Original Article

The American College of Radiology contrast-enhanced ultrasound Liver Imaging Reporting and Data System and its modified version in diagnosing hepatocellular carcinoma via Sonazoid: a meta-analysis

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Background: The American College of Radiology (ACR) developed the contrast-enhanced ultrasound (CEUS) Liver Imaging Reporting and Data System (LI-RADS) for pure blood contrast agents, but Sonazoid was not included. Modifications to LI-RADS have been proposed for Sonazoid. The purpose of this meta-analysis was to identify and compare the diagnostic efficacy of the two LI-RADS algorithms of Sonazoid.

Methods: We searched the PubMed, MEDLINE, Web of Science, Embase, and Cochrane Library databases from databases inception to August 31, 2023, to find original studies on the ACR LI-RADS and/or modified LI-RADS algorithm with Sonazoid used as the contrast agent in patients with high-risk hepatocellular carcinoma (HCC). A bivariate random-effects model was used. Data pooling, meta-regression, and sensitivity analysis were performed for meta-analysis. The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to assess the methodological quality, and the Deeks funnel plot asymmetry test was used to evaluate the publication bias.

Results: A meta-analysis of 10 studies with 1,611 observations was conducted. The pooled data for ACR LI-RADS category 5 (LR-5) and modified LR-5 were respectively as follows: pooled sensitivity, 0.70 [95% confidence interval (CI): 0.64–0.75] and 0.81 (95% CI: 0.76–0.86) ($P<0.05$); pooled specificity, 0.90 (95% CI: 0.82–0.94) and 0.87 (95% CI: 0.81–0.91) ($P>0.05$); and pooled area under the summary receiver operating characteristic curve, 0.84 and 0.91. The diagnostic performance of LI-RADS category M (LR-M) of the two algorithms was comparable. Study heterogeneity was observed.

Conclusions: The results indicated that modified LR-5 algorithm demonstrated improved diagnostic sensitivity compared with the ACR LR-5 algorithm of Sonazoid, with differences observed between the different versions. Further research is needed to validate and explore the optimal diagnostic criteria for HCC using Sonazoid. Before the database search was conducted, this study was registered on PROSPERO (International Prospective Register of Systematic Reviews; CRD42023455220).

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Introduction

Hepatocellular carcinoma (HCC) stands as the most prevalent type of liver cancer, ranking as the third leading cause of cancer-related death globally (1,2). Early and effective diagnosis plays a pivotal role in the prognosis of patients with HCC. Contrast-enhanced ultrasound (CEUS) has been widely used for over a decade due to its radiation-free nature, dynamic imaging capabilities, and cost-effectiveness and is considered to be the second-line imaging modality for HCC diagnosis in Asia and Europe (3,4).

Sonazoid, a second-generation contrast agent, was first launched in Japan in 2007, and has been approved for clinical use in five countries (5), and was recommended in the consensus of the Asian Federation of Societies for Ultrasound in Medicine and Biology (AFSUMB) (6). Sonazoid can be specifically phagocytosed by Kupffer cells and gradually accumulate in the liver parenchyma (7), thus enabling the evaluation of postvascular Kupffer phase (KP) enhancement characteristics and the assessment of dynamic enhancement patterns during the vascular phase (8). With the growing use of Sonazoid in clinical scenarios, its diagnostic efficacy has been widely investigated, and a recently published meta-analysis indicated that the pooled sensitivity and specificity of Sonazoid in diagnosing HCC were 0.90 and 0.97, respectively, although this varied according to the diagnostic criteria (9).

In 2016, the American College of Radiology (ACR) introduced the CEUS Liver Imaging Reporting and Data System (LI-RADS) for the assessment of liver imaging with pure blood agents to provide a standardized lexicon and facilitate communication, which was then updated it in 2017 (10). With the growing application of Sonazoid, the development of a standardized algorithm for it use has garnered increased attention. Some studies examined the applicability of the ACR algorithm for Sonazoid (11,12), and other studies proposed a modified LI-RADS algorithm of Sonazoid (13,14). The modified algorithm integrates the unique KP characteristics of Sonazoid, but whether it should be more widely applied needs to be confirmed with additional research. Some studies have demonstrated that the two algorithms provide a highly similar diagnostic performance (15,16), while others have indicated that the modified algorithm has superiority in diagnostic sensitivity (14,17,18). However, thus far, no meta-analysis comparing the two algorithms of Sonazoid for diagnosing HCC has been conducted. Thus, we undertook to complete a systematic review and meta-analysis to offer a comprehensive evaluation of the diagnostic performance of the Sonazoid-based ACR LI-RADS algorithm and the modified LI-RADS algorithm in patients with risk factors for HCC. We present this article in accordance with the PRISMA-DTA reporting checklist (19) (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1459/rc).

Methods

Study protocol and search strategy

The protocol for this study is available on the PROSPERO platform (CRD 42023455220). We searched various databases (PubMed, Embase, MEDLINE, Web of Science, and Cochrane Library databases) for original articles that reported the diagnostic performance of the ACR and/or modified CEUS LI-RADS algorithms in diagnosing HCCs using Sonazoid. The search was limited to human participants and English language studies published as of August 31, 2023. In addition, we manually researched the reference lists for all included studies to identify additional potential studies. The detailed information of the search strategy is provided in Table S1.

Eligibility criteria

The inclusion criteria were as follows: (I) (population) patients at high-risk for HCC, (II) (index test) Sonazoid-based CEUS examination with the ACR and/or modified CEUS LI-RADS algorithms, (III) (outcomes) data from

which 2×2 tables could be extracted to show the diagnostic performance of HCC, (IV) (reference standard) pathology or imaging follow-up, and (V) a full text that could be assessed and appraised. The following exclusion criteria were applied: (I) studies not in the field of interest; (II) liver nodules already treated or patients without high-risk of HCC; (III) studies without sufficient information to extract 2×2 tables; (IV) obvious duplicate or overlapping publications; and (V) studies including animal studies, case reports, comments, reviews, letters, or abstracts.

Study selection and data extraction

After duplicate studies were excluded, two reviewers separately evaluated the articles according to the title and abstracts and subsequently reviewed the full texts to determine the eligibility of articles and complete data extraction. If there were multiple studies from the same center, we compared the enrollment periods and inclusion criteria for patients to finalize the inclusion decisions. A senior author gave arbitration when there were discrepancies between the reviewers.

The data extracted from eligible studies encompassed four main categories: (I) study characteristics, comprising essential details such as the first author's name, publication year, and detailed attributes for each study (including number of medical centers, design type, study type, and reference standard used); (II) patient characteristics, including patient count, age, and gender distribution; (III) observation characteristics, including quantity and final diagnosis (HCC, non-HCC malignancies, benign lesions); and (IV) outcome characteristics, including true positives (TPs), false positives (FPs), true negatives (TNs), and false negatives (FNs) used for pooled analysis. For studies that reported both the ACR and modified LI-RADS algorithms at the same time, the 2×2 tables were extracted separately.

Quality assessment

Two independent reviewers used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool to evaluate the overall methodological quality and risk of bias of eligible studies. Any discrepancies were resolved through discussion. QUADAS-2 comprises four aspects: patient selection, index test, reference standard, and flow and timing. The risk of bias for each aspect was classified as high, low, or unknown, and the first three of the four above mentioned aspects also included applicability assessment.

Statistical analysis

Meta-DiSc 1.4 software and Stata 14.0 software (StataCorp, College Station, TX, USA) were used for the meta-analysis. The Spearman correlation coefficient was used to identify threshold effect, with a correlation coefficient >0.6 indicating a significant threshold effect. The Cochran Q test and I^2 statistic were used to quantitatively assess heterogeneity, with $P<0.1$ and $I^2 \geq 50\%$ indicating significant heterogeneity. A bivariate random-effects model was used, and the indicators of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and summary receiver operating characteristic curves (SROC) were pooled with their 95% confidence intervals (CIs). The comparison of the differences between pooled sensitivity and specificity was tested using the variance of the logit-transformed percentage method, with $P<0.05$ being considered to indicate a significant difference. Meta-regression was used to trace the sources of heterogeneity based on covariates, and the stability of the results was evaluated by removing the studies one by one through sensitivity analysis. Publication bias was evaluated via the Deeks funnel plot asymmetry test, with $P<0.10$ indicating a significant possibility of publication bias.

Results

Literature search

A total of 58 records were initially identified according to the search strategy, including one record registered on ClinicalTrials.gov entitled "Comparing SonoVue® with Sonazoid® Using CEUS-LIRADS in HCC". After removing duplicates (n=19), screening titles and abstracts (without full text =4; case reports =1; meta-analysis =2; other language =1; review =8; comments =1; conference =2), and screening the full text (beyond the field of interest =6; data extraction failed =4), we identified 10 eligible articles for inclusion in the meta-analysis according to the inclusion and exclusion criteria. The flowchart of the literature search and study selection process is shown in *Figure 1*.

Characteristics of the included studies

The fundamental characteristics of studies and patients are summarized in *Table 1*. The 10 eligible studies analyzed included 1,611 observations with 1,232 HCCs. Eight studies were retrospective (13-18,20,21), two studies

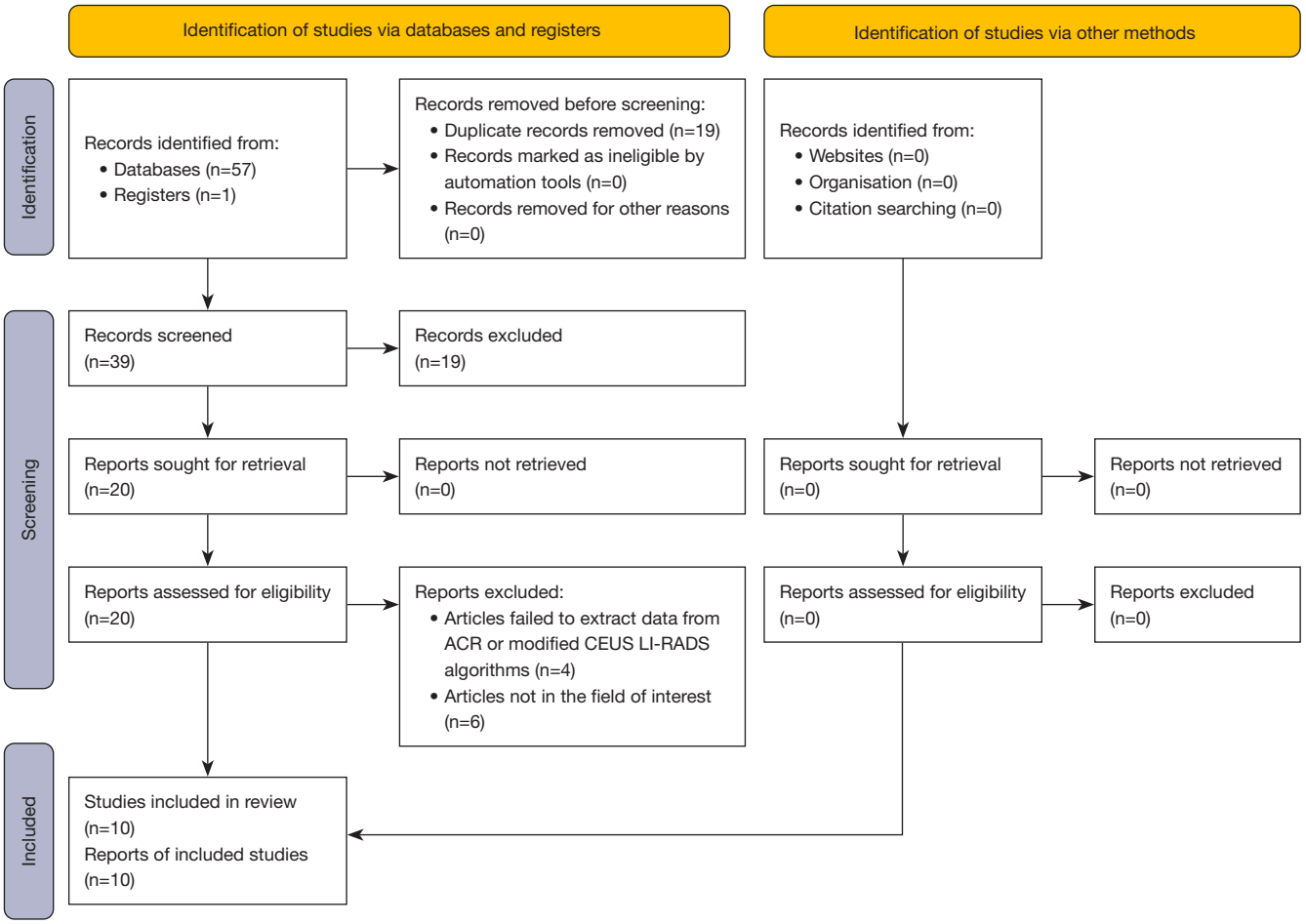

Figure 1 Literature search and study selection process. ACR, American College of Radiology; CEUS, contrast-enhanced ultrasound; LI-RADS, Liver Imaging Reporting and Data System.

were prospective (11,22), and all were conducted in Asian countries [five in China (15,16,20-22), 3 in Korea (11,17,18), and 2 in Japan (13,14)]. Of the 10 included studies, 2 studies had <100 patients (11,15), and the other 8 studies had ≥100 patients (13,14,16-18,20-22). Two were multicenter studies [one was a three-center study (18), and the other was a seven-center study (22)], and the other eight were single-center studies (11,13-17,20,21). Three studies had only one image reviewer (13,14,16), and the other seven studies yielded results from the consensus of multiple reviewers (11,15,17,18,20-22). Two studies used only pathology as the reference standard (16,21), and eight studies adopted pathology or imaging follow-up as the reference standard (11,13-15,17,18,20,22). Two studies reported an average nodule size of less than 20 mm (13,17), and the other eight studies reported an average nodule size of more than 20 mm, ranging from 25 to 47 mm (11,14-16,18,20-22).

There were two versions of the modified LI-RADS reported by the included studies (*Table 2*). Sugimoto *et al.* initially proposed the modified LI-RADS category 5 (LR-5) in 2020 (13), with the amendment of "using KP defect as an alternative of mild and late washout of ACR LR-5" (modified criteria 1). Another version of the modified LR-5 with two modifications (modified criteria 2) to the ACR version was reported by Li *et al.* in 2022 (20). The first modification of modified criteria 2 was analogous to that of modified criteria 1, and the second modification was that observations of nodules measuring at least 1 cm, no rim arterial phase hyperenhancement (APHE), early washout (<60 seconds), and a mild KP defect were classified as LR-5 rather than as category M (LR-M) (20). A 2×2 table for both modified criteria 1 and 2 could be extracted in one study (20),

Table 1 Characteristics of the included studies

Study (year)	Country	Study design	Year of enrollment	Study type	Center	No. of patients	Age (years)*	Male/female	No. of nodules	Nodule size (mm) [range]	No. of HCC	No. of non-HCC malignancy	Benign	Contrast agent	LI-RADS	Image reviewer	Reference standard
Huang J, 2023 (15)	China	Retrospective	June 2021 to Jan 2022	Cohort	Single center	59	54 [51–57]	49/10	62	35 [10–105]	55	3 [CHC: 1; ICC: 1; M: 1]	4	SonoVue/ Sonazoid	ACR v. 2017/modified LI-RADS	Multiple reviewers with consensus	Pathology or imaging follow-up
Liao W, 2023 (16)	China	Retrospective	Jan 2020 to Feb 2022	Cohort	Single center	137	51 [43–58]	117/20	140	35.5 [23.8–61.3]	119	15 [CHC: 3; ICC: 6; M: 2; others: 4]	6	Sonazoid	ACR v. 2017/modified LI-RADS	Single reviewer	Pathology
Hwang JA, 2021 (17)	Korea	Retrospective	Jan 2013 to Dec 2016	Cohort	Single center	203	61.3 [32–83]	159/44	122†	15 [7–50]	89	NA	NA	Sonazoid	ACR v. 2017/modified LI-RADS	Multiple reviewers with consensus	Pathology or imaging follow-up
Hwang JA, 2022 (18)	Korea	Retrospective	Sep 2013 to June 2020	Cohort	Multi-center	123	61.5 [21–86]	98/25	123	25 [10–130]	77	15 [CHC: 2; ICC: 11; others: 2]	31	Sonazoid	ACR v. 2017/modified LI-RADS	Multiple reviewers with consensus	Pathology or imaging follow-up
Kang HJ, 2020 (11)	Korea	Prospective	Feb 2019 to Aug 2019	Cohort	Single center	59	65 [49–86]	47/12	59	28 [11–100]	43	10 [CHC: 3; ICC: 6; others: 1]	6	SonoVue/ Sonazoid	ACR v. 2017	Multiple reviewers with consensus	Pathology or imaging follow-up
Li L, 2022 (20)	China	Retrospective	Mar 2020 to Oct 2020	Cohort	Single center	293	55‡	140/31	304	43 [6–158]	274	14 [CHC: 1; ICC: 8; M: 5]	16	Sonazoid	ACR v. 2017/modified LI-RADS	Multiple reviewers with consensus	Pathology or imaging follow-up
Li L, 2023 (21)	China	Retrospective	March 2020 to May 2021	Cohort	Single center	171	54	140/31	171	47 [9–105]	114	43	14	Sonazoid	Modified LI-RADS	Multiple reviewers with consensus	Pathology
Li L, 2023 (22)	China	Prospective	June 2021 to Dec 2021	Cohort	Multi-center	375	56 [24–86]	318/57	424	37 [7–157]	345	40 [CHC: 4; ICC: 23; M: 10; others: 3]	39	SonoVue/ Sonazoid	ACR v. 2017/modified LI-RADS	Multiple reviewers with consensus	Pathology or imaging follow-up
Sugimoto K, 2020 (13)	Japan	Retrospective	March 2017 to April 2020	Cohort	Single center	104	70 [54.5–78]	74/30	104	17.9 [13.1–29.2]	64	16 [ICC: 6; M: 9; others: 1]	24	Sonazoid	Modified LI-RADS	Single reviewer	Pathology or imaging follow-up
Takahashi H, 2022 (14)	Japan	Retrospective	June 2020 to July 2021	Cohort	Single center	102	71 [63–78]	64/48	102	25.5 [16.8–44.3]	52	36 [ICC: 10; M: 26]	14	Sonazoid	ACR v. 2017/modified LI-RADS	Single reviewer	Pathology or imaging follow-up

*, data are the mean or median value with the range in parentheses; †, only 122 observations with CEUS LI-RADS algorithms; ‡, data only with mean value. y, years; HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; CHC, combined hepatocellular-cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; M, metastasis; ACR, American College of Radiology; v. 2017, 2017 version; NA, not available.

Table 2 Illustration for the Sonazoid modified LR-5 diagnostic criteria

Criteria	Definition
Modified criteria 1	≥1 cm: APHE (excluding rim and peripheral discontinuous globular enhancement) and KP defect
Modified criteria 2	≥1 cm: APHE (excluding rim and peripheral discontinuous globular enhancement) and KP defect; ≥1 cm: APHE (not rim), early washout (<60 s), and mild KP defect

LR-5, Liver Imaging Reporting and Data System category 5; APHE, arterial phase hyperenhancement; KP, Kupffer phase.

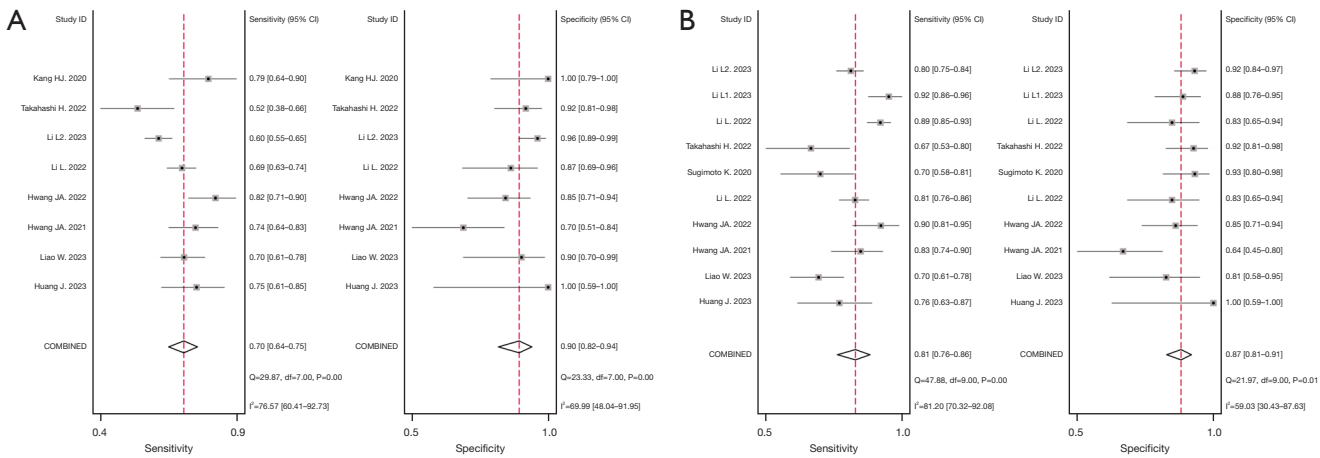

Figure 2 Forest plots of LR-5 for HCC. (A) Pooled sensitivity and pooled specificity of the ACR LR-5 algorithm. (B) Pooled sensitivity and pooled specificity of the modified LR-5 algorithm. CI, confidence interval; LR-5, Liver Imaging Reporting and Data System category 5; HCC, hepatocellular carcinoma; ACR, American College of Radiology.

and we listed them separately for further meta-analysis. Generally, in terms of LR-5, nine of included studies with 1856 nodules reported the diagnostic performance of the modified LR-5, six of them used modified criteria 1 (13-18), two of them used modified criteria 2 (21,22), and one study used both modified criteria 1 and 2 (20). Eight of included studies, comprising 1,336 nodules, evaluated the diagnostic efficacy of ACR LR-5 (11,14-18,20,22). The pooled proportions of HCCs were 94.2% for modified criteria 1, 97.2% for modified criteria 2, and 95.9% of ACR LR-5.

In terms of other LI-RADS categories, only three studies (16,20,22) described the diagnostic performance of LR-M of both CEUS LI-RADS algorithms.

Diagnostic performance of ACR and the modified LR-5 algorithms for HCC

There was no threshold effect observed for LR-5 in the two CEUS algorithms (Spearman correlation coefficient =0.238, P=0.570 for ACR LR-5; Spearman correlation coefficient =0.286, P=0.424 for modified LR-5).

The pooled sensitivity and specificity of ACR LR-5 for the diagnosis of HCC were, respectively, 0.70 (95% CI: 0.64–0.75) and 0.90 (95% CI: 0.82–0.94) (*Figure 2A*). The pooled DOR was 19.84 (95% CI: 11.33–34.75), the pooled PLR was 6.72 (95% CI: 3.96–11.40), and the pooled NLR was 0.34 (95% CI: 0.29–0.40) (Figure S1A,S1B).

The pooled sensitivity and specificity of the modified LR-5 for the diagnosis of HCC were, respectively, 0.81 (95% CI: 0.76–0.86) and 0.87 (95% CI: 0.81–0.91) (*Figure 2B*). The pooled DOR was 29.30 (95% CI: 18.25–47.02), the pooled PLR was 6.24 (95% CI: 4.33–9.00), and the pooled NLR was 0.21 (95% CI: 0.16–0.28) (Figure S2A,S2B).

The area under the SROC of ACR LR-5 for HCC and that of the modified LR-5 were 0.84 (95% CI: 0.80–0.87) and 0.91 (95% CI: 0.88–0.93), respectively (*Figure 3A,3B*).

Diagnostic performance of the ACR and modified LR-M algorithms for non-HCC malignancies

Only three studies (16,20,22) reported the diagnostic performance of the LR-M for non-HCC diagnosis, which

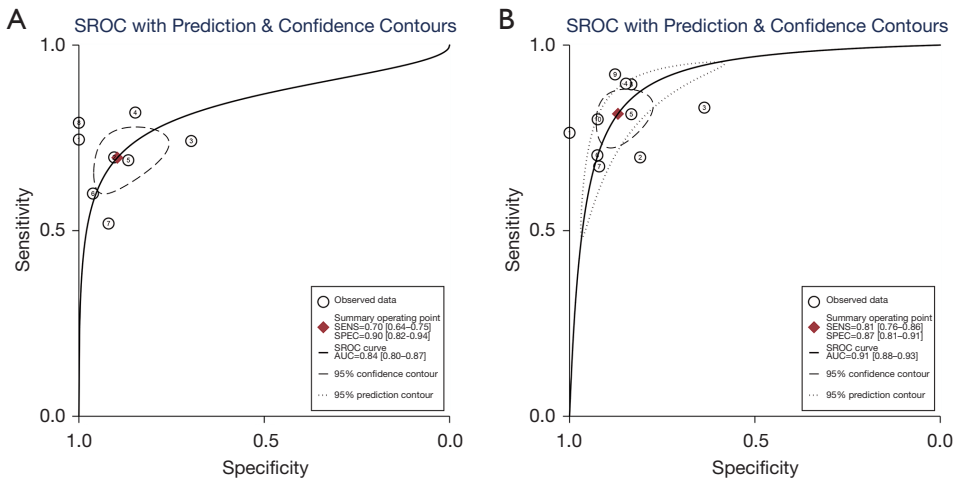

Figure 3 SROC curves of LR-5 for HCC. SROC curve of the ACR LR-5 algorithm (A) and the modified LR-5 algorithm (B). SROC, summary receiver operating characteristic; SENS, sensitivity; SPEC, specificity; AUC, area under the curve; LR-5, Liver Imaging Reporting and Data System category 5; HCC, hepatocellular carcinoma; ACR, American College of Radiology.

Table 3 Results of meta-regression analysis of the modified LR-5 for the detection of HCC

Covariate	Subgroup	Sensitivity (95% CI)	P value	Specificity (95% CI)	P value
Modified criteria	Modified criteria 1 (n=7)	0.78 (0.72–0.83)	<0.01	0.85 (0.79–0.92)	<0.01
	Modified criteria 2 (n=3)	0.87 (0.82–0.93)		0.89 (0.82–0.96)	
Study design	Retrospective (n=9)	0.82 (0.76–0.87)	0.28	0.86 (0.80–0.91)	0.02
	Prospective (n=1)	0.80 (0.64–0.96)		0.93 (0.85–1.00)	
Reviewer	Multi-reviewer (n=7)	0.85 (0.82–0.88)	0.10	0.85 (0.79–0.91)	<0.01
	Single reviewer (n=3)	0.69 (0.61–0.78)		0.90 (0.83–0.97)	

LR-5, Liver Imaging Reporting and Data System category 5; HCC, hepatocellular carcinoma; 95% CI, 95% confidence interval.

included 738 HCCs, 69 non-HCC malignancies, and 61 benign lesions. One study compared the diagnostic efficacy of LR-M in ACR and modified criteria 1, and the other two compared the diagnostic efficacy of LR-M in ACR and modified criteria 2.

The proportion of HCCs in LR-M was 59% in ACR, 72.5% in modified criteria 1, and 55.9% in modified criteria 2. The pooled sensitivity and specificity were 0.87 (95% CI: 0.77–0.94) and 0.82 (95% CI: 0.80–0.85) for the ACR LR-M, respectively, and 0.86 (95% CI: 0.75–0.93) and 0.88 (95% CI: 0.86–0.91), respectively, for the modified LR-M.

Meta-regression and sensitivity analysis

The pooled sensitivity (I^2=81.20%) and specificity (I^2=59.03%) of the modified LR-5 demonstrated considerable heterogeneity. Meta-regression analysis was conducted to investigate the potential sources of heterogeneity, findings of which are presented in *Table 3*. The following covariates were used in the meta-regression: (I) modified criteria (modified criteria 1 *vs.* modified criteria 2), (II) study design (retrospective *vs.* prospective), and (III) number of reviewers (single reviewer *vs.* multiple reviewers). The results indicated that the versions of modified criteria affected the heterogeneity for both sensitivity and specificity (P<0.01). Modified criteria 2 had significantly higher diagnostic sensitivity and specificity compared with modified criteria 1. Moreover, the meta-regression indicated that the reported specificity from prospective studies was superior to the pooled specificity from retrospective studies. This result may also be due to the influence of the version of the modified criteria, as one

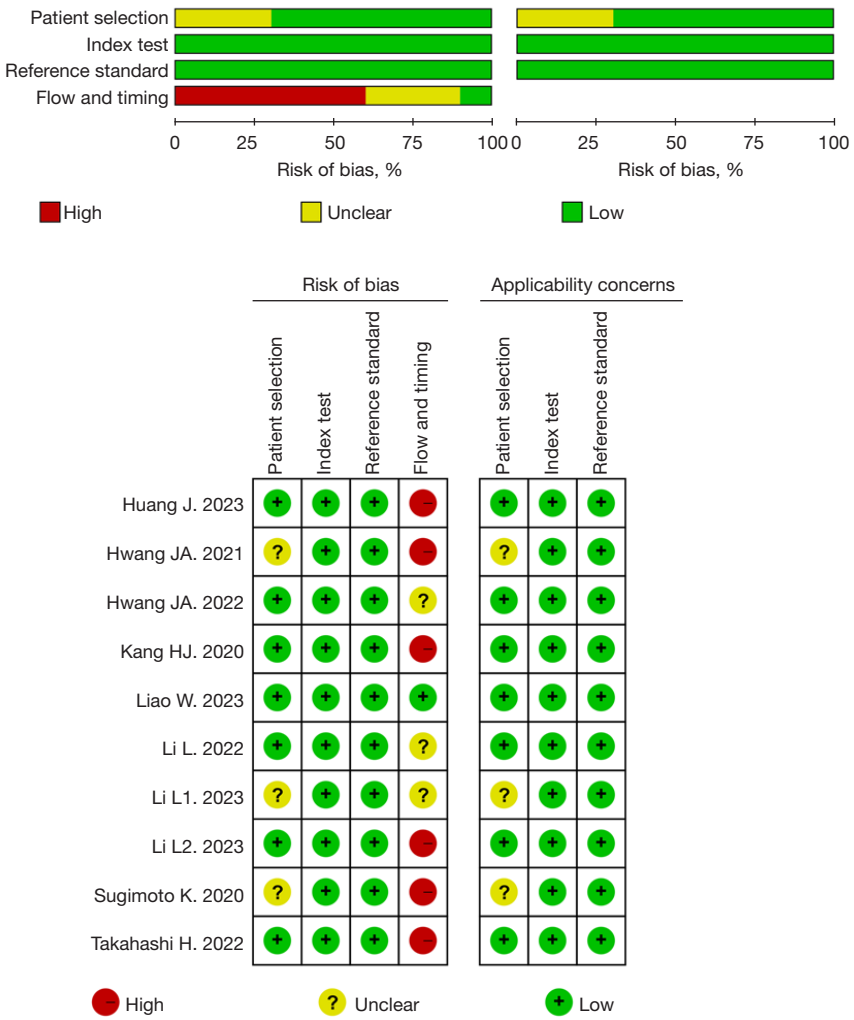

Figure 4 Methodological quality of the studies included (Quality Assessment of Diagnostic Accuracy Studies 2 results).

prospective study used modified criteria 2. Interestingly, we found that the study with a single image reviewer yielded a higher specificity compared with that of the studies with multiple reviewers.

The pooled sensitivity (I^2=76.57%) and specificity of ACR LR-5 (I^2=69.99%) also indicated considerable heterogeneity, and the results from the meta-regression are shown in Table S2. The pooled specificity of the prospective studies was higher than that of the retrospective studies. Additionally, the study with a single reviewer yielded a higher specificity compared with those that had multiple reviewers. The sensitivity analysis results revealed that no individual study significantly impacted the overall pooled estimates for either of the CEUS LR-5 algorithms (Figure S3).

Quality assessment and publication bias

The overall quality of the studies included is summarized in *Figure 4*. The findings in the index test and reference standard domains were deemed satisfactory. Regarding the patient selection domain, two studies (17,21) included patients who had undergone both CEUS and computed tomography or magnetic resonance imaging, and one study (13) included all malignancies based on pathology, all three of which were rated as unclear risk of bias due to potential selection bias. Regarding the flow and timing domain, six studies (11,13-15,17,22) had a relatively high-risk of bias due to mixed reference standards (pathology and imaging follow-up or only pathology), which might have resulted in validation bias. Pathology should not be

the sole reference standard, as biopsy tends to be applied to HCC cases with atypical imaging manifestations, and HCC is common in patients undergoing hepatic resection (23). Three studies (18,20,21) were marked as having an unclear risk of bias because the time interval between the index test and reference standard was not provided.

Regarding the applicability of risk ratings, three studies (13,17,21) in the patient selection domain were assigned unclear risk ratings. These concerns indicate a need for further investigation to ensure their suitability and accuracy. No significant publication bias was identified by the Deeks funnel plot asymmetry test for either the ACR CEUS LI-RADS algorithm (P=0.99) or the modified CEUS LI-RADS algorithm (P=0.21) (Figure S4A,S4B).

Discussion

Our meta-analysis of comparative studies included 10 articles that reported the diagnostic performance of the ACR LI-RADS algorithm and/or modified LI-RADS algorithm that used Sonazoid as the contrast agent for HCC diagnosis. The results of pooled data indicated that the modified LR-5 algorithm had higher diagnostic sensitivity compared with the ACR LR-5 algorithm (0.81 *vs.* 0.70; P<0.05), and there was no significant difference between the pooled specificity of the two LR-5 algorithms (0.87 *vs.* 0.90; P>0.05).

For the ACR LR-5 without modification for HCC diagnosis with Sonazoid as the contrast agent, the pooled results were similar to those of the meta-analysis evaluating LR-5 for HCC diagnosis with SonoVue as the contrast agent (24), with a pooled sensitivity, specificity, and area under the curve (AUC) of 0.69, 0.92, and 0.79, respectively. These results provide a degree of support for the potential application of the ACR LR-5 algorithm for Sonazoid (25) and offer valuable insights for the upcoming updated version. However, the pooled data demonstrated moderate diagnostic sensitivity. The predetermined time limit for washout of ACR LR-5 was 5 min, and research has revealed that a significant portion (10–33%) of HCC cases only display defects in KP without demonstrating washout in the late vascular phase (11,14,18). The low detection rate of washout (4) in late vascular phase may contribute to the moderate sensitivity of ACR LR-5, as it classifies observations with APHE but no washout into LR-4 (8,10). In a way, the high mechanical index (MI) condition and the time overlap between the late vascular phase and phagocytosis (starting approximately 1 min after administration) (26) of Sonazoid may influence the visualization of washout performance, especially for hyperechogenic nodules (27). Since the ACR LR-5 diagnostic criteria for HCC was initially designed for blood-based contrast agents, some researchers have suggested incorporating adaptations to account for the unique KP performance of Sonazoid, with the aim to enhance diagnostic efficacy. The pooled results of our meta-analysis supported this proposal, indicating that the modified LR-5 may be more effective for detecting HCC lesions. Furthermore, the stability of Sonazoid microbubbles can ensure the ability of repeated scanning and detection of lesions in deep location to reduce omissions (28).

The pooled specificity of both the LR-5 algorithms was relatively high (ACR LR-5: 0.90; modified LR-5: 0.87; P>0.05) but did not achieve a 100% ideal intention as LR-5 category was set to specifically proposed for diagnosing HCC. This may be due to the fact that the absence of Kupffer cells is not specific for HCCs and may also be applicable to non-HCC malignancies (11,21,27). Moreover, some benign lesions, such as atypical hemangioma, might be confused for HCC as they also manifest KP defect (8). Even though the difference of specificity between ACR LR-5 and modified LR-5 was not statistically significant, the pooled results indicated a lower specificity of the modified criteria, and due to the limited number of publications, the modified criteria should be applied with caution. Fortunately, integrating grayscale information with the modified LR-5 criteria has been proposed for addressing this suboptimal specificity, and this addition has been verified by Hwang *et al.* (18). Nonetheless, further studies are needed to further validate this conclusion.

LR-M serves as the diagnostic standard for non-HCC malignancies. Our meta-analysis demonstrated that the pooled sensitivity, specificity, and AUC of ACR LR-M in detecting non-HCC malignancies were comparable to those of the modified LR-M. Due to the limited number of studies available, these pooled results can only be considered as references, and additional studies are necessary to more conclusively determine the diagnostic efficacy of LR-M.

We examined the differences between the two versions of the modified LR-5 (5), which can contribute to a better understanding of LR-M's diagnostic performance for non-HCC malignancies. Lesions exhibiting early washout typically require a biopsy to confirm the diagnosis (8,29); as mentioned earlier, the second modification of the modified criteria 2 emphasizes the "mild" KP defect manifestation to support the diagnosis of HCC, as most

cholangiocarcinoma (CCA) and metastatic lesions may show a complete KP defect (20). The benefit of these improvement was confirmed in our meta-analysis. Our data aggregation revealed that the proportion of HCC cases in LR-M was 59% according to the ACR algorithm and was similar to the pooled proportion from two meta-analyses, with the proportion of HCC cases in LR-M with SonoVue being 54% (30) and 57% (24), which also supports the applicability of the ACR LR-M algorithm for Sonazoid to some extent. However, this proportion was higher in the LR-M modified criteria 1, with HCC accounting for 72.5%, and this proportion reduced to 55.9% in the LR-M modified criteria 2 when the second modification was applied. Moreover, the results of meta-regression indicated that the modified criteria 2 exhibited higher pooled sensitivity (0.87 *vs.* 0.78; P<0.01) and pooled specificity (0.89 *vs.* 0.85; P<0.01) in diagnosing HCC compared with the modified criteria 1, which is encouraging. Although this finding supports the modified criteria 2, due to the limited amount of literature, further investigation is needed to determine the demographic and regional factors and verify the results. The 2023 Korea practice guidelines proposed the following diagnostic criteria for HCC: nodules measuring ≥1 cm in at-risk individuals without rim APHE and characteristics of late and mild washout or KP washout (31). In other words, this guideline adopts both the ACR LR-5 or modified criteria 1 as the diagnostic criteria for HCC. However, modified criteria 2 was not integrated into this guideline, as it was published after the search strategy. Further research is needed to validate and explore the optimal diagnostic criteria for HCC using Sonazoid.

Substantial heterogeneity was noted among the studies included in the meta-regression analysis. Modified criteria, study design, and number of reviewers were associated with study heterogeneity in the meta-regression analysis. Additionally, prospective studies showed significantly higher specificity than those that were retrospective. As retrospective studies involve more confounding factors, additional prospective studies are needed to further determine the effectiveness of the two CEUS LI-RADS algorithms. Interestingly, the study that had a single reviewer showed a significantly higher specificity than did those that had multiple reviewers. The interpretation of CEUS characteristics by clinical physicians is highly correlated with their experience. Our results emphasize the importance of achieving consensus among multiple reviewers, which can reduce bias in diagnostic studies.

Two points should be noted in regard to the process of screening articles and extracting data. First, two studies conducted by the same author from Korea were included (17,18). One (17) of these studies was conducted at a single center over a 3-year patient recruitment period, while the other (18) was a three-center study spanning 8 years of patient inclusion; moreover, their inclusion conditions were different, and both were included in the meta-analysis—even though we failed to obtain a specific duplicate value—given the limited number of studies in this emerging field. Second, two studies (20,21) in China with 34 duplicate patients were both included given that they examined 293 and 171 patients, respectively, with only a small portion overlapping.

This meta-analysis had certain limitations which should be addressed. First, the number of involved articles was limited. Second, only three articles reported data on LR-M algorithms, and these were pooled as a reference without further analysis being conducted. Third, all of the included studies were conducted in Asia, with half being conducted in China, a region where the hepatitis B virus is a predominant risk factor for HCC. Thus, it may not be feasible to extend our findings to Western or European countries where hepatitis C virus and nonalcoholic steatohepatitis are frequent due to possible biases arising. This regional imbalance may be related to the areas where Sonazoid has been approved, and more research should be conducted in other geographic regions to provide more effective guidance for clinical practice.

Conclusions

The modified LR-5 algorithm demonstrated superior diagnostic sensitivity compared to the ACR LR-5 algorithm of Sonazoid, with this difference being observed across other versions. Further research is needed to validate and identify the optimal diagnostic criteria for HCC using Sonazoid.

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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-23-1459/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1459/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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