled studies that applied Sonazoid for CEUS in patients at high risk of HCC and modified CEUS LI-RADS for the diagnosis of intrahepatic nodules. Meta-analyses, evaluations, case studies, correspondences, remarks, and summaries of conferences were excluded. Additionally, studies that fell outside the scope of this study and contained data on the same patients were also excluded. We evaluated the quality of research by employing the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. A bivariate mixed effects model was utilized to conduct a meta-analysis, summarizing the sensitivity and specificity in the diagnosis of HCC. The investigation of potential factors contributing to study heterogeneity was conducted using meta-regression analysis.

Results: Out of the 103 studies screened, 6 studies (835 lesions) were included in the final results. Modified CEUS LR-5 exhibited a sensitivity of 0.77 [95% confidence interval (CI): 0.70–0.82; I^2=71.98%; P=0.00] and a specificity of 0.88 (95% CI: 0.83–0.92; I^2=0.00; P=0.47) for HCC diagnosis, with heterogeneity in sensitivity. The presence of heterogeneity in the study was found to have a significant association with factors such as the study design, the number of image reviewers, the proportion of cirrhosis, the proportion of other non-HCC malignancies (OM) cases, and the type of reference standard (P≤0.05).

Conclusions: The modified CEUS LI-RADS LR-5 categorization demonstrates a reasonable level of sensitivity 0.77, but an insufficient level of specificity 0.88 when diagnosing HCC. KP defects cannot be used as a primary feature in the diagnosis of HCC by CEUS LI-RADS, perhaps as an ancillary feature.

Keywords: Sonazoid; contrast-enhanced ultrasonography (CEUS); hepatocellular carcinoma (HCC); Liver Imaging Reporting and Data System (LI-RADS); diagnosis

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Introduction

Hepatocellular carcinoma (HCC) accounts for 75–85% of primary liver cancer cases, making it the third most common cause of cancer-related death globally, following lung cancer and colorectal cancer, and ranking fifth in terms of cancer incidence (1). Early diagnosis and aggressive treatment are essential to improve the prognosis of patients with HCC. Currently, HCC is the sole form of cancer that can be noninvasively diagnosed in high-risk individuals using various imaging tests, without the need for pathological findings (2-6). Due to the benefits of pure blood pool imaging, the ability to observe in real-time, and the high level of safety for patients with renal insufficiency and iodine allergy, contrast-enhanced ultrasound (CEUS) has been widely used in clinical diagnostic workups (7). In Europe and Asia, CEUS has been adopted as the primary diagnostic technique for HCC and has gained recognition from numerous national and international professional organizations (2-6). The American College of Radiology (ACR) released the first version of the CEUS Liver Imaging Reporting and Data System (LI-RADS) in 2016, which was subsequently revised in 2017. The algorithm is offered for the diagnosis of patients with a high risk for HCC (8). CEUS LI-RADS categorizes liver nodules based on the probability of HCC occurrence in high-risk patients, ranging from LR-1 (definitely benign) to LR-5 (definitely HCC), and also includes LR-M and LR-TIV classifications. LR-M indicates that the observations are probably or definitely malignant, but they do not exhibit typical features of HCC. LR-TIV represents 100% certainty malignant lesion with tumor in the vein. In recent meta-analyses on CEUS LI-RADS, it was found that LR-5 had a sensitivity of 0.71, 0.69 and specificity of 0.93, 0.93 for diagnosing HCC (9,10). The algorithm showed high and stable specificity. According to the present edition of CEUS LI-RADS (v2017), this categorization is specifically for exclusive blood pool contrast agents and should not be used for CEUS examinations that involve both blood pools and a Kupffer cells agent such as perfluorobutane (Sonazoid; GE Healthcare, Chicago, IL, USA). Furthermore, it is clearly mentioned that the utilization of these contrast agents will be incorporated in the upcoming edition.

Sonazoid is composed of microspheres coated with hydrogenated egg phosphatidyl serine (HEPS) and filled with perfluorobutane gas (PFB) (11). Unlike SonoVue (Bracco, Milan, Italy), it has the capability to be phagocytosed by Kupffer cells within the liver and/or reticuloendothelial cells. Therefore, Sonazoid has been shown to provide a unique Kupffer phase (KP) of hepatic parenchyma in addition to a dynamic vascular phase (12,13). The KP happens 10 minutes following the injection of contrast, and cancerous growths exhibit defects compared to the nearby healthy liver tissue because of the decrease or lack of Kupffer cells (7). The characteristic appearance of HCC on Sonazoid ultrasonography usually involves hyperenhancement during the arterial phase, decreased or unchanged enhancement during the portal or late phase, and the presence of KP defects. This typical pattern is observed in over 97% of HCC cases (14).

It has been found that when Sonazoid was used for CEUS, a longer observation time resulted in more HCCs showing hypoenhancement. Defects in the KP have been observed in certain HCCs that did not exhibit washout during the vascular phase (15). The application of KP is anticipated to enhance the sensitivity of HCC detection in individuals at high risk. Enhancing the sensitivity of HCC diagnosis is crucial in regions where radical surgical removal and local ablation are the primary therapeutic choices for HCC (16). Researchers have recently suggested a modified CEUS LI-RADS LR-5 by replacing the mild and late (≥60 seconds) washout with KP defects as the primary imaging features. They have conducted original studies to investigate the significance of KP in diagnosing HCC (17-24). Currently, numerous meta-analyses have examined the accuracy of contrast-enhanced computed tomography/magnetic resonance imaging (CT/MRI) LI-RADS and CEUS LI-RADS in detecting HCC and other non-HCC malignancies (OM) (9,25-27), whereas other studies have compared the diagnostic performance of

different imaging modalities (10). Nevertheless, there is a lack of a comprehensive assessment or meta-analysis to appraise the diagnostic effectiveness of LR-5 in modified CEUS LI-RADS using Sonazoid contrast agent for HCC. We hypothesized that the modified CEUS LI-RADS LR-5 would exhibit significant sensitivity and specificity in diagnosing HCC in high-risk patients. Hence, we conducted a meta-analysis to assess the accuracy of LR-5 in modified CEUS LI-RADS for diagnosing HCC. We present this article in accordance with the PRISMA-DTA reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1184/rc) (25).

Methods

Our research program is registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) with registration number INPLASY202380044.

Search strategy

A thorough and organized search was performed using the databases of PubMed, Embase, the Cochrane Library, and Web of Science until 13 July 2023, without any limitations on language. Table S1 displays the specific search strategies utilized, incorporating search terms like "liver neoplasms", "LI-RADS", "CEUS", and "Sonazoid".

Eligibility criteria

The study included original research that used Sonazoid contrast agents for CEUS in patients who were at a high risk of HCC. The study aimed to assess the effectiveness of LR-5 in modified CEUS LI-RADS for diagnosing HCC. According to CEUS LI-RADS (v2017), individuals with cirrhosis, chronic infection of hepatitis B virus, and current or previous HCC are considered at a high risk for HCC. Patients under 18 years old, without the mentioned risk factors, with cirrhosis caused by congenital hepatic fibrosis, and with cirrhosis from vascular disorder (e.g., hereditary hemorrhagic telangiectasia, Budd-Chiari syndrome, chronic portal vein occlusion, cardiac congestion, or diffuse nodular regenerative hyperplasia) do not conform to this risk group (8). The definition of Modified CEUS LI-RADS LR-5 includes arterial phase hyperenhancement (APHE) (excluding rim and peripheral discontinuous globular enhancement) and KP defects.

In this study, the literature exclusion criteria consisted of the following: (I) meta-analyses, reviews, evaluations, case studies, correspondences, remarks, and summaries of conferences; (II) research that falls outside the scope of this study; (III) studies that had patient data in common; (IV) lack of adequate data prevents the extraction of diagnostic performance 2×2 data table research.

Study selection and data extraction

Following a duplicate check of the literature, both automated and manual, 2 investigators individually assessed the title and abstract of the article, eliminating irrelevant studies, and subsequently perused the complete text of the potentially suitable articles. They independently extracted data from eligible studies using pre-designed data tables, as indicated in Table S2. In the case of disagreement between the 2 investigators, a third investigator would engage in discussion with them until a consensus was reached.

Quality assessment

Using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (28), both investigators individually evaluated the potential for bias and the clinical relevance of every study, assessing the risk of bias and clinical applicability. The QUADAS-2 tool comprises 4 distinct sections, encompassing patient and lesion choice, index text, reference standard, and flow and timing. In the case of disagreement between the 2 investigators, a third investigator made the final decision after evaluating the reasons for both.

Statistical analysis

Statistical analysis was performed using Stata version 13.0 (StataCorp, College Station, TX, USA), Review Manager version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark), and Meta-DiSc 1.4 (Ramóny Cajal Hospital, Madrid, Spain). Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and 95% confidence interval (CI) were calculated using a bivariate mixed effects model. A summary receiver operating characteristic (sROC) curve was plotted and the area under the curve (AUC) was calculated. The closer the AUC was to 1, the more efficient the diagnosis. The evaluation of threshold effects was conducted using the Spearman correlation coefficient. The Q test and I^2 index

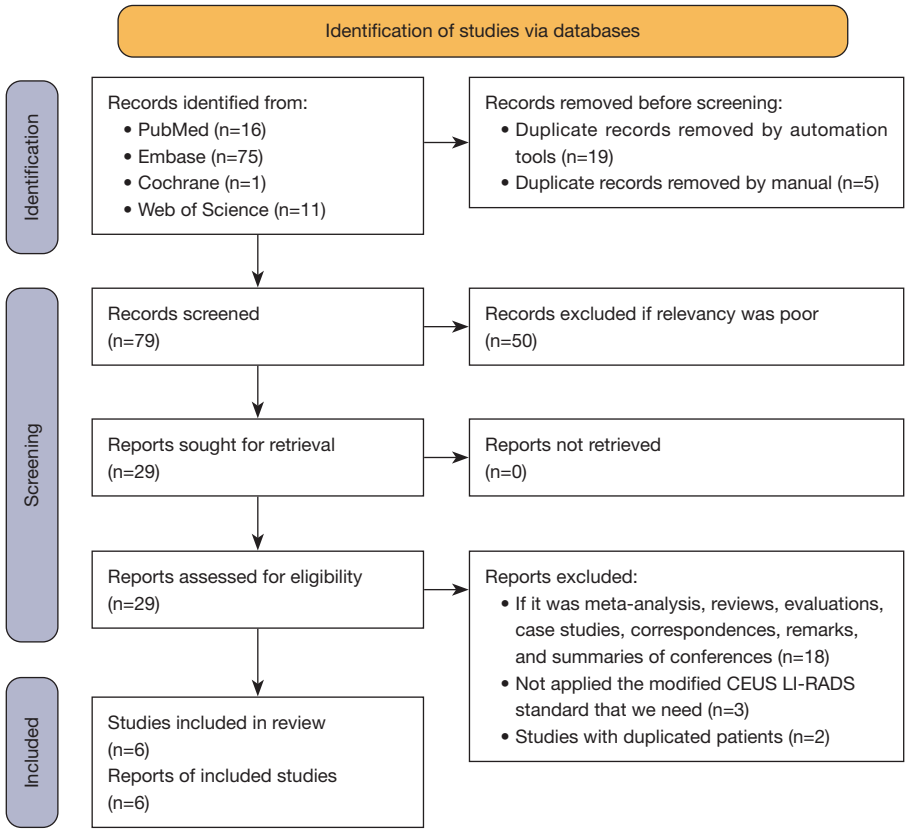

Figure 1 The flow diagram of study selection. CEUS LI-RADS, contrast-enhanced ultrasound Liver Imaging Reporting and Data System.

were employed to identify the heterogeneity of outcome measures across studies (if the Q test is less than or equal to 0.1 and I^2 exceeds 50%, it may indicate significant heterogeneity). The heterogeneity was investigated by employing meta-regression analysis to examine the possible origin. Hypothesis tests were conducted using bilateral tests at a significance level of 0.05.

Results

Literature search

A total of 103 studies were retrieved, and 6 original studies were finally included. The research screening flow chart is shown in *Figure 1*.

Study characteristics

Table 1 displays the foundational data provided in the research. In the end, a grand total of 835 lesions were incorporated, comprising of 641 HCC, 98 OM, and 96 benign lesions. *Table 2* displays the fundamental details of the encompassed lesions.

Quality assessment

As shown in Figure S1, a moderate level of bias was detected in the 6 studies' overall risk. The risk of deviation mainly comes from reference standard and patient and lesion selection. A total of 3 studies exhibited potential bias in the reference standard by relying on CT/MRI for diagnosis without subsequent monitoring or follow-up. In terms of patient and lesion selection, 1 study excluded nodules that were markedly hyperechoic on gray-scale ultrasound. It was deemed to have a significant potential for bias. The other study did not specify if patients were included in consecutive order, which we deemed to have an uncertain level of risk. Regarding flow and timing, 3 studies failed to consider the time gap between CEUS examination and pathological findings, leading us to perceive the risk of bias as uncertain.

Table 1 Basic information of the included studies

Author, year	Background								Patients		
	Country	Centre	Study type	Study design	Years of enrollment	Image reviewer	No. of US systems	No. of patients	Average age (y)	Male, %	Cirrhosis, %
Huang J, 2023 (17)	China	Single	Cohort	Prospective	2021.06–2022.01	Multiple	Multiple	59	54	83.1	67.8[§]
Hwang JA, 2022 (18)	Korea	Multiple	Cohort	Retrospective	2013.09–2020.06	Multiple	Multiple	123	61.5	76.7	41.5[§]
Liao W, 2023 (19)	China	Single	Cohort	Retrospective	2020.01–2022.02	Single	Multiple	137	51	85.4	44.6[§]
Li L, 2022 (20)	China	Single	Cohort	Retrospective	2020.03–2020.10	Multiple	Single	293	55	88.4	61.1[§]
Sugimoto K, 2020 (21)	Japan	Single	Cohort	Retrospective	2017.03–2020.04	Single	Single	104	70.0	71.2	87.9[‡]
Takahashi H, 2022 (22)	Japan	Single	Cohort	Prospective	2020.06–2021.07	Single	Single	102	71	62.7	79.4[†]

[†], cirrhosis diagnosed by using ultrasound elastography; [‡], proportion of cirrhosis in the population with pathological findings; [§], not reported method of diagnosis of cirrhosis. US, ultrasound.

Table 2 Lesions and their reference standards

Author, year	Lesions						Reference standards	
	n	Average lesion size (mm)	HCC, n (%)	OM, n (%)	Benign, n (%)	Pathology, %	Interval from index test to pathology	Interval from index test to follow-up
Huang J, 2023 (17)	62	3.5 (1.0–10.5)[†]	55 (88.7)[§¶]	3 (4.8)[§]	4 (6.5)[§¶]	93.5	NR	NR
Hwang JA, 2022 (18)	123	25 (10–130)[†]	77 (62.6)[§]	15 (12.2)[§]	31 (25.2)[§‖]	92.7	≤3 m	≥2 y
Liao W, 2023 (19)	140	35.5 (23.8, 61.3)[‡]	119 (85.0)[§]	15 (10.71)[§]	6 (4.29)[§]	100	≤30 d	N/A
Li L, 2022 (20)	304	43 (6–158)[†]	274 (90.1)[§¶]	14 (4.5)[§]	16 (5.4)[§‖]	57.6	≤1 m	Benign ≥12 m
Sugimoto K, 2020 (21)	104	17.9 (13.1, 28.2)[‡]	64 (61.5)[§]	15 (14.4)[§]	25 (24.0)[§‖]	87.5	NR	≥1 y
Takahashi H, 2022 (22)	102	25.5 (16.8, 44.3)[‡]	52 (51.0)[§¶]	36 (35.3)[§]	14 (13.7)[§¶‖]	78.4	NR	Some benign ≥6 m

[†], median (range); [‡], median (interquartile range); [§], pathological analysis; [¶], contrast-enhanced CT or MRI; [‖], follow-up. HCC, hepatocellular carcinoma; OM, other non-HCC malignancies; d, days; m, months; y, years; NR, not reported; N/A, not applicable.

Diagnostic performance of LR5 for diagnosing HCC

In the modified CEUS LI-RADS, the LR-5 overall sensitivity for diagnosing HCC in high-risk individuals was 0.77 (95% CI: 0.70–0.82; I^2=71.98%; P=0.00) (*Figure 2A*), and the overall specificity was 0.88 (95% CI: 0.83–0.92; I^2=0.00; P=0.47) (*Figure 2B*). The diagnostic odds ratio (DOR) was 25.04 (95% CI: 15.04–41.67) (*Figure 2C*). Additionally, the AUC for modified CEUS LR5 was 0.91 (95% CI: 0.88–0.93) (*Figure 3*). The analysis of threshold effect indicated that there was no heterogeneity caused by threshold effect, as the Spearman correlation coefficient was 0.03 with a P value of 0.96.

Meta-regression analysis

The findings of the meta-regression analysis are summarized in *Table 3*. There was significant heterogeneity in sensitivity. Significant associations with study heterogeneity were found among the covariates examined, including study design, number of image reviewers, proportion of cirrhosis, proportion of OM cases, and type of reference standard (P≤0.05). The sensitivity of the retrospective analysis was greater than that of the prospective analysis (0.78 *vs.* 0.72,

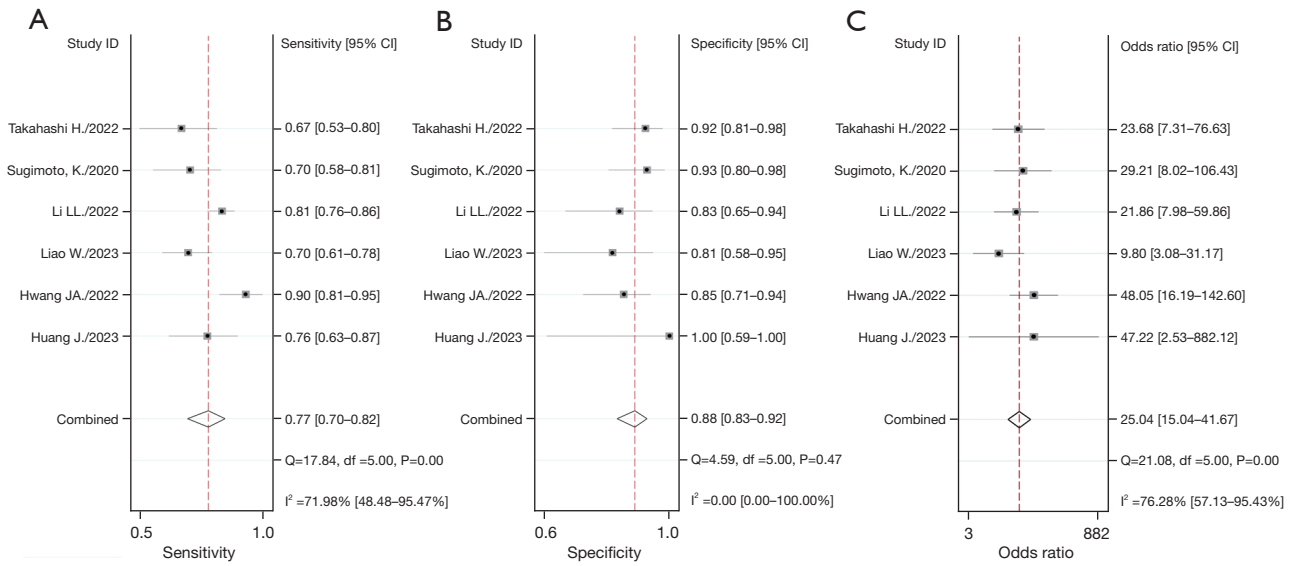

Figure 2 Diagnostic performance of modified LR5 on CEUS for HCC. (A) Sensitivity of modified CEUS LR5 for diagnosing HCC; (B) specificity of modified CEUS LR5 for diagnosing HCC; (C) DOR of modified CEUS LR5 for diagnosing HCC. CI, confidence interval; LR5, Liver Imaging Reporting and Data System category 5; CEUS, contrast-enhanced ultrasound; HCC, hepatocellular carcinoma; DOR, diagnostic odds ratio.

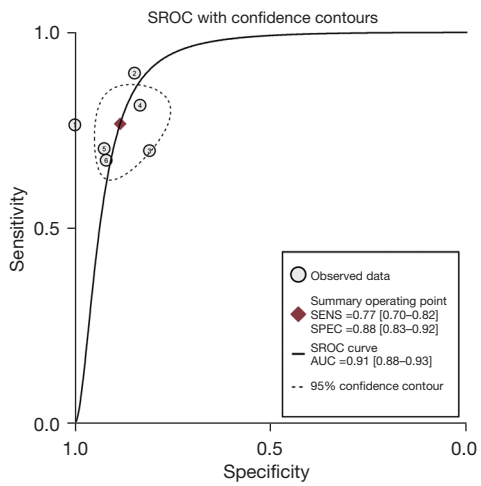

Figure 3 SROC curves of modified CEUS LR5 for diagnosing HCC. CEUS, contrast-enhanced ultrasound; LR5, Liver Imaging Reporting and Data System category 5; HCC, hepatocellular carcinoma; SENS, sensitivity; SPEC, specificity; AUC, area under the curve; SROC, summary receiver operating characteristic.

P=0.01). Multiple reviewers exhibited greater sensitivity compared to a single reviewer (0.82 *vs.* 0.69, P=0.01). The sensitivity of cirrhosis ≥50% and OM ≥10% was found to be lower compared to cirrhosis <50% (0.75 *vs.* 0.80, P=0.02) and studies with OM <10% (0.75 *vs.* 0.80, P=0.01). The study's sensitivity, when relying solely on pathology, was inferior to that of the study that included both pathology and imaging follow-up (0.70 *vs.* 0.78, P=0.02).

Discussion

Our study was conducted on the basis of 6 diagnostic tests to investigate the performance of Sonazoid-based modified CEUS LI-RADS LR-5 for the diagnosis of HCC. It was found that the modified CEUS LI-RADS LR-5 exhibited an overall sensitivity of 0.77, overall specificity of 0.88, DOR of 25.04, and AUC of 0.91 for the detection of HCC. There was a large heterogeneity in sensitivity (I^2=71.98%) and no heterogeneity in specificity (I^2=0.00) in our study. The heterogeneity was significantly associated with study design, number of image reviewers, proportion of liver cirrhosis, proportion of OM cases, and type of reference standard (P≤0.05).

In the recent meta-analyses on CEUS LI-RADS with blood pool agents, it was found that LR-5 had a sensitivity of 0.71, 0.69 and specificity of 0.93, 0.93 for diagnosing HCC (9,10). Our study utilized blood pools combined with Kupffer cells as contrast agents, resulting in an increase in sensitivity but a decrease in specificity compared to them. A recent meta-analysis using Sonazoid for intrahepatic HCC diagnostics reported combined sensitivity and

Table 3 The results of meta-regression of the sensitivity and specificity of CEUS LR5 for diagnosing HCC

Parameter	Sensitivity (95% CI)	P value
Study design		0.01*
Prospective (n=2)	0.72 (0.60–0.85)	
Retrospective (n=4)	0.78 (0.72–0.85)	
Image reviewer		0.01*
Multiple (n=3)	0.82 (0.79–0.86)	
Single (n=3)	0.69 (0.63–0.75)	
Cirrhosis% ≥50%		0.02*
Yes (n=4)	0.75 (0.67–0.83)	
No (n=2)	0.80 (0.70–0.90)	
OM% ≥10%		0.01*
Yes (n=4)	0.75 (0.67–0.83)	
No (n=2)	0.80 (0.7–0.94)	
Reference standard		0.02*
Pathology (n=1)	0.70 (0.55–0.85)	
Mixed (n=5)	0.78 (0.72–0.84)	

*, P<0.05. CEUS, contrast-enhanced ultrasound; LR5, Liver Imaging Reporting and Data System category 5; HCC, hepatocellular carcinoma; CI, confidence interval; OM, other non-HCC malignancies.

specificity of 0.90 and 0.97, respectively (29). However, the included studies used different diagnostic criteria for HCC, which can affect its diagnostic performance and introduce potential bias. The results obtained in our study by uniformly using APHE combined with KP defects as a diagnostic criterion were different from those of the above studies. There is a possibility that the modified CEUS LI-RADS algorithm may decrease the specificity of diagnosing HCC. Decreased specificity results in more false-positive cases. False-positive diagnosis of HCC may lead to inappropriate or unneeded treatment of patients with OMs or benign lesions and LI-RADS is associated with the Organ Procurement and Transplantation Network (OPTN), so a high level of specificity is necessary for LI-RADS. Li *et al.* (20) showed that KP defects could be observed in 100% of OMs and 56.3% of benign lesions, and similarly, Kang *et al.* (30) found KP defects in 92% of malignant tumors and 33% of benign lesions when Sonazoid was used for CEUS. Hemangioma may show APHE and KP defects with Sonazoid, and can be misdiagnosed as HCC. Hemangiomas measuring less than 15 mm might display homogeneous hyperenhancement in the arterial phase, resembling the CEUS presentation of HCC (31). Research has indicated that some hepatic hemangiomas in CEUS using Sonazoid typically exhibit iso- or hypo-enhancement in the KP compared to the surrounding liver parenchyma (32). The primary factor contributing to the hypoenhancement of hemangiomas in the KP might be the manifestation of relatively reduced enhancement when Sonazoid is used, resulting from the enhanced peripheral liver parenchyma caused by Kupffer cell phagocytosis (32). This phenomenon is also present in MRI using hepatocyte-specific contrast agent and is known as the pseudo-washout effect (33,34). Therefore, we cannot rely solely on KP defects to distinguish benign and malignant tumors and HCC from OM, and we have to integrate gray-scale image features and portal phase information. As in the study by Hwang *et al.* (18), an additional diagnostic criterion was applied in order to avoid the reduced specificity of modified CEUS LI-RADS. That is, the downgrading of LR-5 nodules with indistinct borders and no hypoechoic halo on gray-scale ultrasound. The specificity of LR-5 for diagnosing HCC after downgrading increased from 0.84 to 0.91.

The findings of our research indicated that the modified CEUS LI-RADS exhibited a reasonable level of sensitivity in detecting HCC. The main diagnostic feature in KP defects replaces the mild and late (≥60 seconds) washout, distinguishing it from CEUS LI-RADS v2017. However, whether KP defects can improve the diagnostic sensitivity of HCC is controversial. A previous study reported that 13.4% of HCCs exhibited hypoenhancement solely in the KP, without showing it in the late portal venous phase (24). This could be due to the decrease in Kupffer cells that occurs before the decline in sinusoidal structure and portal blood flow within the tumor during HCC dedifferentiation. Several other studies observed the lesions at 1, 5, and 10 minutes after Sonazoid injection. They found that an increasing number of nodules exhibited hypoenhancement with longer observation time (15,22). The pathological examination of the lesions revealed that the majority of the lesions exhibiting hypoenhancement at 1 minute were HCCs with poor differentiation, whereas those not exhibiting hypoenhancement until 10 minutes were well-differentiated HCCs. Kupffer cells decrease with poor differentiation. In a separate investigation, the hypoenhancement of lesions was observed at different time intervals: 2, 5, and 10 minutes. Interestingly, the 5-minute interval demonstrated equal sensitivity and specificity compared to the 10-minute interval. However,

when the 10-minute interval was employed, two false positive lesions were detected (35). Another study found that using a 6-minute cutoff for KP had high specificity and sensitivity, which did not significantly differ from using a 10-minute cutoff. The use of a 10-minute criterion did not lead to increased diagnosis of HCC (36). Therefore, although our research demonstrated reasonable sensitivity when considering KP defects as the primary criterion and surpassing SonoVue CEUS LI-RADS, further investigation is required to determine the cutoff time of KP and the role of KP defects in diagnosing HCC. When Sonazoid is applied for CEUS, the post-contrast image contains signals not only from the contrast agent, but also from tissue harmonic signals. Additionally, Sonazoid microbubbles require a moderate mechanical index (e.g., 0.2–0.3), which increases tissue harmonics and interferes with image observation, especially in KP images. If a hyperechoic lesion appears in grayscale ultrasound, it may interfere with the observation of portal phase washout and KP defects.

Joo *et al.* (34) investigated whether presenting hypointensity in the hepatobiliary phase (HBP) could serve as a substitute for washout in the portal phase when utilizing MRI with hepatocyte-specific contrast agent for diagnosing HCC. The study concluded that when combined with transitional phase (TP) or HBP, hypodensity increased diagnostic sensitivity but decreased specificity, similar to our findings using Sonazoid. They concluded that the portal-venous phase (PVP) should still be used as the main diagnostic criterion in order to ensure specificity. Unlike SonoVue, Sonazoid can be phagocytosed by Kupffer cells, and there is some overlap between the vascular phase and KP (7,14). Additionally, there is a transition period similar to that of the hepatocyte-specific MRI contrast agent TP. Therefore, it remains unclear to us whether and to what extent this imaging modality affects the washout pattern of the vascular phase of Sonazoid. KP defects could potentially serve as an ancillary feature for diagnosing HCC. Since there is a negative correlation between sensitivity and specificity, when it is not possible to harmonize the 2, it may be feasible to develop different algorithms to meet the therapeutic needs based on the varying requirements of these 2 factors in different regions.

Although the studies were carefully selected and assessed for methodological quality, there was heterogeneity in the statistical outcomes among the included studies. Inter-study heterogeneity may arise from random factors, errors in analytical methods, differences in patient selection and clinical settings, disease severity, details of indicators and reference tests, as well as interobserver variability (37,38). In our analysis, the 4 retrospective studies had higher sensitivity than the 2 prospective studies. Ensuring the authenticity and completeness of retrospective study records is challenging, leading to a low level of evidence and a potentially high risk of bias (37). Images reviewed by multiple individuals exhibited higher sensitivity compared to those reviewed by a single individual. When multiple people review the image and reach an agreement through discussion or arbitration, a more comprehensive analysis of the image can be conducted, thus avoiding the omission of important information that may occur when reviewed by a single person. Studies with a greater percentage of cirrhosis patients showed decreased sensitivity in comparison to those with a lower percentage. Severe cirrhosis frequently presents with a rough texture of the liver tissue, showing widespread shrinkage and a higher prevalence of Kupffer cell depletion and/or compromised functionality. Multiple nodules at different stages of HCC development, such as dysplastic nodules (DN), early HCC, and so on, may be present in the context of cirrhosis. Therefore, the identification of benign and malignant nodules in the setting of cirrhosis may be a challenge (14). Studies with high proportions of OM have shown relatively lower sensitivity than those with low proportions. The heterogeneity of studies when using CEUS LI-RADS can be attributed to the variation in the performance of the index test, which is influenced by the prevalence of the disease (39). A total of 5 studies, which utilized either pathology or imaging diagnosis as a reference standard, demonstrated higher sensitivity compared to a single study that solely relied on pathology. Studies that utilize an alternative imaging finding as a reference standard without follow-up may encounter potential biases related to reference standard and inclusion (40).

Our meta-analysis had several limitations. The main methodological limitation is the scarcity of original studies on modified CEUS LI-RADS, particularly prospective and head-to-head studies. The estimation of the diagnostic performance of modified CEUS LI-RADS and the identification of sources of heterogeneity could be impacted by this. Additionally, it can enhance the impact of individual research and skew the findings of the present study (41). Further, more comprehensive original research is anticipated to be conducted in order to investigate the applicability of CEUS LIRADS version for Sonazoid contrast agent. Secondly, Sonazoid contrast agent had been approved for use in a few Asian countries, and the included studies were all from these countries, but there are regional

variations in the etiology of HCC (1). In Asian countries, there is a higher prevalence of chronic infection caused by the hepatitis B virus or hepatitis C virus, whether or not cirrhosis is present. Meanwhile, the rise in prevalence in European countries in recent years can be attributed to the increase in overweight individuals and cases of diabetes. Therefore, these studies may not have been able to cover a larger population and the results may be biased. Furthermore, the limited quantity of OM lesions and non-malignant lesions incorporated in this meta-analysis might have influenced the evaluation of specificity. In addition, because of inadequate data reporting, we refrained from conducting additional subgroup analyses considering factors such as lesion size and the cause of liver disease.

Conclusions

The modified CEUS LI-RADS LR-5 categorization demonstrates a reasonable level of sensitivity but an insufficient level of specificity when diagnosing HCC. KP defects cannot be used as a primary feature in the diagnosis of HCC by CEUS LI-RADS, although perhaps as an ancillary feature.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1184/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1184/coif). The authors have no conflicts of interest to declare.

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

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Supplementary

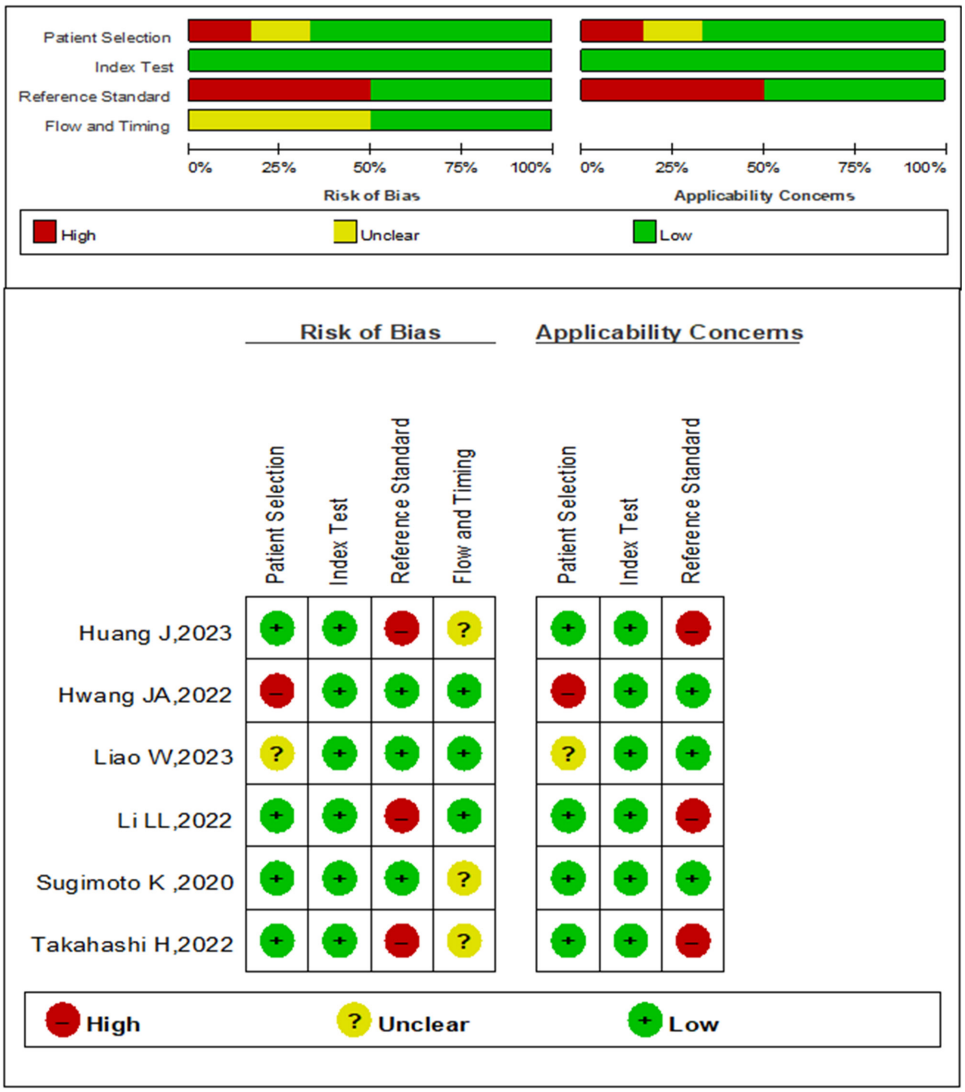

Figure S1 Results of quality assessments of the articles according to the QUADAS-2 criteria. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2.

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Table S1 Details of search strategy

History	Search query	Entry
Database: EMBASE (https://www.embase.com/)		
#1	'liver neoplasms'/exp OR 'liver neoplasms' OR (('liver'/exp OR liver) AND ('neoplasms'/exp OR neoplasms))	585608
#2	'liver neoplasms'/exp OR 'liver neoplasms' OR (('liver'/exp OR liver) AND ('neoplasms'/exp OR neoplasms)) OR 'neoplasms, hepatic' OR (('neoplasms,'/exp OR neoplasms,) AND hepatic) OR 'neoplasms, liver' OR (('neoplasms,'/exp OR neoplasms,) AND ('liver'/exp OR liver)) OR 'liver neoplasm'/exp OR 'liver neoplasm' OR 'neoplasm, liver' OR (('neoplasm,'/exp OR neoplasm,) AND ('liver'/exp OR liver)) OR 'hepatic neoplasms' OR 'hepatic neoplasm' OR 'neoplasm, hepatic' OR (('neoplasm,'/exp OR neoplasm,) AND hepatic) OR 'cancer of liver' OR 'hepatocellular cancer'/exp OR 'hepatocellular cancer' OR 'cancers, hepatocellular' OR (('cancers,'/exp OR cancers,) AND hepatocellular) OR 'hepatocellular cancers' OR 'hepatic cancer'/exp OR 'hepatic cancer' OR 'cancer, hepatic' OR (('cancer,'/exp OR cancer,) AND hepatic) OR 'cancers, hepatic' OR (('cancers,'/exp OR cancers,) AND hepatic) OR 'hepatic cancers' OR 'liver cancer'/exp OR 'liver cancer' OR 'cancer, liver'/exp OR 'cancer, liver' OR (('cancer,'/exp OR cancer,) AND ('liver'/exp OR liver)) OR 'cancers, liver' OR (('cancers,'/exp OR cancers,) AND ('liver'/exp OR liver)) OR 'liver cancers' OR 'cancer of the liver'/exp OR 'cancer of the liver' OR 'cancer, hepatocellular' OR (('cancer,'/exp OR cancer,) AND hepatocellular)	679052
#3	'carcinoma, hepatocellular'/exp OR carcinoma, hepatocellular	207359
#4	'carcinomas, hepatocellular' OR (carcinomas, AND hepatocellular) OR 'hepatocellular carcinomas' OR 'liver cell carcinoma, adult' OR (('liver'/exp OR liver) AND ('cell'/exp OR cell) AND ('carcinoma,'/exp OR carcinoma,) AND ('adult'/exp OR adult)) OR 'liver cancer, adult' OR (('liver'/exp OR liver) AND ('cancer,'/exp OR cancer,) AND ('adult'/exp OR adult)) OR 'adult liver cancer' OR 'adult liver cancers' OR 'cancer, adult liver' OR (('cancer,'/exp OR cancer,) AND ('adult'/exp OR adult) AND ('liver'/exp OR liver)) OR 'cancers, adult liver' OR (('cancers,'/exp OR cancers,) AND ('adult'/exp OR adult) AND ('liver'/exp OR liver)) OR 'liver cancers, adult' OR (('liver'/exp OR liver) AND ('cancers,'/exp OR cancers,) AND ('adult'/exp OR adult)) OR 'liver cell carcinoma'/exp OR 'liver cell carcinoma' OR 'carcinoma, liver cell'/exp OR 'carcinoma, liver cell' OR (('carcinoma,'/exp OR carcinoma,) AND ('liver'/exp OR liver) AND ('cell'/exp OR cell)) OR 'carcinomas, liver cell' OR (carcinomas, AND ('liver'/exp OR liver) AND ('cell'/exp OR cell)) OR 'cell carcinoma, liver' OR (('cell'/exp OR cell) AND ('carcinoma,'/exp OR carcinoma,) AND ('liver'/exp OR liver)) OR 'cell carcinomas, liver' OR (('cell'/exp OR cell) AND carcinomas, AND ('liver'/exp OR liver)) OR 'liver cell carcinomas' OR 'hepatocellular carcinoma'/exp OR 'hepatocellular carcinoma' OR 'hepatoma'/exp OR hepatoma OR hepatomas	442686
#5	#1 OR #2 OR #3 OR #4	707190
#6	'li rads'/exp OR 'li rads'	1123
#7	'lirads'/exp OR lirads	1152
#8	('liver imaging reporting' OR (('liver'/exp OR liver) AND ('imaging'/exp OR imaging) AND ('reporting'/exp OR reporting))) AND ('data system'/exp OR 'data system' OR (data AND system))	1246
#9	'lr 1' OR 'lr 2' OR 'lr 3' OR 'lr 4' OR 'lr 5' OR'lr 5v' OR 'lr m' OR 'lr om' OR 'lr tiv' OR lr1 OR lr2 OR lr3 OR lr4 OR lr5 OR lrm OR lrom OR lr5v OR lrtiv	5374
#10	#6 OR #7 OR #8 OR #9	6394
#11	ceus OR 'contrast enhanced ultrasound'/exp OR 'contrast enhanced ultrasound' OR 'contrast-enhanced ultrasound'/exp OR 'contrast-enhanced ultrasound'	13121
#12	'sulfur hexafluoride'/exp OR 'sulfur hexafluoride' OR (('sulfur'/exp OR sulfur) AND hexafluoride) OR 'hexafluoride, sulfur' OR (hexafluoride, AND ('sulfur'/exp OR sulfur)) OR 'sonazoid'/exp OR sonazoid OR 'kupffer phase' OR 'post vascular phase' OR 'post-vascular phase'	8791
#13	#5 AND #10 AND #11AND #12	75
Database: PubMed (PubMed (nih.gov))		
#1	"liver neoplasms"[MeSH Terms] OR Liver Neoplasms[Text Word] OR (Neoplasms, Hepatic) OR (Neoplasms, Liver) OR "Liver Neoplasm" OR (Neoplasm, Liver) OR "Hepatic Neoplasms" OR "Hepatic Neoplasm" OR (Neoplasm, Hepatic) OR "Cancer of Liver" OR "Hepatocellular Cancer" OR (Cancers, Hepatocellular) OR "Hepatocellular Cancers" OR "Hepatic Cancer" OR (Cancer, Hepatic) OR (Cancers, Hepatic) OR "Hepatic Cancers" OR "Liver Cancer" OR (Cancer, Liver) OR (Cancers, Liver) OR "Liver Cancers" OR "Cancer of the Liver" OR (Cancer, Hepatocellular)	354352
#2	("Liver Neoplasms"[Mesh]) AND "Carcinoma, Hepatocellular"[Mesh] OR (Carcinomas, Hepatocellular) OR "Hepatocellular Carcinomas" OR (Liver Cell Carcinoma, Adult) OR (Liver Cancer, Adult) OR "Adult Liver Cancer" OR "Adult Liver Cancers" OR (Cancer, Adult Liver) OR (Cancers, Adult Liver) OR (Liver Cancers, Adult) OR "Liver Cell Carcinoma" OR (Carcinoma, Liver Cell) OR (Carcinomas, Liver Cell) OR (Cell Carcinoma, Liver) OR (Cell Carcinomas, Liver) OR " Liver Cell Carcinomas" OR "Hepatocellular Carcinoma" OR Hepatoma OR Hepatomas	205498
#3	#1 or #2	384639
#4	LI-RADS OR LIRADS	710
#5	"liver imaging reporting and data system"	503
#6	LR-1 OR LR-2 OR LR-3 OR LR-4 OR LR-5 OR LR-5V OR LR-M OR LR-TIV OR LR1 OR LR2 OR LR3 OR LR4 OR LR5 OR LRM OR LROM OR LR5V OR LRTIV	3650
#7	#4 or #5 or #6	4097
#8	CEUS OR Contrast enhanced ultrasound OR Contrast-enhanced ultrasound	62728
#9	"sulfur hexafluoride"[MeSH Terms] OR sulfur hexafluoride[Text Word] OR (Hexafluoride, Sulfur) OR Sonazoid OR "Kupffer phase" OR "post vascular phase" OR "post-vascular phase"	3923
#10	#3 and #7 and #8 and #9	16

Table S1 (*continued*)

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Table S1 (*continued*)

History	Search query	Entry
Database: Cochrane Library (Cochrane | Trusted evidence. Informed decisions. Better health.)		
#1	MeSH descriptor: [Liver Neoplasms] explode all trees	3910
#2	("liver neoplasms" OR (Neoplasms, Hepatic) OR (Neoplasms, Liver) OR "Liver Neoplasm" OR (Neoplasm, Liver) OR "Hepatic Neoplasms" OR "Hepatic Neoplasm" OR (Neoplasm, Hepatic) OR "Cancer of Liver" OR "Hepatocellular Cancer" OR (Cancers, Hepatocellular) OR "Hepatocellular Cancers" OR "Hepatic Cancer" OR (Cancer, Hepatic) OR (Cancers, Hepatic) OR "Hepatic Cancers" OR "Liver Cancer" OR (Cancer, Liver) OR (Cancers, Liver) OR "Liver Cancers" OR "Cancer of the Liver" OR (Cancer, Hepatocellular)):ti,ab,kw (Word variations have been searched)	17854
#3	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	2393
#4	("Carcinoma, Hepatocellular" OR (Carcinomas, Hepatocellular) OR “Hepatocellular Carcinomas” OR (Liver Cell Carcinoma, Adult) OR (Liver Cancer, Adult) OR “Adult Liver Cancer” OR “Adult Liver Cancers” OR (Cancer, Adult Liver) OR (Cancers, Adult Liver) OR (Liver Cancers, Adult) OR “Liver Cell Carcinoma” OR (Carcinoma, Liver Cell) OR (Carcinomas, Liver Cell) OR (Cell Carcinoma, Liver) OR (Cell Carcinomas, Liver) OR “ Liver Cell Carcinomas” OR “Hepatocellular Carcinoma” OR Hepatoma OR Hepatomas):ti,ab,kw (Word variations have been searched)	11645
#5	#1 or #2 or #3 or #4	20302
#6	(LI-RADS):ti,ab,kw (Word variations have been searched)	9
#7	(LIRADS):ti,ab,kw (Word variations have been searched)	9
#8	("liver imaging reporting and data system"):ti,ab,kw (Word variations have been searched)	3
#9	(lr-1 OR lr-2 OR lr-3 OR lr-4 OR lr-5 OR lr-5V OR lr-M OR lr-OM OR lr-TIV OR lr1 OR lr2 OR lr3 OR lr4 OR lr5 OR lr M OR lr OM OR lr5V OR lr TIV):ti,ab,kw (Word variations have been searched)	643
#10	#6 or #7 or #8 or #9	649
#11	(CEUS OR “Contrast enhanced ultrasound” OR “Contrast-enhanced ultrasound”):ti,ab,kw (Word variations have been searched)	376
#12	("sulfur hexafluoride" OR (Hexafluoride, Sulfur) OR Sonazoid OR “Kupffer phase” OR "post vascular phase" OR "post-vascular phase"):ti,ab,kw (Word variations have been searched)	205
#13	#5 and #10 and #11 and #12	1
Database: Web of Science		
Search query		Entry
(TS=("liver neoplasms") OR AB=(Liver Neoplasms OR Neoplasms, Hepatic OR Neoplasms, Liver OR "Liver Neoplasm" OR Neoplasm, Liver OR "Hepatic Neoplasms" OR "Hepatic Neoplasm" OR Neoplasm, Hepatic OR "Cancer of Liver" OR "Hepatocellular Cancer" OR Cancers, Hepatocellular OR "Hepatocellular Cancers" OR "Hepatic Cancer" OR Cancer, Hepatic OR Cancers, Hepatic OR "Hepatic Cancers" OR "Liver Cancer" OR Cancer, Liver OR Cancers, Liver OR "Liver Cancers" OR "Cancer of the Liver" OR Cancer, Hepatocellular) OR TS=(Carcinoma,Hepatocellular) OR AB=(Carcinomas, Hepatocellular OR "Hepatocellular Carcinomas" OR Liver Cell Carcinoma, Adult OR Liver Cancer, Adult OR "Adult Liver Cancer" OR "Adult Liver Cancers" OR Cancer, Adult Liver OR Cancers, Adult Liver OR Liver Cancers, Adult OR "Liver Cell Carcinoma" OR Carcinoma, Liver Cell OR Carcinomas, Liver Cell OR Cell Carcinoma, Liver OR Cell Carcinomas, Liver OR " Liver Cell Carcinomas" OR "Hepatocellular Carcinoma" OR Hepatoma OR Hepatomas))AND (AB=(LI-RADS OR LIRADS OR "liver imaging reporting and data system"OR lr-1 OR lr-2 OR lr-3 OR lr-4 OR lr-5 OR lr-5V OR lr-M OR lr-OM OR lr-TIV OR lr1 OR lr2 OR lr3 OR lr4 OR lr5 OR lrM OR lrOM OR lr5V OR lrTIV)) AND (AB=(CEUS OR "Contrast enhanced ultrasound" OR "Contrast-enhanced ultrasound")) AND (TS=("sulfur hexafluoride") OR AB=(sulfur hexafluoride OR Hexafluoride, Sulfur OR Sonazoid OR "Kupffer phase" OR "post vascular phase" OR "post-vascular phase"))		11

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Table S2 Data form

Background
Name of primary study
First author
Country
Center (single or multiple)
Journal
Year
Study design
Study period
Study design (retrospective or prospective)
Study type (case-control or cohort)
Subject enrollment (consecutive or selective or unclear)
Image reviewer (multiple or single; independently or consensus; and working experience)
Blind to other imaging or examinations or pathology? (YES/NO/UNCLEAR)
Patients
Number of patients
Male (n/%)
Average age
Cirrhosis (n/%)
Lesions
Number of lesions
Number of HCC
Number of OM
Number of benign
Lesion limited? (YES/NO)
Average lesion size (mm)
Reference standards
Interval between index test and pathological assessment
Interval between index test and follow-up
Reference standard for HCC
Reference standard for OM
Reference standard for benign
Number of patients with pathological assessment (%)
CEUS
Quantity of contrast agent
No. of US systems (Single or multiple)
Device/probe
Mechanical index
The modified LR5 category for HCC diagnosis
Sensitivity
Specificity
PPV
NPV
TP
FP
TN
FN

HCC, hepatocellular carcinoma; OM, other non-HCC malignancies; CEUS, contrast-enhanced ultrasound; US, ultrasound; LR5, Liver Imaging Reporting and Data System category 5; PPV, positive predictive value; NPV, negative predictive value; TP, true positive; FP, false positive; TN, true negative; FN, false negative.

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