Original Article

Compared with SonoVue® LR-5, Sonazoid® modified LR-5 has better diagnostic sensitivity for hepatocellular carcinoma: a systematic review and meta-analysis

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Background: The contrast-enhanced ultrasound (CEUS) liver imaging reporting and data system (LI-RADS) is a standardized system for reporting liver nodules in patients at risk of developing hepatocellular carcinoma (HCC) and is only recommended for pure blood pool agents such as SonoVue®. A modified LI-RADS was proposed for Sonazoid®, a Kupffer cell-specific contrast agent. This meta-analysis was conducted to compare the diagnostic efficiency of the CEUS LI-RADS for SonoVue® and the modified LI-RADS for Sonazoid®.

Methods: The PubMed, Medline, Web of Science, Embase, and Cochrane Library databases were systematically searched to retrieve studies on the diagnostic efficiency of the CEUS LI-RADS algorithms in diagnosing HCC using SonoVue® and/or Sonazoid® from January 2016 to June 2023. Histopathology or imaging follow-up served as the reference standards. Only articles published in English on retrospective or prospective studies with full reports were included in the meta-analysis. A bivariate random-effects model was used. Data pooling, meta-regression, and sensitivity analysis were performed for the meta-analysis. Deeks' funnel plot asymmetry test was used to evaluate publication bias, and the QUADAS-2 tool was used to assess the methodological quality of eligible studies.

Results: In total, 26 studies comprising 8,495 patients with 9,244 lesions were included in the meta-analysis. The pooled data results for SonoVue® LI-RADS category 5 (LR-5) and Sonazoid® modified LR-5 were as follows: pooled sensitivity: 0.68 [95% confidence interval (CI): 0.64–0.73, I^2=89.20%; P<0.01] and 0.82 (95% CI: 0.74–0.87, I^2=85.39%; P<0.01) (P<0.05); pooled specificity: 0.93 (95% CI: 0.90–0.96, I^2=86.52%; P<0.01) and 0.86 (95% CI: 0.79–0.91, I^2=59.91%; P=0.01) (P<0.05); pooled area under the curve (AUC): 0.86 (95% CI: 0.82–0.89) and 0.91 (95% CI: 0.88–0.93) (P<0.05), respectively. The meta-regression analysis revealed that the study design, subject enrollment method, and reference standard contributed to the heterogeneity of SonoVue® LR-5, and the number of lesions was a source of heterogeneity for Sonazoid® modified LR-5. The diagnostic performance of the LI-RADS category M (LR-M) algorithms of SonoVue® and Sonazoid® was comparable.

Conclusions: The Sonazoid® modified LR-5 algorithm had a higher diagnostic sensitivity, lower

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specificity, and higher AUC than SonoVue® LR-5.

Keywords: Meta-analysis; contrast-enhanced ultrasound (CEUS); liver imaging reporting and data system (LI-RADS); SonoVue; Sonazoid

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Introduction

Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer and the third highest cause of cancer-related deaths worldwide (1,2). Fortunately, HCC can be diagnosed non-invasively by imaging methods. As a radiation-free, real-time, and cost-effective imaging modality, contrast-enhanced ultrasound (CEUS) has been recommended for the screening of high-risk populations and has been shown to exhibit good diagnostic performance in diagnosing HCC (3,4).

SonoVue® and Sonazoid® are two contrast agents (CAs) that are widely used in clinical practice for liver imaging (5). SonoVue® is a pure vascular agent that cannot pass through endothelial cells (6). Conversely, Sonazoid® can be phagocytosed by Kupffer and reticuloendothelial cells. This property allows Sonazoid® to provide detailed information about both the vascular phase and the post-vascular Kupffer phase (KP), thus providing additional diagnostic assistance (7). Some non-inferiority studies have revealed that the diagnostic accuracy of the two CAs is comparable (8,9), while other studies have indicated that in terms of diagnostic accuracy, Sonazoid® outperforms SonoVue® (10). However, these studies mainly focused on comparing the image characteristics of different time phases and did not specifically explore the diagnostic efficiency of the CEUS liver imaging reporting and data system (LI-RADS) algorithms between the two CAs.

To standardize reporting and enhance communication, the American College of Radiology (ACR) introduced the CEUS LI-RADS as a standardized system for reporting liver nodules in patients at high risk of HCC in 2016, and the system was further updated in 2017 (11). Under this system, liver lesions are categorized based on the potential risk of HCC. Patients with LI-RADS category 5 (LR-5) lesions can be treated for HCC without undergoing a biopsy, while those with LI-RADS category M (LR-M) lesions undergo further examination via a pathological assessment. However, the current version of the CEUS LI-RADS is only recommended for pure blood pool agents such as SonoVue®. With the increasing use of Sonazoid® in clinical practice, there have been proposals to modify the CEUS LI-RADS algorithms based on the distinct characteristics of Sonazoid® in the KP. It is crucial to compare the two algorithms to determine whether the modified Sonazoid® LI-RADS is worthy of popularization. To address this issue, we conducted a meta-analysis to compare the diagnostic efficiency of the LI-RADS algorithms between SonoVue® and Sonazoid®. We present this article in accordance with the PRISMA-DTA reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1616/rc) (12).

Methods

Study protocol and search strategy

We registered the protocol for this study on the PROSPERO platform (CRD42023434246). A thorough search of the PubMed, Medline, Web of Science, Embase, and Cochrane Library databases was conducted to retrieve original research articles investigating the diagnostic performance of the CEUS LI-RADS algorithms using SonoVue® and/or Sonazoid®. The search terms focused on three main concepts: LI-RADS, CEUS, and HCC. Table S1 lists all the search terms used. The search was restricted to human subjects and English-language studies published from January 2016 to June 2023. Additionally, the reference lists of the included studies were manually reviewed to identify any additional relevant studies.

Eligibility criteria

To be eligible for inclusion in this meta-analysis, the articles had to meet the following inclusion criteria: (I) include patients at high risk of HCC; (II) have the full text available that could be assessed and appraised; (III) concern studies that sought to detect lesions by CEUS using SonoVue® and/

or Sonazoid®; (IV) include two-by-two tables that could be extracted to show the diagnostic efficiency of the LI-RADS for suspected liver nodules; and (V) use histopathology or imaging follow-up as the reference standards.

Articles were excluded from this meta-analysis if they met any of the following exclusion criteria: (I) examined patients with liver nodules who had already received treatment; (II) the total number of lesions examined in the study was less than 50; (III) lacked sufficient information for the pooled analysis; (IV) were duplicates or overlapping publications; and/or (V) concerned case reports, editorials, letters to the editor, reviews, or conference abstracts.

Study selection and data extraction

Two reviewers independently reviewed the articles to determine their eligibility and conducted the data extraction. A senior author was consulted if any disagreements arose.

The following information was extracted: (I) study characteristics: first author, publication year, country, medical center (single center or multi-center), study design (prospective or retrospective), study type (cohort study or case-control study), and reference standard (pathology or imaging follow-up); (II) patient characteristics: patient number, mean age, and gender; (III) lesion characteristics: number of observations and final diagnosis (HCC, non-HCC malignancy, or benign lesion); (IV) CEUS characteristics: CA (SonoVue® or Sonazoid®), LI-RADS version (ACR LI-RADS or modified LI-RADS); and (V) study outcomes: true positives (TPs), false positives (FPs), true negatives (TNs), and false negatives (FNs) for the CEUS LI-RADS. If an article contained multiple sets of diagnostic performance data (TPs, FPs, TNs, and FNs) from different reviewers, the data of the most experienced reviewer were selected for the meta-analysis if information about the reviewers' relevant clinical experience was provided; if no information was provided about the reviewers' experience, the average results were used to reduce bias.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the overall methodological quality and risk of bias of the articles by the two reviewers independently, and any disagreement was resolved by discussion. The QUADAS-2 tool includes the following four aspects: patient selection, index test, reference standard, and flow and timing.

Statistical analysis

The meta-analysis was performed using Meta-DiSc 1.4 software (Clinical Biostatistics unit, Madrid, Spain) and Stata 14.0 software (Stata Corporation, College Station, TX, USA). The threshold effect was tested by the Spearman correlation coefficient; a P value <0.05 was considered statistically significant. A bivariate random-effects model was used to determine the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and the areas under the summary receiver operating characteristic (SROC) curves, and their 95% confidence intervals (CIs). The variance of the logit-transformed percentage method was used to test the difference between the pooled sensitivity and specificity, and the Z-value test was used to test whether the areas under the SROC curves (AUCs) were significantly different between the two LI-RADS algorithms; a P value <0.05 was considered statistically significant. Cochran's Q test and the I^2 statistic were used to quantitatively assess the heterogeneity; a P value <0.1 and an I^2 value ≥50% indicated significant heterogeneity. A meta-regression analysis was conducted to explore the potential causes of heterogeneity, and a sensitivity analysis was conducted to evaluate the stability of the results. Deeks' funnel-plot asymmetry test was used in the diagnostic meta-analysis to evaluate the possible presence of publication bias when there were more than 10 studies; a P value <0.10 indicated a significant possibility of publication bias.

Results

Literature selection

Figure 1 illustrates the process employed for the literature search and study selection. The search strategy yielded 1,177 articles. After removing the duplicate articles, 852 articles remained. Among these, an additional 814 articles were excluded by screening titles and abstracts because they did not meet the inclusion criteria or met the exclusion criteria, and 38 further articles were further excluded after the full-text review. Ultimately, 26 articles were included in the meta-analysis.

Study characteristics

Table 1 summarizes the study and patient baseline characteristics of the included studies. The 26 studies comprised a total of 8,495 patients with 9,244 lesions. Of the studies, 17 used

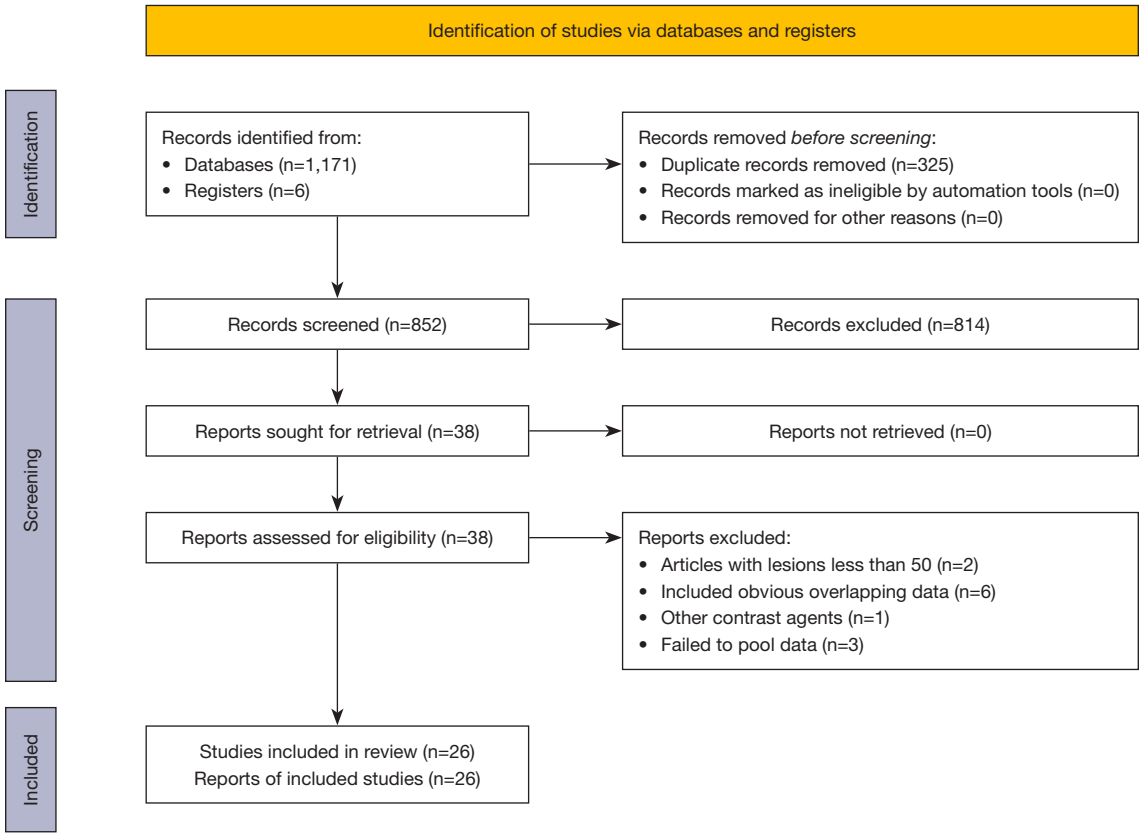

Figure 1 Literature search and study selection process.

SonoVue® as the CA (13-29), seven used Sonazoid® (30-36), and two used both SonoVue® and Sonazoid® (37,38). Three studies were prospective (13,19,38) and 23 were retrospective (14-18,20-37). Of the studies, 10 used histopathology only as the reference standard (15,16,19,21,23-25,27,30,33) and 16 used both histopathology and imaging follow-up as the reference standard (13,14,17,18,20,22,26,28,29,31,32,34-38).

Nineteen studies (13-29,37,38) with 8,178 nodules examined the diagnostic performance of SonoVue® LR-5 in detecting HCC, of which, two studies employed the 2016 version (13,14), 17 studies employed the 2017 version (15-29,37,38). One of the nine studies using Sonazoid® as the CA evaluated the diagnostic performance of Sonazoid® using the ACR LR-5 criteria and thus was not included in the further analysis. Eight studies with 1,128 nodules examined the diagnostic efficiency of Sonazoid® modified LR-5 (30-37), of which, two used version 1 and six used version 2. The detailed criteria of SonoVue® LR-5 and Sonazoid® modified LR-5 are set out in *Table 2*.

In terms of the LR-M algorithms, 15 studies (13-17,20-28,38) examined the diagnostic performance of ACR LR-M of SonoVue®. However, only three studies (30,34,35) examined the diagnostic performance of the modified LR-M in diagnosing non-HCC malignancies, and reported 457 HCCs, 45 non-HCC malignancies, and 46 benign lesions.

Diagnostic performance of the LR-5 algorithms for HCC

The Spearman correlation coefficients for SonoVue® LR-5 and Sonzaoid® modified LR-5 were 0.133 and 0.190, with P values of 0.586 and 0.651, respectively; thus, no threshold effect was found in our study. *Figure 2* shows the forest plot of the pooled sensitivity and specificity of SonoVue® LR-5 and Sonazoid® modified LR-5. The pooled sensitivity values of SonoVue® LR-5 and Sonazoid® modified LR-5 were 0.68 (95% CI: 0.64–0.73, I^2=89.20%; P<0.01) and 0.82 (95% CI: 0.74–0.87, I^2=85.39%; P<0.01) (P<0.05), respectively. The pooled specificity values of SonoVue® LR-5 and Sonazoid® modified LR-5 were 0.93 (95% CI: 0.90–0.96, I^2=86.52%; P<0.01) and 0.86 (95% CI: 0.79–0.91, I^2=59.91%; P=0.01)

Table 1 Characteristics of the included articles

Study (ref., year)	Country	Study design	Study type	Center	No. of patients	Age, y [range]	Male/female	No. of nodules	Nodule size, mm [range]*	No. of HCCs	No. of non-HCC malignancies	Benign	Contrast agent	LI-RADS	Reference standard
Schellhaas B (13) (2017)	Germany	Prospective	Cohort	Single center	100	66.1 [42–85]	85/15	100	52.2 [10–290]	87	6 [ICC]	7	SonoVue	ACR v2016	Pathology or imaging follow-up
Terzi E (14) (2018)	Italy	Retrospective	Cohort	Multi-center	848	70 [31–89]	457/391	1,006	20 [5–150]	820	53 [ICC: 40; CHC: 9; Others: 4]	133	SonoVue	ACR v2016	Pathology or imaging follow-up
Chen LD (15) (2019)	China	Retrospective	Case-control	Single center	210	55†, 54‡ [32–84]	163/47	210	NA [≤30 mm: 25; 31–50 mm: 47; >50 mm: 138]	105	105 [ICC]	0	SonoVue	ACR v2017	Pathology
Li J (16) (2019)	China	Retrospective	Cohort	Single center	1,366	52.3 [18–90]	1,097/269	1,366	47 [5–200]	985	139 [ICC: 59; CHC: 14; M: 62; Others: 4]	242	SonoVue	ACR v2017	Pathology
Zheng W (17) (2020)	China	Retrospective	Cohort	Single center	1,826	54 [44–62]	1,642/184	2,020	NA	1,514	138 [ICC: 57; CHC: 24; M: 53; Others: 4]	368	SonoVue	ACR v2017	Pathology or imaging follow-up
Wang JY (18) (2020)	China	Retrospective	Cohort	Single center	258	52 [21–82]	192/66	355	25 [6–183]	115	5 [ICC: 2; CHC: 1; Others: 2]	235	SonoVue	ACR v2017	Pathology or imaging follow-up
Zhou H (19) (2022)	China	Prospective	Cohort	Multi-center	96	58.8 [35–87]†/ 61.8 [45–79]‡	81/15	96	42.7 [9.9–169]†/ 46.3[9.8–100.0]‡	67	22	7	SonoVue	ACR v2017	Pathology
Li S (20) (2021)	China	Retrospective	Cohort	Single center	84	57.3 [26–86]	67/17	86	25.7 [5.5–96.2]	53	1 [ICC]	32	SonoVue	ACR v2017	Pathology or imaging follow-up
Huang Z (21) (2021)	China	Retrospective	Case-control	Single center	158	53 [28–75]†/ 55 [37–67]‡	143/15	158	NA	106	52 [ICC: 32; M: 10; CHC: 4; Others: 6]	0	SonoVue	ACR v2017	Pathology
Zuo DS (22) (2021)	China	Retrospective	Cohort	Single center	215	NA	151/67	218	NA	99	27 [ICC: 10; Others: 17]	92	SonoVue	ACR v2017	Pathology or imaging follow-up
Ding J (23) (2021)	China	Retrospective	Cohort	Single center	264	59.4 [26–80]	202/62	264	32 [10–95]	223	23 [ICC: 16; CHC: 3; M: 4]	18	SonoVue	ACR v2017	Pathology
Lv K (24) (2021)	China	Retrospective	Cohort	Single center	250	61.32 [24–87]	186/64	259	52.39 [6–158]	172	61	26	SonoVue	ACR v2017	Pathology
Yang D (25) (2022)	China	Retrospective	Cohort	Single center	205	52 [19–83]	162/43	205	34 [10–50]	142	26 [ICC: 13; M: 8; Others: 5]	37	SonoVue	ACR v2017	Pathology
Vidili G (26) (2022)	Italy	Retrospective	Cohort	Single center	269	69 [43–88]	219/50	511	24 [5–200]	423	29 [ICC: 23; M: 3; Others: 3]	59	SonoVue	ACR v2017	Pathology or imaging follow-up

Table 1 (*continued*)

Table 1 (*continued*)

Study (ref., year)	Country	Study design	Study type	Center	No. of patients	Age, y [range]	Male/ female	No. of nodules	Nodule size, mm [range]*	No. of HCCs	No. of non-HCC malignancies	Benign	Contrast agent	LI-RADS	Reference standard
Huang W (27) (2023)	China	Retrospective	Cohort	Single center	179	53.2 [28–80]	147/32	194	21 [9–30]	144	29 [ICC: 11; CHC: 4; M: 9; Others: 5]	21	SonoVue	ACR v2017	Pathology
Ghiuchici AM (28) (2021)	Romania	Retrospective	Cohort	Single center	382	63 [24–89]	261/121	464	46 [8–170]	359	37	68	SonoVue	ACR v2017	Pathology or imaging follow-up
Pan JM (29) (2021)	China	Retrospective	Cohort	Single center	534	NA	460/74	545	NA	503	29	13	SonoVue	ACR v2017	Pathology or imaging follow-up
Liao W (30) (2023)	China	Retrospective	Cohort	Single center	137	51 [43–58]	117/20	140	35.5 [23.8–61.3]	119	15 [ICC: 6; CHC: 3; M: 2; Others: 4]	6	Sonazoid	ACR v2017/ Modified LI-RADS	Pathology
Hwang JA (31) (2022)	Korea	Retrospective	Cohort	Multi-center	123	61.5 [21–86]	98/25	123	25 [10–130]	77	15 [ICC: 11; CHC: 2; Others: 2]	31	Sonazoid	ACR v2017/ Modified LI-RADS	Pathology or imaging follow-up
Hwang JA (32) (2021)	Korea	Retrospective	Cohort	Single center	203	61.3 [32–83]	159/44	122§	15 [7–50]	89	NA	NA	Sonazoid	ACR v2017/ Modified LI-RADS	Pathology or imaging follow-up
Li L (33) (2023)	China	Retrospective	Cohort	Single center	171	54	140/31	171	47 [9–105]	114	43	14	Sonazoid	Modified LI-RADS	Pathology
Li L (34) (2022)	China	Retrospective	Cohort	Single center	293	55	140/31	304	43 [6–158]	274	14 [ICC: 8; CHC: 1; M: 5]	16	Sonazoid	ACR v2017/ Modified LI-RADS	Pathology or imaging follow-up
SugimotoK (35) (2020)	Japan	Retrospective	Cohort	Single center	104	70.0 [54.5–78.0]	74/30	104	17.9 [13.1–28.2]	64	16 [ICC: 6; M: 9; Others: 1]	24	Sonazoid	Modified LI-RADS	Pathology or imaging follow-up
Takahashi H (36) (2022)	Japan	Retrospective	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 v2017/ Modified LI-RADS	Pathology or imaging follow-up
Huang J (37) (2023)	China	Retrospective	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 v2017/ Modified LI-RADS	Pathology or imaging follow-up
Kang HJ (38) (2020)	Korea	Prospective	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 v2017	Pathology or imaging follow-up

*, the data are presented as the mean or median value with the range in brackets; †, the data are presented as the mean values for the HCC patients; ‡, the data are presented as the mean values for the non-HCC patients; §, only 122 nodules ≥1 cm and had Sonazoid modified LI-RADS category. HCC, hepatocellular carcinoma; LI-RADS, liver imaging reporting and data system; ICC, intrahepatic cholangiocarcinoma; ACR, American College of Radiology; v2016, version 2016; CHC, combined hepatocellular cholangiocarcinoma; NA, not available; v2017, version 2017; M, metastases.

Table 2 LR-5 diagnostic criteria

Criteria	Definition
ACR CEUS LR-5	≥1 cm: APHE, late and mild washout
Modified LR-5 (version 1)	≥1 cm: APHE (not rim and not peripheral globular) and KP defect; APHE (not rim and not peripheral globular), early washout, and mild KP defect
Modified LR-5 (version 2)	≥1 cm: APHE (not rim and not peripheral globular) and KP defect

ACR, American College of Radiology; CEUS, contrast-enhanced ultrasound; LR-5, LI-RADS category 5; LI-RADS, liver imaging reporting and data system; APHE, arterial phase hyperenhancement; KP, Kupffer phase.

(P<0.05), respectively. The PLRs of SonoVue® LR-5 and Sonazoid® modified LR-5I were 9.99 (95% CI: 6.51–15.34, I^2=80.10%; P<0.01) and 5.89 (95% CI: 3.85–9.00, I^2=28.81%; P=0.01), and the NLRs were 0.34 (95% CI: 0.30–0.39, I^2=88.07%; P<0.01) and 0.21 (95% CI: 0.15–0.30, I^2=82.12%; P<0.01), respectively (Figure S1). The DORs of SonoVue® LR-5 and Sonazoid® modified LR-5 were 29.36 (95% CI: 18.05–47.74, I^2=100.00%; P<0.01) and 27.67 (95% CI: 15.40–49.70, I^2=98.43%; P<0.01), respectively (Figure S2). The AUC values of SonoVue® LR-5 and Sonazoid® modified LR-5 were 0.86 (95% CI: 0.82–0.89) and 0.91 (95% CI: 0.88–0.93), respectively (*Figure 3*). The Z value of SonoVue® LR-5 and Sonazoid® modified LR-5 was 2.057>1.96 (P<0.05).

Diagnostic performance of the LR-M algorithms for non-HCC

A meta-analysis of the ability of the LR-M algorithms to diagnose non-HCC malignancies was conducted in accordance with the above-mentioned procedure, and the results are set out in *Table 3*. The pooled sensitivity and specificity of Sonazoid® modified LR-M for non-HCC malignancies were comparable to those of SonoVue® LR-M. The area under the SROC curve values for Sonazoid® modified LR-M and SonoVue® LR-M were 0.93 and 0.93, respectively, and the Z value was 0.0481<1.96 (P>0.05); however, the difference between the LR-M algorithms for the non-HCC malignancies was not significant.

Meta-regression and sensitivity analysis

The I^2 statistics revealed that substantial heterogeneity was present in this study, and a meta-regression analysis was performed to explore the causes of heterogeneity. Among the various covariates in this study, we analyzed the study design (prospective *vs.* retrospective), the study type (cohort *vs.* case-control), the number of medical centers (single center *vs.* multi-center), the subject enrollment (consecutive *vs.* selective), the number of lesions (<100 *vs.* ≥100), the LI-RADS version (version 2016 *vs.* version 2017 for SonoVue®, and version 1 *vs.* version 2 for Sonazoid®), and the reference standard (pathology *vs.* pathology and imaging follow-up).

The meta-regression results for SonoVue® LR-5 are set out in Table S2. Among the seven covariates, the study design was the source that contributed to the heterogeneity of the sensitivity, and the subject enrollment method was the source that significantly influenced the heterogeneity of the specificity. In relation to the reference standard, the results of the meta-regression analysis showed that the sensitivity and specificity of the studies using pathology and imaging follow-up as the reference standards were significantly higher than those using only pathology as the reference standard (sensitivity: 0.70 *vs.* 0.67, P=0.01; specificity: 0.95 *vs.*0.90, P=0.01).

As all of the eight studies had retrospective designs and employed consecutive subject enrollment, four covariates were included in the meta-regression analysis, and the results are set out in Table S3. The results indicated that the number of lesions was the source that significantly influenced the heterogeneity of the specificity. However, among the included eight studies, only one study reported <100 lesions.

The sensitivity analysis was conducted by removing each study one by one, and the results (Figure S3) indicated that no single study had a significant effect on the overall pooled estimates.

Publication bias and quality assessment

Based on the results of the Deeks' funnel plot (Figure S4), no significant publication bias was observed in the literature related to SonoVue® LI-RADS (P=0.26); the funnel

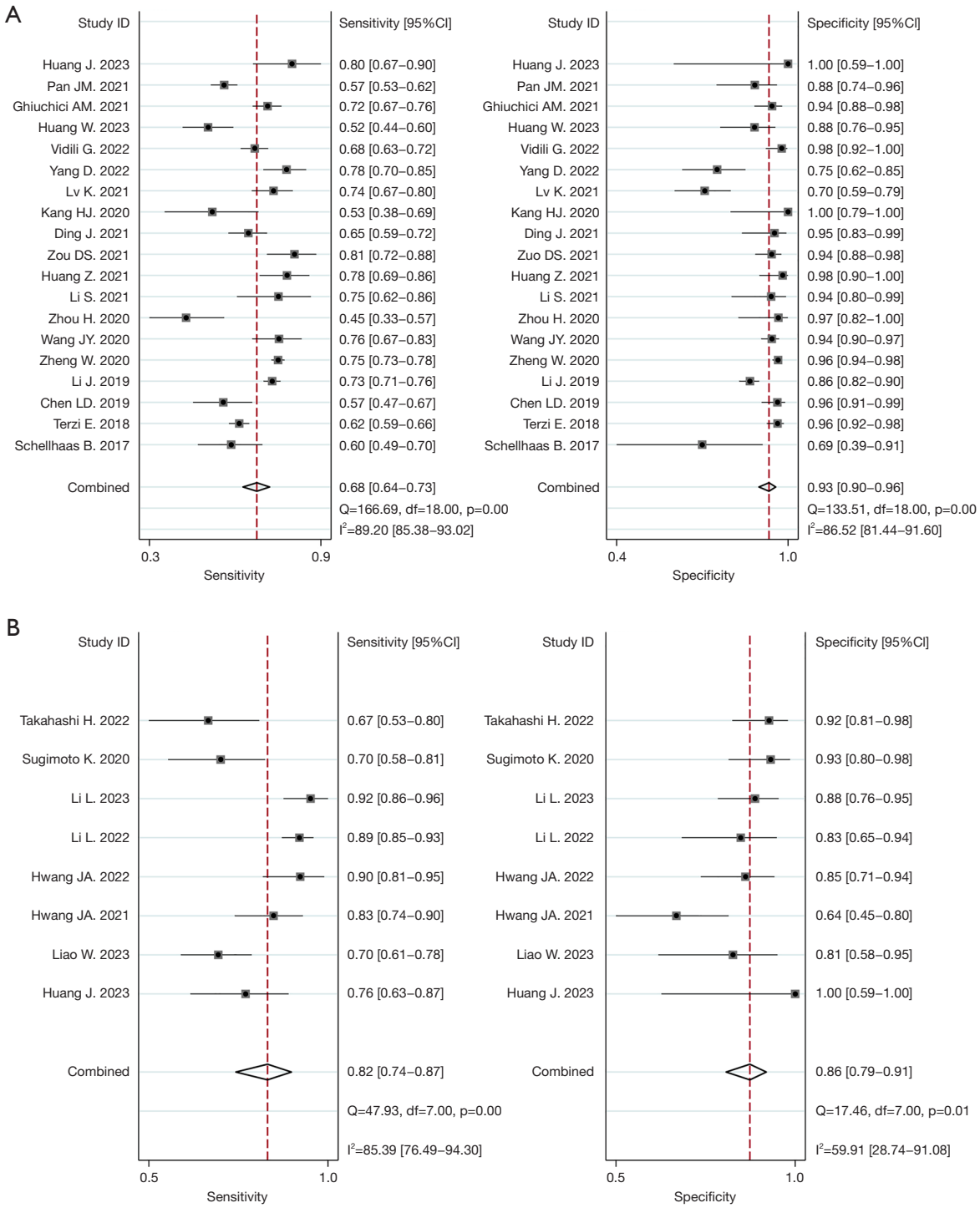

Figure 2 Forest plots of LR-5 for HCC. (A) Pooled sensitivity and specificity of the SonoVue LR-5 algorithm; (B) pooled sensitivity and specificity of the Sonazoid modified LR-5 algorithm. CI, confidence interval; LR-5, LI-RADS category 5; HCC, hepatocellular carcinoma; LI-RADS, liver imaging reporting and data system.

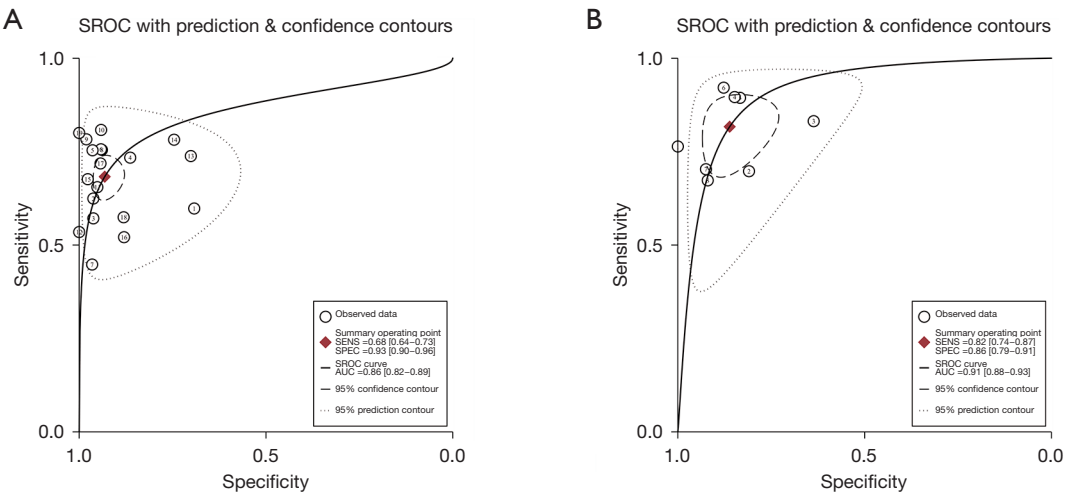

Figure 3 SROC curves of LR-5 for HCC. SROC curve of the SonoVue LR-5 algorithm (A) and Sonazoid modified LR-5 algorithm (B). SROC, summary receiver operating characteristic; SENS, sensitivity; SPEC, specificity; AUC, area under the curve; LR-5, LI-RADS category 5; HCC, hepatocellular carcinoma; LI-RADS, liver imaging reporting and data system.

Table 3 Diagnostic performance of SonoVue® LR-M and Sonazoid® modified LR-M for non-HCC malignancies

Diagnostic performance	SonoVue LR-M		Sonazoid modified LR-M	
	Value (95% CI)	I^2	Value (95% CI)	I^2
Pooled sensitivity	0.82 (0.79–0.84)	88.7%	0.89 (0.76–0.96)	70.6%
Pooled specificity	0.86 (0.86–0.87)	97.4%	0.89 (0.86–0.92)	91.1%
PLR	6.36 (4.41–9.17)	95.4%	8.13 (2.88–22.94)	91.5%
NLR	0.20 (0.12–0.33)	90.4%	0.12 (0.02–0.72)	67.2%
DOR	38.59 (19.96–74.61)	82.7%	69.99 (5.46–897.41)	79.5%

LR-M, liver imaging reporting and data system definite or probable malignancy, not specific for hepatocellular carcinoma; HCC, hepatocellular carcinoma; 95% CI, 95% confidence interval; PLR, positive likelihood value; NLR, negative likelihood value; DOR, diagnostic odds ratio.

plot for Sonazoid® LI-RADS was omitted, as there were <10 publications on Sonazoid® LI-RADS. The results concerning the overall quality of the included studies are presented in *Figure 4*. The results of the index test and reference standard domain were satisfactory. In relation to the patient selection domain, two studies had a high risk of selection bias due to their case-control study designs (15,21), and seven studies had a unclear risk, as the inclusion criteria for the nodule size was not specified (13,22,25,27,32,33,39). In relation to the flow and timing domain, the quality of the included studies was relatively low, which might be due to the use of mixed reference standards (pathology and imaging diagnosis or pathology only) and unclear the time interval between the index test(s) and reference standards.

Discussion

The ACR CEUS LI-RADS was introduced to standardize the clinical management (i.e., assessment, communication, and recommendation) of HCC based on the final classification of liver nodules in patients at risk for HCC, and it is only recommended for pure blood pool CAs such as SonoVue®. The combined blood pool and KP CA Sonazoid® is also useful for the diagnosis of hepatic nodules, and modified LI-RADS algorithms were first proposed in 2020 (35). Compared with the SonoVue® LI-RADS, research on the Sonazoid® modified LI-RADS is limited. Thus, we conducted this meta-analysis to compare the diagnostic performance of the two algorithms.

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

The CEUS LR-5 is considered the diagnostic criteria for HCC. The results of our meta-analysis showed that the Sonazoid® modified LR-5 algorithm had better diagnostic sensitivity (0.82 *vs.* 0.68, P<0.05), lower specificity (0.86 *vs.* 0.93, P<0.05), and a higher AUC (0.91 *vs.* 0.86, P<0.05) than SonoVue® LR-5. This indicated that the overall diagnostic performance of the Sonazoid® modified LR-5 algorithm was superior to that of SonoVue® LR-5, especially in detecting lesions. As both CAs provide similar enhancement in the arterial phase (40), we speculate that the difference is mainly related to the distinct performances of the two CAs in the portal/venous phase and KP. The SonoVue® LR-5 algorithm focuses on late and mild washout in the portal/venous phase, which relies on the difference in portal vein blood supply between the liver parenchyma and the tumor (6). Conversely, the Sonazoid® modified LR-5 algorithm uses the KP defect as the primary imaging feature, which is based on the difference in Kupffer cell uptake (7,40). Research has shown that 10–33% of HCCs exhibit defects in the KP phase, without showing washout in the late vascular phase (31,36,38). This may be because the decrease in Kupffer cells occurs earlier than changes in blood supply during hepatocarcinogenesis (41). Therefore, the high sensitivity of Sonazoid® modified LR-5 is beneficial for the early detection of HCC in clinical settings for patients with risk factors. In addition, SonoVue® microbubbles are prone to rupture (38), while Sonazoid® microbubbles have better stability and are more tolerant to high mechanical index and high frame rate scanning conditions (42), which enables comprehensive and long-lasting scanning of the liver to increase the ability to detect lesions (40,43). The high sensitivity of the Sonazoid® modified LI-RADS has significant advantages in clinical practice, particularly in cases in which radical resection or local therapy are more prevalent (44).

Additionally, in some western countries, diagnosis methods with high specificity are required to determine liver transplantation allocations. The LR-5 algorithm was set to specifically diagnose HCC, aiming for a specificity of 100%. Our meta-analysis indicates that SonoVue® has high specificity (0.93), which is consistent with the findings of previous studies (45), and shows the accuracy of SonoVue® LR-5 in diagnosing HCC without pathological evidence. However, the pooled specificity of Sonazoid® modified LR-5 was not desirable. The absence of Kupffer cells is one of the distinctive features of hepatic malignant lesions (46) in both HCC and non-HCC malignancies (33,38). Meanwhile, atypical hemangioma (47) and dysplastic nodules (31) might also be a diagnostic pitfall. Fortunately, as Hwang reported, the integration of gray-scale features could improve the insufficient specificity of Sonazoid® (31). Further research needs to be conducted to verify and establish a sound diagnostic standard for Sonazoid®-enhanced ultrasound.

LR-M was used as the diagnostic criteria for non-HCC malignancies. Our meta-analysis results revealed that the pooled sensitivity, specificity, and AUC of Sonazoid® modified LR-M for non-HCC malignancies were comparable to those of SonoVue® LR-M. Our SonoVue® LR-M results are consistent with the results of previous studies (48). However, the limited number of publications on Sonazoid® modified LR-M may limit its generalized value, and more research needs to be conducted in the future to verify this conclusion.

In the process of evaluating which articles were to be included in the meta-analysis, some studies were specifically included due to the limited number of studies focusing on the Sonazoid® LI-RADS. Two studies in China that included the same 34 patients were included in this meta-analysis, as they included a total of 293 and 171 patients, respectively, and thus only a small number of the patients overlapped (33,34). Another two studies from Korea with a partial time overlap were included; one (32) of which was a single-center study with a patient inclusion period of three years, and the other (31) of which was a three-center study with an inclusion period of eight years with different inclusion conditions. Both of these studies were included in the further analysis, although we failed to obtain the original data. One eligible study from Japan was ultimately removed (39) because of the inclusion overlaps with another two studies (35,36). Another point needs to be made. As there is currently no officially adopted version of the Sonazoid® LI-RADS, different researchers have made slightly different modification suggestions. Two studies (33,34) used modified LR-5 proposed by their institutions, which differed slightly from Sugimoto's criteria; they rectified the supplementary definition of modified LR-5 to no rim arterial phase hyperenhancement (APHE), early washout, and mild KP defects. The lack of a unified standard is one of the limitations of our study.

Generally, diagnostic efficacy, time efficiency, and safety are all factors influencing the choice of CA in clinical practice. Both SonoVue® and Sonazoid® have shown good safety and tolerance for liver imaging; however, individuals who are allergic to eggs need to consider the pros and cons before choosing Sonazoid® (40,49,50). It should be noted that there was a difference in the time periods during the

examination. An examination using SonoVue® that includes all three vascular phases often takes <5 minutes, while an examination using Sonazoid® usually takes >10 minutes due to the presence of the KP (40). If a CA re-injection is necessary, the difference in the examination times increases further.

Our meta-analysis had some limitations. First, there are no unified criteria for the Sonazoid® modified LR-5. Second, substantial heterogeneity was observed. Third, there was a disequilibrium of the involved studies using the two CAs. Further research needs to be conducted to decrease the inclusion bias and verify the results. Fourth, we failed to compare the diagnostic efficiency of the SonoVue modified criteria (the onset time of washout should be revised to 45 seconds), as the research in this area is limited; however, the reported results were encouraging. Finally, it should be noted that of the 26 studies included in this meta-analysis, 22 were from Asia. Thus, the results of this study should be carefully generalized to other populations.

Conclusions

In conclusion, the Sonazoid® modified LR-5 algorithm had better diagnostic sensitivity, lower specificity, and a higher AUC than SonoVue® LR-5. Given the limited number of studies focused on the Sonazoid® modified LI-RADS, these results require further verification.

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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-23-1616/rc

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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

Table S1 Literature search strategy

Database	Search strategy
Pubmed	(((CEUS) OR (contrast-enhanced ultrasound)) OR (contrast enhanced ultrasound)) AND (((((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-TIV or LR-M or LR1 or LR2 or LR3 or LR4 or LR5 or LRTIV or LRM)) AND ((HCC) OR (Carcinomas, Hepatocellular)))
Embase	1. (LI-RADS or LIRADS). tw, kw, k f. 2. (liver imaging reporting and data system). mp. 3. (LR-1 or LR-2 or LR-3 or LR-4 or LR-5 or LR-TIV or LR-M or LR1 or LR2 or LR3 or LR4 or LR5 or LRTIV or LRM). tw. 4. 1 or 2 or 3 5. exp liver cell carcinoma/ 6. exp contrast-enhanced ultrasound/ 7. (CEUS or contrast enhanced ultrasound). tw. 8. 6 or 7 9. 4 and 5 and 8
Medline	1. (LI-RADS or LIRADS). tw, kw, kf. 2. (liver imaging reporting and data system).tw,kw. 3. (LR-1 or LR-2 or LR-3 or LR-4 or LR-5 or LR-TIV or LR-M or LR1 or LR2 or LR3 or LR4 or LR5 or LRTIV or LRM). tw. 4. 1 or 2 or 3 5. Radiology Information Systems/ 6. Carcinoma, Hepatocellular/ or Cholangiocarcinoma/ 7. (hepatocellular carcinoma* or hepatocellular neoplasm* or hepatocellular cancer or hepatic cell carcinoma* or HCC or cholangiocarcinoma* or hepatic nodule* or liver lesion* or adrenocortical carcinoma*). tw, kw, kf. 8. Liver Neoplasms/dg 9. exp Liver Diseases/dg or liver disease*. tw, kw, kf. 10. Liver/dg [Diagnostic Imaging] 11. liver imaging. tw, kw. 12. 6 or 7 or 8 or 9 or 10 or 11 13. 5 and 12 14. 4 or 13 15. Ultrasonography, Doppler, Color/ 16. (CEUS or contrast enhanced ultrasound). tw, kw. 17. 15 or 16 18. 14 and 17
Web of Science	1. ((ALL=(Carcinoma, Hepatocellular)) OR ALL=(Cholangiocarcinoma)) OR ALL=(HCC) 2. (((ALL=(LI-RADS)) OR ALL=(LIRADS)) OR ALL=(liver imaging reporting and data system)) AND ALL=(LR-1 or LR-2 or LR-3 or LR-4 or LR-5 or LR-5V or LR-OM or LR-TIV or LR-M or LR1 or LR2 or LR3 or LR4 or LR5 or LR5v or LRTIV or LRM or LROM) 3. #2 AND #1 4. (((ALL=(ultrasound)) OR ALL=(CEUS)) OR ALL=(contrast-enhanced ultrasound)) OR ALL=(contrast enhanced ultrasound) 5. #4 AND #3
Cochrane Central Register of Controlled Trials	1. ('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-TIV' or 'LR-M' or 'LR1' or 'LR2' or 'LR3' or 'LR4' or 'LR5' or 'LRTIV' or 'LRM'): ab, ti, kw 2. ('Carcinoma, Hepatocellular' or 'Cholangiocarcinoma' or 'hepatocellular carcinoma*' or 'hepatocellular neoplasm*' or 'hepatocellular cancer' or 'hepatic cell carcinoma*' or HCC or cholangiocarcinoma* or 'hepatic nodule*' or 'liver lesion*' or 'liver nodule*' or 'liver neoplasm*'): ab, ti, kw 3. ('CEUS' or 'contrast enhanced ultrasound' or 'contrast-enhanced ultrasound'): ab, ti, kw 4. 1 and 2 and 3 5. publication year from 2016 to 2023

HCC, hepatocellular carcinoma; LI-RADS, liver imaging reporting and data system; CEUS, contrast-enhanced ultrasound.

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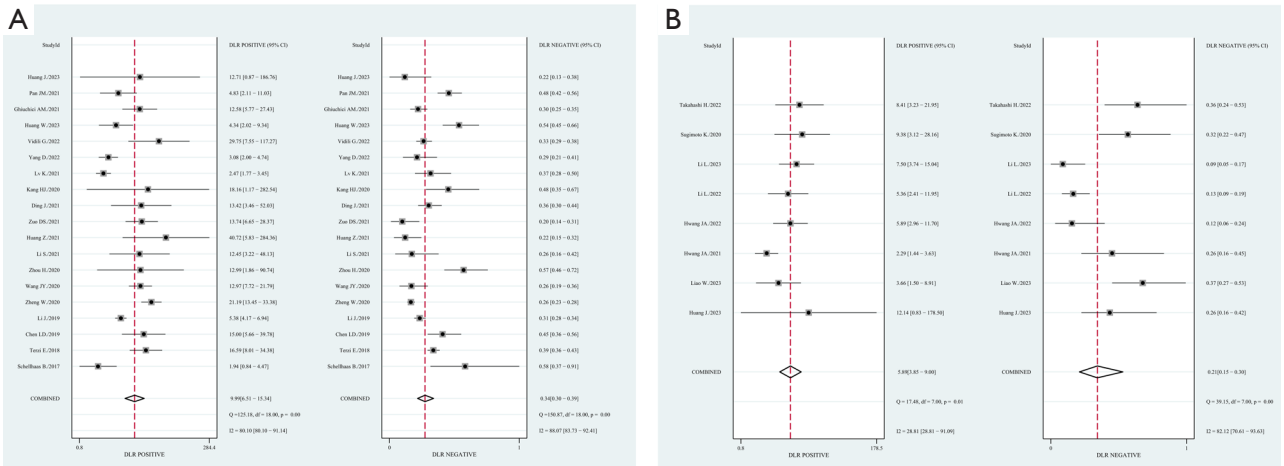

Figure S1 Forest plots of LR-5 for HCC. (A) Pooled +LR and –LR of the SonoVue LR-5 algorithm. (B) Pooled +LR and –LR of the Sonazoid modified LR-5 algorithm. LR-5, LI-RADS category 5; HCC, hepatocellular carcinoma; +LR, positive likelihood ratio; –LR, negative likelihood ratio; LI-RADS, liver imaging reporting and data system.

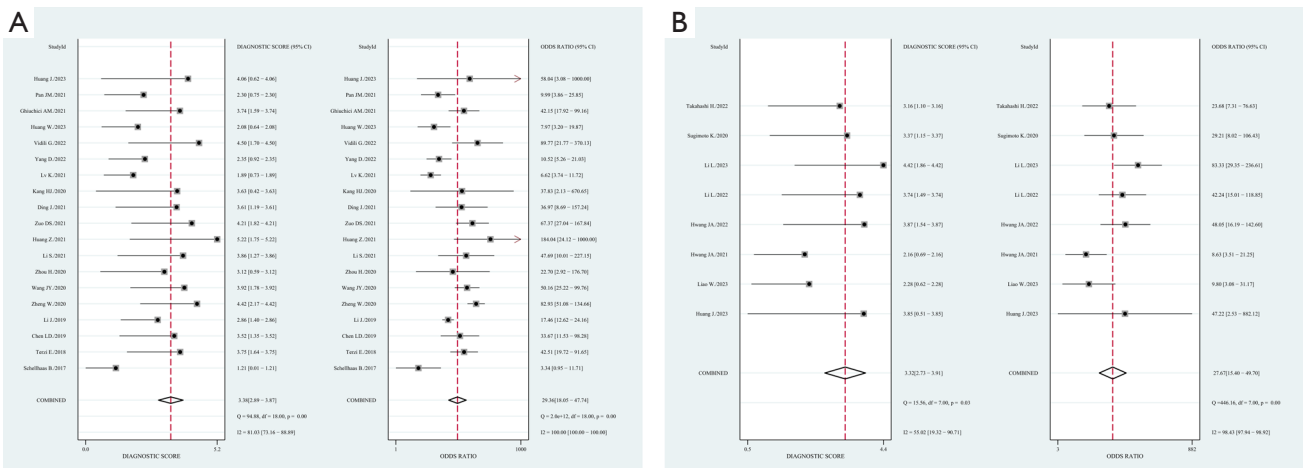

Figure S2 Forest plots of LR-5 for HCC. (A) Pooled DOR of the SonoVue LR-5 algorithm. (B) Pooled DOR of the Sonazoid modified LR-5 algorithm. LR-5, LI-RADS category 5; HCC, hepatocellular carcinoma; DOR, diagnostic odds ratio; LI-RADS, liver imaging reporting and data system.

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Table S2 Results of the meta-regression analysis of SonoVue LR-5 for the detection of HCC

Covariates	Subgroup	Studies (n)	Meta-analysis summary estimates of SonoVue LR-5			
			Sensitivity (95% CI)	P	Specificity (95% CI)	P
Study design	Prospective	3	0.53 (0.41–0.65)	<0.01	0.93 (0.83–1.00)	0.34
	Retrospective	16	0.70 (0.66–0.74)		0.93 (0.90–0.96)	
Study type	Cohort	17	0.68 (0.64–0.73)	0.15	0.92 (0.89–0.96)	0.69
	Case-control	2	0.68 (0.55–0.82)		0.97 (0.93–1.00)	
Center	Multi-center	3	0.63 (0.52–0.75)	0.24	0.92 (0.84–1.00)	0.18
	Single center	16	0.69 (0.65–0.74)		0.93 (0.90–0.96)	
Subject enrollment*	Consecutive	16	0.69 (0.64–0.74)	0.16	0.93 (0.90–0.96)	0.04
	Selective	2	0.68 (0.54–0.83)		0.97 (0.93- 1.00)	
Lesions	<100	4	0.64 (0.53–0.75)	0.19	0.97 (0.94–1.00)	0.05
	≥100	15	0.69 (0.64–0.74)		0.92 (0.89–0.96)	
LI-RADS version	v2016	2	0.62 (0.47–0.76)	0.51	0.91 (0.79–1.00)	0.73
	v2017	17	0.69 (0.65–0.74)		0.93 (0.90–0.96)	
Reference standard	Pathology	8	0.67 (0.60–0.73)	0.01	0.90 (0.85–0.95)	0.01
	Pathology and imaging follow-up	11	0.70 (0.64–0.75)		0.95 (0.92–0.97)	

*, the study conducted by Schellhaas et.al did not explicitly mention the subject enrollment method employed and was thus excluded from the meta-analysis. LR-5, LI-RADS category 5; HCC, hepatocellular carcinoma; CI, confidence interval; LI-RADS, liver imaging reporting and data system; v2016, version 2016; v2017, version 2017.

Table S3 Results of the meta-regression analysis of Sonazoid modified LR-5 for the detection of HCC

Covariates	Subgroup	Studies (n)	Meta-analysis summary estimates of Sonazoid modified LR-5			
			Sensitivity (95% CI)	P	Specificity (95% CI)	P
Center	Multi-center	1	0.90 (0.78–1.00)	0.08	0.85 (0.69–1.00)	0.51
	Single center	7	0.80 (0.73–0.87)		0.86 (0.80–0.93)	
Lesions	<100	1	0.77 (0.54–1.00)	0.31	1.00 (1.00–1.00)	<0.01
	≥100	7	0.82 (0.75–0.89)		0.85 (0.79–0.92)	
LI-RADS version	Version 1	2	0.90 (0.86–0.95)	0.18	0.87 (0.76–0.92)	0.15
	Version 2	6	0.77 (0.71–0.82)		0.86 (0.79–0.93)	
Reference standard	Pathology	2	0.83 (0.71–0.95)	0.12	0.86 (0.75–0.98)	0.17
	Pathology and imaging follow-up	6	0.81 (0.73–0.89)		0.86 (0.79–0.93)	

LR-5, LI-RADS category 5; HCC, hepatocellular carcinoma; CI, confidence interval; LI-RADS, liver imaging reporting and data system.

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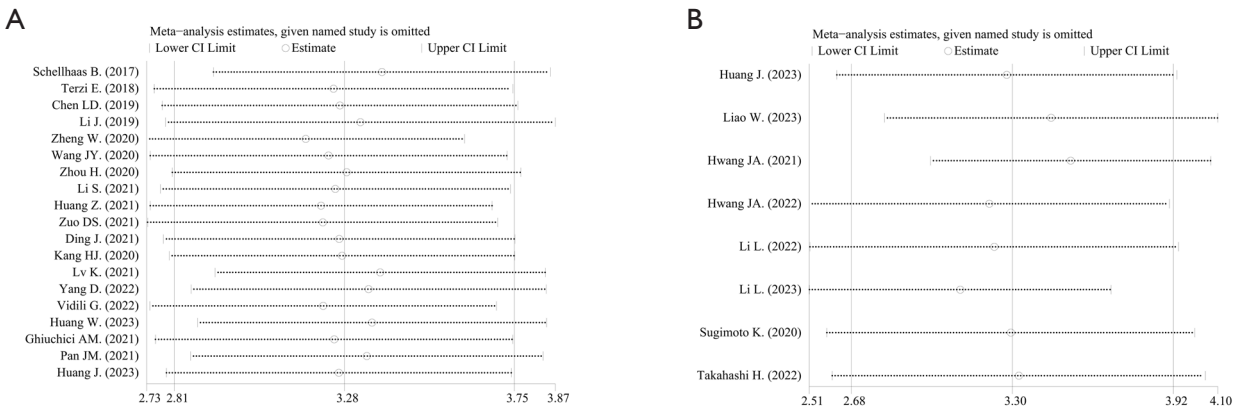

Figure S3 Results of the sensitivity analysis of the SonoVue LR-5 and Sonazoid modified LR-5 algorithms. (A) Sonazoid LR-5 algorithm and (B) Sonazoid modified LR-5 algorithm. LR-5, LI-RADS category 5; LI-RADS, Liver Imaging Reporting and Data System.

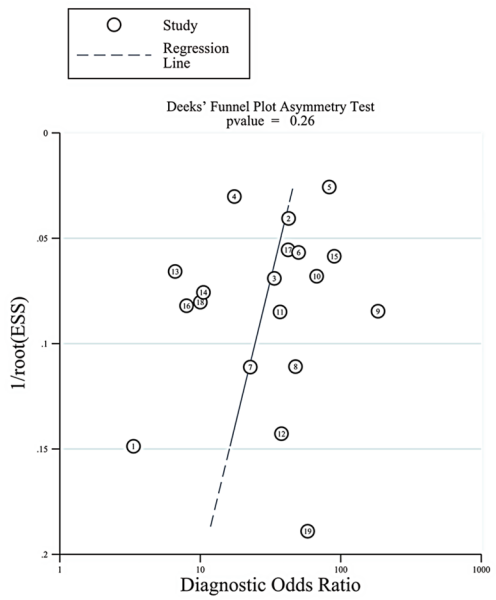

Figure S4 Results of the publication bias and quality assessment. (A) Deeks' funnel plot of SonoVue LR-5. (B) Deeks' funnel plot of Sonazoid modified LR-5. ESS, effective sample sizes; LR-5, LI-RADS category 5; LI-RADS, liver Imaging Reporting and Data System.

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