Original Article

Compared with CT/MRI LI-RADS, whether CEUS LI-RADS is worth popularizing in diagnosis of hepatocellular carcinoma?—a direct head-to-head meta-analysis

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Background: Until now, there has been no systematic review or meta-analysis of direct head-to-head studies that compare two liver imaging reporting and data system (LI-RADS) algorithms, contrast-enhanced ultrasound (CEUS) LI-RADS and contrast-enhanced computed tomography/magnetic resonance imaging (CT/MRI) LI-RADS, for the diagnostic efficacy of hepatocellular carcinoma. The purpose of this study was to identify and head-to-head compare the diagnostic performance of both LI-RADS algorithms for hepatocellular carcinoma.

Methods: We searched the PubMed, EMBASE, Web of Science, and Cochrane Library databases from the inception of each database to April 26, 2022, to find the comparative study of both LI-RADS algorithms for hepatocellular carcinoma at risk of patients who underwent both LI-RADS algorithms. Eligibility criteria included only studies published in English, full reports published, both retrospective and prospective studies. Liver histology or imaging follow-up results served as the reference standard. We analyzed the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and summary receiver operating characteristic curve to determine summary estimates. The Quality Assessment of Diagnostic Accuracy Studies was utilized to assess the methodological quality.

Results: In 5 included studies (831 patients, 877 lesions), the pooled sensitivity and pooled specificity of CEUS LR-5 were 0.79, 0.81, and 0.78, 0.79 in CT/MRI LR-5, respectively. The pooled sensitivity and pooled specificity of CEUS LR-4/5 were 0.86, 0.70, and 0.93, 0.59 in CT/MRI LR-4/5, respectively. There was no obvious difference between the two LI-RADS algorithms for hepatocellular carcinoma, and there was no significant statistical difference between two LR-M algorithms for non-hepatocellular carcinoma malignancies.

Conclusions: The results of our analysis demonstrated that CEUS LI-RADS has satisfactory diagnostic performance similar to that of CT/MRI LI-RADS, which provides a theoretical basis for the popularization of CEUS LI-RADS for diagnosing HCC. This work was supported by Sichuan Science and Technology Program (No. 2020YFS0211). We registered this study on the international prospective register of systematic reviews (PROSPERO, CRD42022328107) before the search step.

Keywords: Meta-analysis; contrast-enhanced ultrasound liver imaging reporting and data system (CEUS LI-RADS); hepatocellular carcinoma (HCC); diagnostic performance; contrast-enhanced computed tomography/magnetic resonance imaging liver imaging reporting and data system (CT/MRI LI-RADS)

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Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and ranks third in mortality worldwide (1). It can be clinically diagnosed without histopathological confirmation by analyzing the typical imaging manifestations of contrast-enhanced computed tomography (CECT) or contrast-enhanced magnetic resonance imaging (CEMRI), such as arterial phase enhancement, portal venous phase and/or delayed phase washout. For patients who are at the high risk of HCC, early detection and surveillance are particularly important.

However, significant differences in image interpretation and reporting hinder the correct diagnosis of HCC. The CT/MRI liver imaging reporting and data system (LI-RADS) is an imaging and reporting diagnostic tool for patients who are at risk of HCC, which was first presented in 2011. It assigns a probability of HCC, benign or non-HCC malignancies to liver nodules based on specific criteria. With the application of CT/MRI LI-RADS in clinical practice, the specific criteria of CT/MRI LI-RADS has drawn much attention and has been updated for several times. Contrast-enhanced ultrasound (CEUS) is a first-line method for HCC in Europe and Asia, and it has been recognized by several national and international professional societies (2,3). American College of Radiology (ACR) released CEUS LI-RADS in 2016, and updated it in 2017. At present, CECT, CEMRI, and CEUS are the three most widely used diagnostic modalities for HCC (4).

Regrettably, the performance of CEUS in diagnosing HCC remains controversial. Due to the possibility of misdiagnosis, the HCC guidelines of American Association for the Study of Liver Diseases (5) did not include CEUS as a diagnostic technique for HCC. In clinical practice and research, CEUS plays an important role in the diagnosis of HCC with application for more than ten years. Especially with the emergence of CEUS LI-RADS, some studies (6,7) pointed out that CEUS LI-RADS has a significant diagnostic performance equivalent to that of CT/MRI LI-RADS for diagnosing non-HCC malignancies in high-risk patients. Several studies (8,9) have indirectly compared the diagnostic performance of the two diagnostic algorithms (CEUS LI-RADS and CT/MRI LI-RADS were compared with pathology separately) and indicated CEUS LI-RADS is qualified to characterize HCC and non-HCC malignancies. Up till now, there has been no systematic review or meta-analysis using head-to-head comparisons to evaluate both algorithms in patients who are at risk of HCC. There is an urgent need for direct comparison of the two diagnostic methods to confirm whether CEUS LI-RADS is worthy of popularization. At the base of the reasons, our study aimed to explore the best evidence-based recommendations for application of the two diagnostic algorithms where possible by systematic literature retrieval. In this meta-analysis, the diagnostic efficacy of CEUS LI-RADS and CT/MRI LI-RADS was head-to-head compared in patients who were at risk of HCC and underwent both LI-RADS-based algorithms. We present this article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1383/rc) (10).

Methods

Study protocol and search strategy

The protocol of this systematic review is available on the PROSPERO database. We searched PubMed, Web of Science, Embase, and the Cochrane Library databases. The MeSH terms and key words used in the search included 'Carcinomas, Hepatocellular', 'liver imaging reporting and data system' or 'LI-RADS' or 'LIRADS'. The range of search date was from the inception of each database to April 26, 2022.

Study selection and data extraction

The inclusion criteria were as follows: (I) only studies published in English; (II) full reports in the published literature; (III) both retrospective and prospective articles; (IV) adult patients who were at risk of HCC (risk factors for HCC were defined according to the guidelines of the American Association for the Study of Liver Diseases (5), including chronic hepatitis B virus (HBV) and HBV-related

cirrhosis); (V) lesions detected by both CEUS and CT/MRI and have been investigated by both LI-RADS algorithms. LI-RADS algorithm categorizes lesions into well-defined benign (LR-1), probably benign (LR-2), intermediate malignancy probability (LR-3), probably HCC (LR-4), definitely HCC (LR-5), as well as probably or definitely malignant but not HCC specific (LR-M) and definite tumor in vein (LR-TIV) (11). (VI) The reference standard for HCC include pathological diagnosis (biopsy, surgical pathology) or at least 6 months of imaging follow-up; (VII) the values (TP: true-positive, FP: false-positive, TN: true-negative, FN: false-negative) of both LI-RADS-based algorithms for diagnosing HCC could be simultaneously extracted either directly or indirectly. The exclusion criteria were as follows: (I) liver cancer patients who had undergone treatment; (II) the number of lesions would be greater than 3; (III) case reports, review articles, editorials, letters, erratum, comments, and conference abstracts. Articles with duplicate publication were removed. There are two authors reviewing the titles and abstracts of the remaining publication. In accordance with the inclusion and exclusion criteria, the full text of the included abstracts was searched and read to determine whether or not inclusion by the same two reviewers independently. We also searched the reference lists of the included articles and relevant reviews to identify additional studies. Disagreements regarding study selection were resolved by consensus.

The following information was extracted: (I) study characteristics, including the first author's name, year of publication, type of the study (prospective or retrospective), country, and reference standard; (II) characteristics of the study population, including the number of participants, mean age, gender, and influential risk factors; (III) characteristics of lesions, such as lesion size, total number of lesions, and final diagnosis (HCC, non-HCC malignancies, benign); (IV) characteristics of the imaging modalities, including instrumental information, contrast agent (type and dose), and LI-RADS version; and (V) study outcomes, such as the values of TP, FP, TN, and FN for HCC. Two reviewers independently collected data from reports, and they shall be reconciled by consensus when there are disagreements regarding data extraction.

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (12) was utilized to evaluate the risk of bias and concern for applicability of each study in four areas: patient selection, index test, reference standard, and flow and timing. Two reviewers independently conducted the quality assessment and coordinated to resolve any differences.

Statistical analysis

The LR-5 criteria included LR-5, and LR-TIV in this study. The meta-analysis was conducted using Meta-Disc software (Clinical Biostatistics unit, Madrid, Spain, version 1.4). Threshold effect was estimated by analyzing the Spearman correlation coefficient. It was considered significant if $P<0.05$. Heterogeneity was quantitatively assessed using the Chi-squared test and I^2 statistic, and $P<0.1$ and $I^2 \geq 50\%$ indicated a significant heterogeneity. A fixed-effects model or a random-effects model was used for analysis based on the heterogeneity. The unit of assessment is the number of lesion. The effect size was measured in terms of pooled sensitivity, pooled specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with their 95% confidence intervals. Forest plots and summary receiver operating characteristic (sROC) curves were used to summarize the data. Furthermore, Z-value test was performed to test whether the area under the curve (AUC) values were significantly different between two LI-RADS algorithms, and statistical significance was achieved if $P<0.05$. To trace the source of heterogeneity, meta-regression analysis was carried out according to different factors, such as country, sample size (number of patients <50 *vs.* that ≥50), and tumor size (visible on medical imaging *vs.* ≤3 cm). In order to evaluate the stability of the results of the meta-analysis, our study also undertook sensitivity analysis by removing individual studies one by one.

Egger's test was used to evaluate publication bias, by the Stata 14.0 software (Stata Corporation, College Station, TX, USA), and $P<0.05$ was set as the threshold for statistical significance.

Results

Study characteristics and evaluation

Figure 1 illustrated the process of the literature research. According to the search strategy, the total number of retrieved articles was 1,789. The number was reduced to 39 by removing duplicate articles and scanning the titles and abstracts. Of the 39 full text articles reviewed, 5 head-to-head articles (13-17), which met the eligibility criteria, were included in this meta-analysis.

The characteristics of the included studies are summarized in *Tables 1,2*. In addition, 5 studies comprised the data of 831 patients, including a total of 877 nodules with 667 HCC malignancies, 91 non-HCC malignancies, and

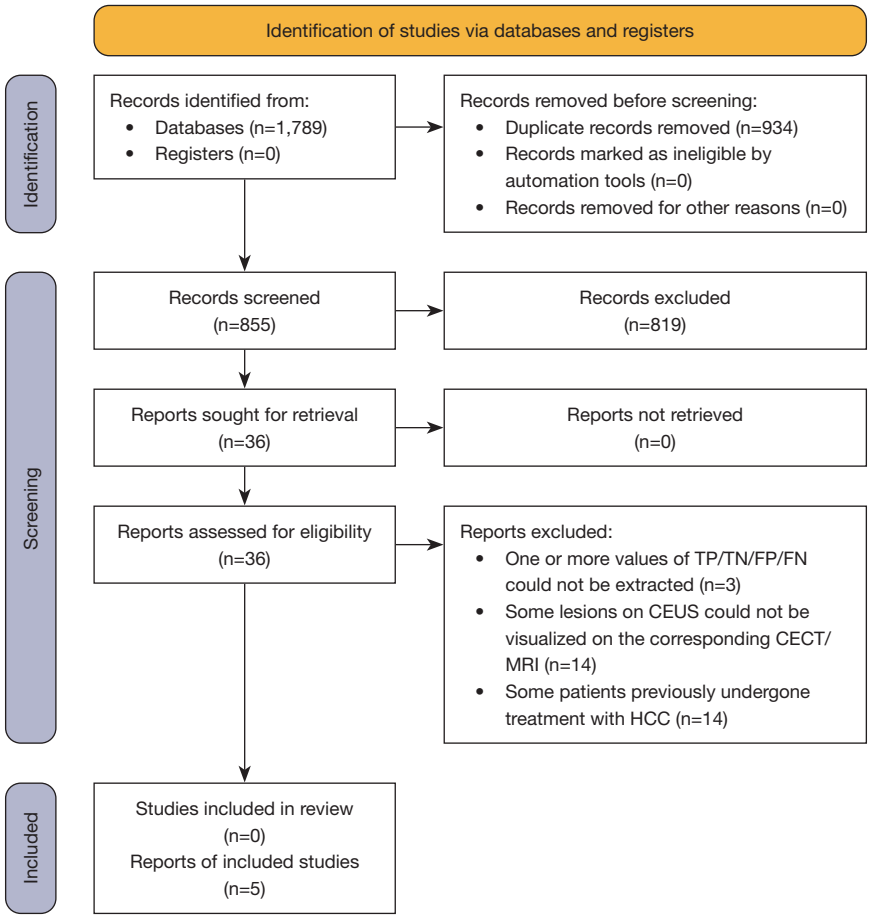

Figure 1 Selection process of eligible studies. TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative; CECT/MRI, contrast-enhanced computed tomography/magnetic resonance imaging; CEUS, contrast-enhanced ultrasound; HCC, hepatocellular carcinoma.

119 benign lesions. There was an obvious male prevalence (76.7%). All the 5 included studies were single-center and retrospective. The CEUS LI-RADS (2017 version) was used in all the 5 included studies. The CT/MRI 2017 version was used in 1 study, and CT/MRI LI-RADS 2018 version in 4 studies. For CEMRI, the strength field was 1.5–3.0 T. Only CEUS and CEMRI were compared in Li *et al.*'s study (17). Zhou *et al.*'s study (13) included only lesions less than or equal to 3 cm (measured on CT/MRI), and other studies included visible lesions on medical imaging. Only 6 patients were injected with Sonazoid (GE Healthcare, Waukesha, WI, USA) as an ultrasound contrast agent in Tan *et al.*'s study (15), and information from the post-vascular Kupffer phase for Sonazoid was not involved in the analysis. Other patients were injected with SonoVue in CEUS. Of the 5 included studies, 4 studies were conducted in China with number of patients ≥50, and 1 study in Singapore (15) with number of patients <50. The year of publication of the included studies ranged from 2020 to 2022.

Proportions of HCC and non-HCC malignancies in both LI-RADS algorithms

The values of TP, FN, FP, and TN in each modality are shown in *Table 3*. A total of 667 HCC were included in the study. The proportion of HCC gradually increased as the probability of HCC increases in two LI-RADS algorithms categories. No HCC was classified as CEUS LR-1 and LR-2. In all included lesions, only one of HCC was classified as CT/MRI LR-2 (15). In CEUS LR-3, -4, and -5, the proportions of HCC were 24.2%, 57.3%, and 93.1%, while those in CT/MRI LR-3, -4, and -5 were 60.3%, 70.2%, and 93.6%, respectively. It can be seen that the proportion of CEUS LR-3 was lower than that of CT/MRI LR-3 (24.2%

Table 1 Characteristics of included studies

Study (ref.)	Country	Study design	Age (year, mean ± SD)	No. of pts (M/F)	No. of nodules	No. of HCC/non-HCC	No. of benign lesions	Study time	Tumor size (cm, mean ± SD)	CEUS LI-RADS version	CT/MRI LI-RADS version	Reference standard	Prevailing risk factor (number)
Zhou *et al.* (13), 2022	China	Retrospective	58.3±7.9	213 (170/43)	213	180/8	25	Unknown	CT/MRI: 2.0±0.58	2017	2018	Pathology	Hepatitis B virus: 185; hepatitis C virus: 16; alcohol: 6; other: 6
Ding *et al.* (14), 2021	China	Retrospective	59.1±8.0	239 (182/57)	273	225/22	26	Jun 2017 to Jan 2019	CEUS: 3.07±1.94; CT/MRI: 2.85±1.89	2017	2017	Pathology	Hepatitis B virus: 195; hepatitis C virus: 20; alcohol: 9; autoimmune hepatitis: 8; other causes: 7
Tan *et al.* (15), 2020	Singapore	Retrospective	63.1	45 (32/13)	46	37/0	9	Jul 2010 to Apr 2017	HCC: 2.5; non-HCC: 1.4	2017	2018	Pathology or follow-up imaging	Alcohol: 4; hepatitis B virus: 28; hepatitis C virus: 6; non-alcoholic steatohepatitis: 4; idiopathic 3
Lv *et al.* (16), 2021	China	Retrospective	61.32±10.76	250 (186/64)	259	172/61	26	Jun 2017 to Jun 2020	CEUS: 5.24±3.35; CT/MRI: 5.15±3.1	2017	2018	Pathology	Unknown
Li *et al.* (17), 2021	China	Retrospective	57.3±12.4	84 (67/17)	86	53/0	33	Jan 2014 to Dec 2018	2.57±1.68	2017	2018	Pathology or follow-up imaging	Unknown

pts, patients; M/F, male/female; HCC, hepatocellular carcinoma; CEUS LIRADS, comparing contrast-enhanced ultrasound liver imaging reporting and data system; CT/MRI LI-RADS, contrast-enhanced computed tomography/magnetic resonance liver imaging reporting and data system imaging.

vs. 60.3%). In CEUS LI-RADS, the majority of HCC were in LR-5 (78.7%). Most of the rest HCC were distributed in LR-M (12%) and LR-4 (7.0%). Similarly, the majority of HCC in CT/MRI LI-RADS were in LR-5 (77.7%). Moreover, 5.7%, 14.8%, and 1.6% of the remaining HCC were distributed in CT/MRI LR-3, -4, and -M, respectively. The proportions of HCC in both LR-4/5 algorithms were 85.8% and 92.5%, respectively.

There were more lesions assigned as CEUS LR-M than CT/MRI LR-M (153 *vs.* 73). The proportion of HCC in CEUS LR-M was 52.3%, higher than that in CT/MRI LR-M (15.1%). Accordingly, the proportion of non-HCC malignancies in CEUS LR-M was lower than that in CT/MRI LR-M (39.9% *vs.* 75.3%, P<0.05). No non-HCC malignancy was classified as CEUS and CT/MRI LR-1, -2.

Diagnostic analysis of LR-5 for HCC

No threshold effect of LR-5 was identified for the two indices (P=1.0 in CEUS; P=0.39 in CT/MRI). The pooled sensitivity, pooled specificity, and diagnostic odds ratio (DOR) of both LR-5 algorithms for detecting HCC are presented in *Figure 2A*,*2B*. The pooled sensitivity values of CEUS and CT/MRI were 0.79 and 0.78, respectively, without a significant difference in sensitivity of both LR-5 algorithms. The pooled specificity values were 0.81 and 0.79, respectively, without a significant difference in specificity of both LR-5 algorithms. The DORs of CEUS and CT/MRI were 28.98 and 15.18, respectively. The positive predictive values (PPVs) of CEUS and CT/MRI were 7.66 and 3.62, respectively. The negative predictive values (NPVs) of CEUS and CT/MRI were 0.25 and 0.31, respectively.

The specificity of CEUS (P<0.01, I^2=86.9%), PPV of CEUS (P<0.01, I^2=85.2%), sensitivity of CT/MRI (P<0.01, I^2=89.8%), and NPV of CT/MRI (P<0.01, I^2=89.0%) demonstrated a significant heterogeneity. Meta-regression analysis of the results, shown in Table S1, suggested that country/sample size and tumor size were not the sources of heterogeneity. Sensitivity analysis was carried out by removing individual studies one by one, and the result (Figure S1) indicated that no single study had a significant effect on the overall pooled estimates.

In addition, sROC analysis was used to compare the performance of the both noninvasive diagnostic modalities (*Figure 2C*). The AUC values of CEUS and CT/MRI were 0.877 and 0.866, respectively. The Q* indices of two LR-5 algorithms were 0.807 and 0.797, respectively. The Z value of CEUS LR-5 and CT/MRI LR-5 was 0.4472<1.96,

Table 2 imaging modality characteristics of included studies

Study (ref.)	CEUS			CEMRI			CECT		
	Instrument	Type of contrast agent	Dose of contrast agent	Instrument	Type of contrast agent	Dose of contrast agent	Instrument	Type of contrast agent	Dose of contrast agent
Zhou *et al.* (13), 2022	Philips EPIQ 7, Siemens Acuson S3000	SonoVue	1.2 to 2.0 mL	3.0 T	Primovist	1.0 mL/s	Somatom Definition Flash	Iohexol	1.2 mL/kg, 3.5 mL/s
Ding *et al.* (14), 2021	Philips EPIQ 7, Siemens Acuson S3000	SonoVue	1.2 to 2.0 mL	3.0 T	Primovist, EOB-DTPA	0.025 mmol/kg (1.0 mL/s)	Somatom Definition Flash	Iohexol	1.2 mL/kg, 3.5 mL/s
Tan *et al.* (15), 2020	GE LOGIQ E9, Aplio 500	SonoVue, Sonazoid	Standard recommended dosage	1.5 T	Gadoterate meglumine, gadopentetate dimeglumine, gadoxetate disodium	Standard recommended dosage	Aquilion Canon Medical Systems	Iohexol, Iopamidol	350 mgI/mL, 3–4 mL/s; 370 mgI/mL, 3–4 mL/s
Lv *et al.* (16), 2021	Mindray Resona-7	SonoVue	2.4 mL	3.0 T	Gd-DTPA	10 mL (0.1 mmol/kg)	Somatom Definition Flash	Iohexol	350 mgI/mL
Li *et al.* (17), 2021	Philips IU22, EPIQ 5; GE LOGIQ E9	SonoVue	1.5–2.4 mL	3.0 T	Gd-DTPA	0.2 mL/kg (3 mL/s)	N/A	N/A	N/A

CEUS, contrast-enhanced ultrasound; CEMRI, contrast-enhanced magnetic resonance imaging; CECT, contrast-enhanced computed tomography; EOB-DTPA, ethoxybenzyl diethylenetriamine pentaacetic acid; Gd-DTPA, gadolinium diethylenetriamine pentaacetic acid; N/A, not available.

P>0.05, without a significant difference between two LR-5 algorithms.

Diagnostic analysis of LR4/5 for HCC

Meta-analysis of LR-4 and LR-5 for diagnosing HCC was performed following the above-mentioned procedure. No threshold effect of CEUS and CT/MRI LR-4/5 was identified for the two indices (P=0.391 in CEUS; P=0.188 in CT/MRI). *Figure 3A,3B* showed the pooled sensitivity, pooled specificity, and DOR of two LR-4/5 algorithms. The PPVs of CEUS and CT/MRI LR-4/5 were 2.74 and 2.28, respectively. The NPVs of CEUS and CT/MRI LR-4/5 were 0.21 and 0.15, respectively. The diagnostic indices of CT/MRI showed heterogeneity. The results of regression (Table S2) and sensitivity analyses (Figure S2) indicated no source of heterogeneity. No significant difference was found between the sensitivity and specificity of two LR-4/5 algorithms for diagnosing HCC. The results of sROC analysis for both LR4/5 algorithms in the diagnosis of HCC are illustrated in *Figure 3C*. The AUC values of CEUS and CT/MRI were 0.877 and 0.903, respectively. The Q* indices of two LR-4/5 algorithms were 0.807 and 0.835, respectively. The Z value of both LR4/5 algorithms was 0.4798<1.96, P>0.05, without a significant difference between both LR4/5 algorithms.

Diagnostic analysis of LR-M for non-HCC malignancies

Table 4 showed the diagnostic performance of two LR-M algorithms for non-HCC malignancies. The pooled specificity in CT/MRI LR-M was 0.98, which was higher than that in CEUS LR-M (0.88). The pooled sensitivity in CT/MRI LR-M (0.6) was similar to that in CEUS LR-M (0.67). The AUC values of CEUS and CT/MRI were 0.9218 and 0.4982, respectively. The Q* indices of two LR-M algorithms were 0.8554 and 0.4986, respectively. The SE (AUC) values of CEUS and CT/MRI were 0.0271 and 0.2688, respectively. The SE (Q*) values of CEUS and CT/MRI were 0.0313 and 0.2016, respectively. The Z value of two LR-M algorithms was 1.57 <1.96, P>0.05, without a significant difference between both LR-M algorithms for non-HCC malignancies.

Publication bias and quality assessment

According to the results of the Egger's test, there was no

Table 3 The values used for meta-analysis in each study

LI-RADS	Zhou *et al.* (13), 2022	Ding *et al.* (14), 2021	Tan *et al.* (15), 2020	Lv *et al.* (16), 2021	Li *et al.* (17), 2021
CEUS LR-5					
TP	140	170	32	143	40
FP	3	3	0	31	2
FN	40	55	5	29	13
TN	30	45	9	56	31
CT/MRI LR-5					
TP	129	188	15	147	39
FP	8	8	1	24	3
FN	51	37	22	25	14
TN	25	40	8	63	30
CEUS LR-4/5					
TP	154	185	36	151	46
FP	14	13	1	29	7
FN	26	40	1	21	7
TN	19	35	8	58	26
CT/MRI LR-4/5					
TP	171	211	22	165	48
FP	22	20	1	36	7
FN	9	14	15	7	5
TN	11	28	8	51	26

TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative; CEUS, contrast-enhanced ultrasound; CT/MRI, contrast-enhanced computed tomography/magnetic resonance.

significant publication bias (P>0.05), and the results are shown in *Figure 4A*. As for the methodological quality of the included studies (*Figure 4B*), the results were satisfactory, but "Flow and Timing" had a relatively low quality, which was due to the relatively low quality of the answers to "Was there an appropriate interval between index test(s) and reference standard?" in the included studies.

Discussion

Imaging manifestations exert important function in the diagnosis, management and surveillance of HCC (18). CT/MRI LI-RADS was proposed to provide standardization for both assessment and communicating the imaging observations in patients who are at risk of HCC (19). With the wildly application of CEUS in clinical practice, an official CEUS LI-RADS was released in 2016 (20). Two latest versions, CEUS LI-RADS (2017 version) and CT/MRI LI-RADS (2018 version) have been proposed. Both LI-RADS algorithms assign lesions to different categories according to major and ancillary imaging features. According to the LI-RADS system, the untreated and non-pathological lesions confirmed high-risk for HCC are assigned LR-NC, LR-1–5, LR-M, and LR-TIV. Compared with CT/MRI LI-RADS, CEUS LI-RADS has not been broadly utilized. In the present study, we performed the first systematic head-to-head, direct comparison of the two diagnostic algorithms.

LR-4 indicates a high probability for HCC, and LR-5 indicates that the lesion can be confirmed as HCC by imaging findings (19). Our meta-analysis results revealed that when diagnosing HCC, LR-5 and LR-4/5 of both LI-RADS algorithms maintained a satisfactory diagnostic efficiency with high values of sensitivity. Our results also

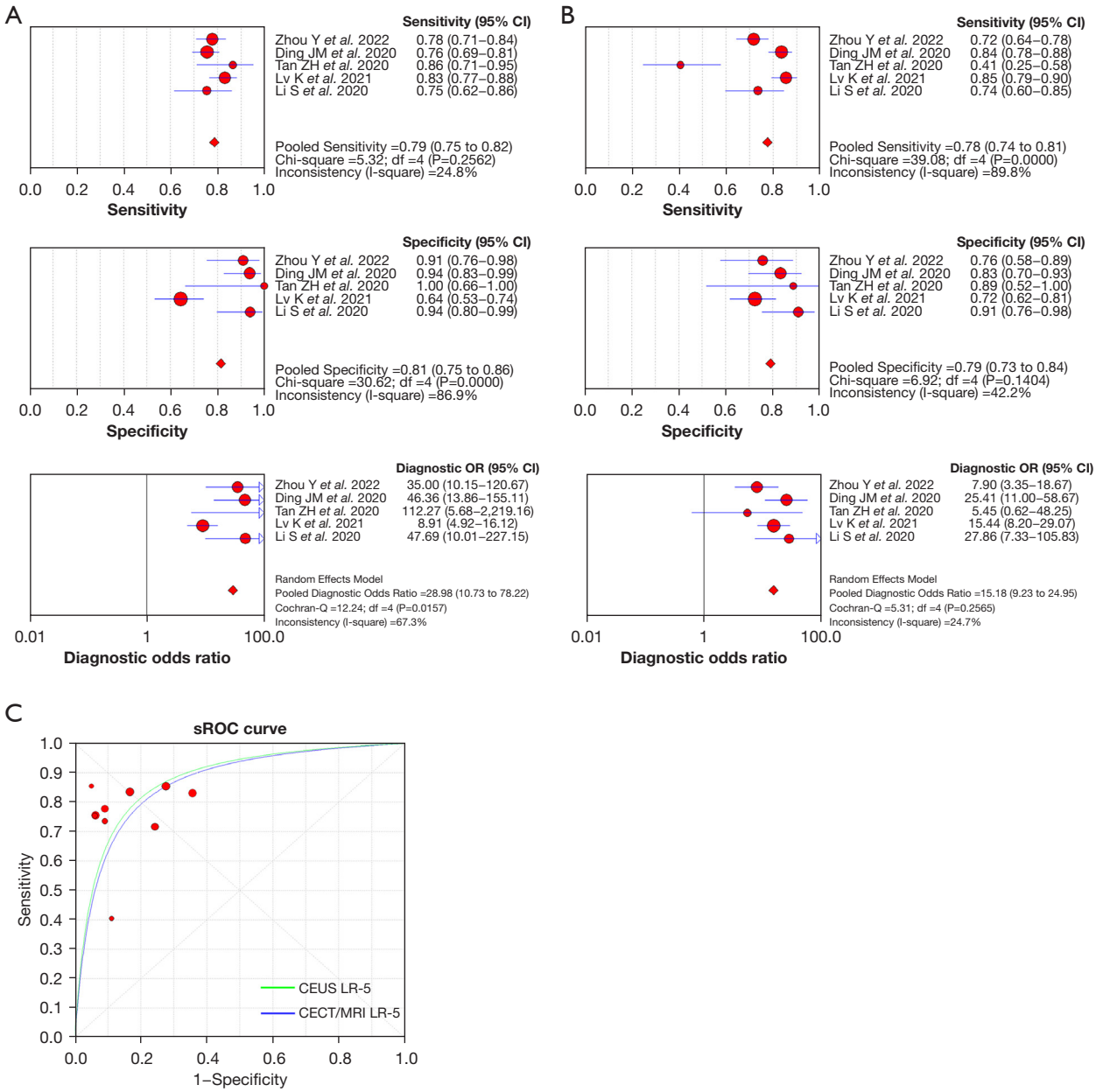

Figure 2 Forest plots and sROC curves of LR-5. (A) Pooled sensitivity, pooled specificity, and DORs of CEUS LR-5; (B) pooled sensitivity, pooled specificity, and DORs of CT/MRI LR-5. (C) sROC curve of CEUS LR-5 and CT/MRI LR-5. CEUS LR-5: AUC =0.8769, SE(AUC) =0.0183, Q* =0.8073, SE(Q*) =0.0183. CT/MRI LR-5: AUC =0.8659, SE(AUC) =0.0246, Q* =0.7965, SE(Q*) =0.0240. sROC, summary receiver operating characteristic; DOR, diagnostic odds ratio; CT/MRI, computed tomography/magnetic resonance imaging; CEUS, contrast-enhanced ultrasound; AUC, area under the curve; SE, standard error.

demonstrated that LR-4/5 and LR-5 of CEUS showed the higher specificity than that of CT/MRI (0.70 versus 0.59; 0.81 versus 0.79, respectively), which could be related to the different scanning methods, imaging principles, and type of contrast agent between CEUS and CT/MRI (4,21,22). We speculated that the differences may be due to SonoVue-enhanced ultrasound having an advantage over CECT/MRI in delineating artery phase contrast of HCC (23), especially in LR4/5. The LR-5 category of both LI-RADS algorithms showed a higher specificity, while the LR-4/5

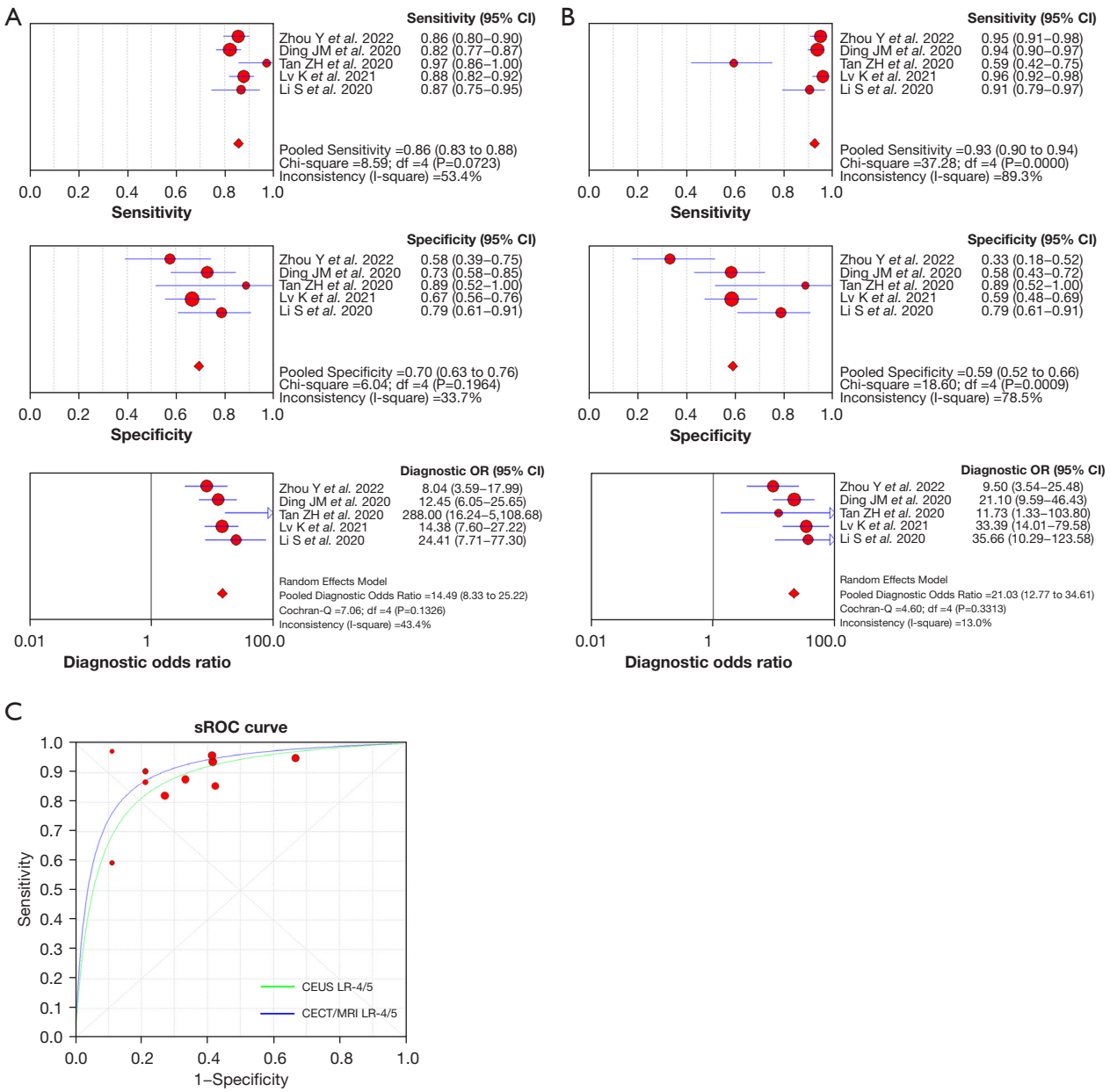

Figure 3 Forest plots and sROC curves of LR-4/5. (A) Pooled sensitivity, pooled specificity, and DORs of CEUS LR-4/5; (B) pooled sensitivity, pooled specificity, and DORs of CT/MRI LR-4/5. (C) sROC curve of CEUS LR-5 and CT/MRI LR-4/5. CEUS LR-4/5: AUC =0.8765, SE(AUC) =0.0422, Q* =0.8069, SE(Q*) =0.0423. CT/MRI LR-4/5: AUC =0.9033, SE(AUC) =0.0366, Q* =0.8347, SE(Q*) =0.0396. sROC, summary receiver operating characteristic; DOR, diagnostic odds ratio; CT/MRI, computed tomography/magnetic resonance imaging; CEUS, contrast-enhanced ultrasound; AUC, area under the curve; SE, standard error.

category exhibited a greater sensitivity, without a significant difference between two LI-RADS algorithms. Both LI-RADS algorithms rely on major and ancillary imaging features. In terms of the main diagnostic criteria, CEUS can provide a more accurate assessment of arterial phase hyperenhancement (APHE) over CT/MRI (24,25). Some lesions without APHE on CT/MRI would escalate from LR-3 to LR-4 or from LR-4 to LR-5 through CEUS. CEUS holds some advantages on washout appearance (26). Lesions assigned LR-3 or LR-4 on CT/MRI can also be

Table 4 Diagnostic performance of CEUS and CT/MRI LR-M for non-HCC malignancies

Diagnostic performance	CEUS		CT/MRI	
	(95% CI)	I^2	(95% CI)	I^2
Pooled sensitivity	0.67 (0.56 to 0.76)	67.80%	0.6 (0.50 to 0.70)	0.00%
Pooled specificity	0.88 (0.86 to 0.9)	58.70%	0.98 (0.96 to 0.99)	82%
PLR	6.0 (4.65 to 7.74)	11.70%	27.43 (8.42 to 89.32)	57.80%
NLR	0.31 (0.12 to 0.75)	57.50%	0.41(0.32 to 0.53)	0.00%
DOR	21.85 (7.49 to 63.68)	40.60%	83.51 (21.18 to 329.23)	44.10%

CEUS, contrast-enhanced ultrasound; CT/MRI, computed tomography/magnetic resonance imaging; HCC, hepatocellular carcinoma; LR-M, liver imaging reporting and data system definite or probable malignancy, not specific for hepatocellular carcinoma; PLR, positive likelihood value; NLR, negative likelihood value; DOR, diagnostic odds ratio; 95% CI, 95% confidence intervals.

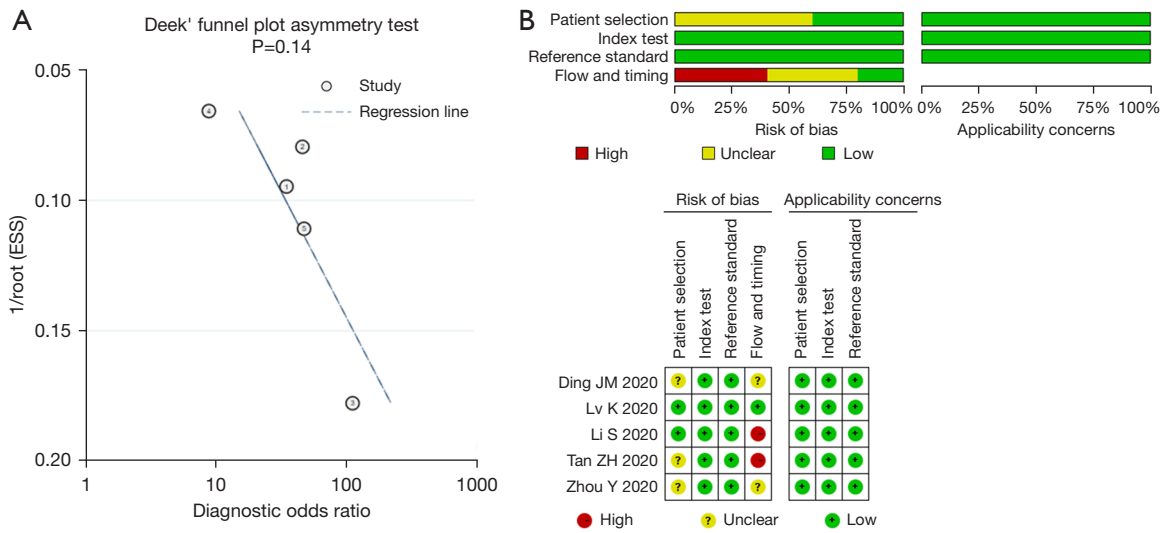

Figure 4 The results of publication bias and quality assessment. (A) Deeks' funnel plot of the publication bias summary for meta-analysis of the diagnostic odds ratio; (B) methodological quality of the studies included (QUADAS-2 results). ESS, effective sample size.

reclassified to LR-5 if APHE occurs on CEUS, so as to avoid biopsy. A previous study (14) has shown that regrade of lesions classified as LR-3 and LR-4 on CT/MRI by CEUS may lead to an accurate diagnosis. Threshold growth and an enhancing capsule are considered as less important in CEUS than in CT/MRI (27,28). Ancillary features can upgrade or downgrade the LI-RADS category. Some studies (24,29) concentrated on the contribution of CEUS to accurately define indeterminate observations. These findings suggested that CEUS LI-RADS can be applicable for diagnosing patients with HCC, and can also be used as an examination method after CT/MRI to identify lesions as definite benign or definite HCC. Moreover, CEUS possesses other advantages. CECT and CEMRI only can display static frames at various time points after contrast injection, while CEUS provides a consecutive, real-time assessment of lesion's behavior. CEUS is also more appropriate for patients who are claustrophobic for CT/MRI or contraindicated for contrast agents in CT/MRI.

LR-M indicates lesions may or must be malignant, rather than necessarily HCC. In our study, we found that more lesions were classified into CEUS LR-M than CT/MRI LR-M (153 *vs.* 73). This difference might be caused by discrepancies in the diagnostic criteria between two LI-RADS algorithms. In CEUS LI-RADS, lesions should be classified as LR-M if lesions exhibit rim APHE or early (<60 s) or significant washout within the first two minutes (19). LR-M in CT/MRI LI-RADS is assigned when lesions

were presented as a targetoid morphology or other features including infiltrative appearance, significant restriction of diffusion, necrosis or severe ischemia (30). The proportion of HCC in CEUS LR-M was higher than that in CT/MRI LR-M (52.3% *vs.* 15.1%), while the proportion of non-HCC malignancies in CEUS LR-M was lower than that in CT/MRI LR-M (39.9% *vs.* 75.3%). At present, lesions have the same recommended management in both of LR-M algorithms. The proportion of HCC in CEUS LR-M is higher, while the proportion of non-HCC malignancies is lower, indicating that more patients can be included in the biopsy to avoid missed diagnosis of malignant lesions. Additionally, the proportion of HCC in CEUS LR-3 was lower than that in CT/MRI LR-3 in this study, demonstrating that accurate assignment of nodules to the CEUS LR-3 categories requires an in-depth familiarity with CEUS LI-RADS.

In the process of screening articles, some articles were excluded. Schellhaas *et al.*'s study (31), which concentrated on the observer agreement of the two algorithms, was excluded due to the lack of enough data for the better observer. Wang *et al.*'s study (32), which compared CEUS LI-RADS with CEMRI LI-RADS, and Hwang *et al.*'s study (33) were both excluded due to incomplete data. Sugimoto *et al.*'s study (34), which compared Sonazoid-based CEUS LI-RADS with CT/MRI LI-RADS, was also excluded due to the use of Sonazoid and the inclusion of information from the post-vascular Kupffer phase. Sonazoid, a Kupffer cell-specific contrast agent, shows the unique property of accumulation in the liver and spleen. Studies (35-37) have shown that with the employment of both the vascular and late phases, Sonazoid can improve the diagnostic ability of HCC. A meta-analysis conducted by Yang *et al.* (38) indicated that Sonazoid-enhanced ultrasound exhibited a significantly improved diagnostic efficiency compared with CEUS for HCC. At present, in addition to the guidelines of Japan Society of Hepatology (JSH) and Asian Pacific Association for the Study of the Liver (APASL) guidelines, Sonazoid is also recommended for use in 2022 Korean Liver Cancer Association-National Cancer Center (KLCA-NCC) Korea Practice Guideline for management of HCC (39,40). With the improvement of the modified CEUS LI-RADS criteria for Sonazoid, Sonazoid-enhanced ultrasound must play a greater role in the diagnosis of HCC.

In the present study, for the first time, direct head-to-head comparisons of the diagnostic performance between both LI-RADS algorithms for HCC were performed. Due to the strict inclusion criteria of this study (lesions have been investigated by both CEUS and CT/MRI), 5 high-quality research articles, which were published in English and presented data of 831 cases with 877 HCC lesions, were brought into our study with a small publication bias. Because it contained studies that undertook a head-to-head comparison of samples within the same study, confounding factors were removed. The results of this study can realistically reflect the diagnostic performance of both LI-RADS algorithms, which is advantageous for the promotion of CEUS in clinical practice. In addition, with the continuous improvement and extensive practice of CEUS, CEUS LI-RADS can exert significant clinical value. Several limitations of this study should be pointed out. First, all the included studies are retrospective, and we could not include a sufficient number of studies, which might contribute to unconscious bias and limit the ability to detect meaningful differences. Second, 4 of the 5 eligible studies were proceeded in China, where HBV is the major risk of HCC. However, chronic hepatitis C virus and nonalcoholic steatohepatitis are more frequent in European and Western countries. Demographic factors and territories may contribute to some differences in the performance of both LI-RADS algorithms across populations with different risk factors. Third, although meta-regression analysis was performed in this study, we failed to find source of heterogeneity. In addition, the operator-dependency of CEUS and limited sonic window are considerable issues. In future work, various measures are needed to strengthen the cultivation and construction of the sonographer.

Conclusions

This study revealed that the diagnostic value of both LI-RADS algorithms for diagnosing HCC was similar, suggesting that both LI-RADS algorithms could play a vital role in the diagnosis of HCC. Although further studies regarding survival benefit and cost-effectiveness are warranted to clarify the benefits of CEUS as a surveillance tool of HCC in high-risk patients, it is concluded that with the continuous verification by the next multi-center, large-scale studies and the feedback of clinical summaries, CEUS LI-RADS can be popularized for diagnosing HCC worldwide.

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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-22-1383/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1383/coif). WL reports that this work was supported by Sichuan Science and Technology Program (No. 2020YFS0211). The other 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

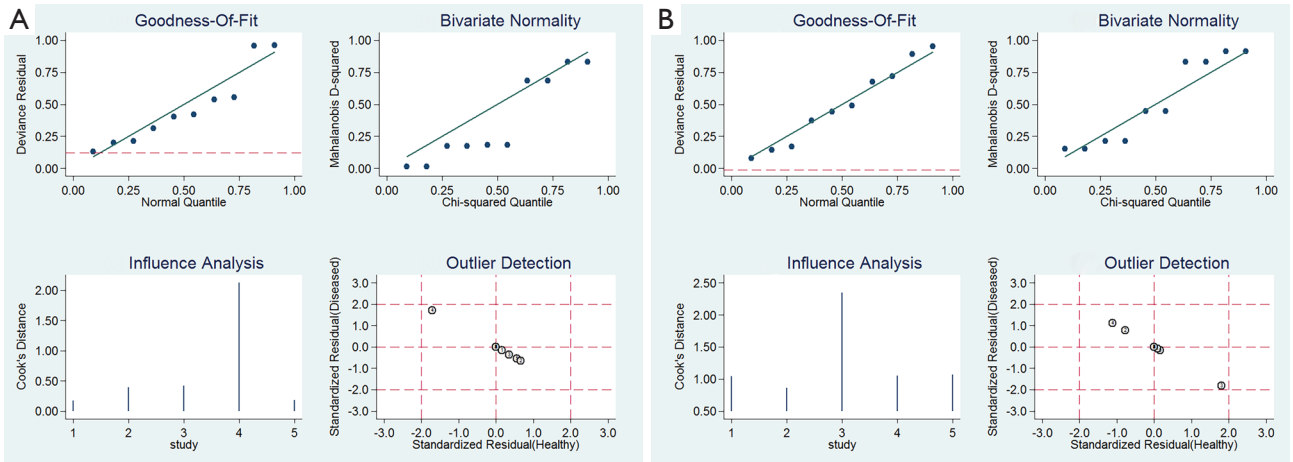

Figure S1 The result of the sensitivity analysis of LR-5. (A) CEUS LR-5; (B) CT/MRI LR-5. CEUS, contrast-enhanced ultrasound. CT/MRI, computed tomography/magnetic resonance imaging.

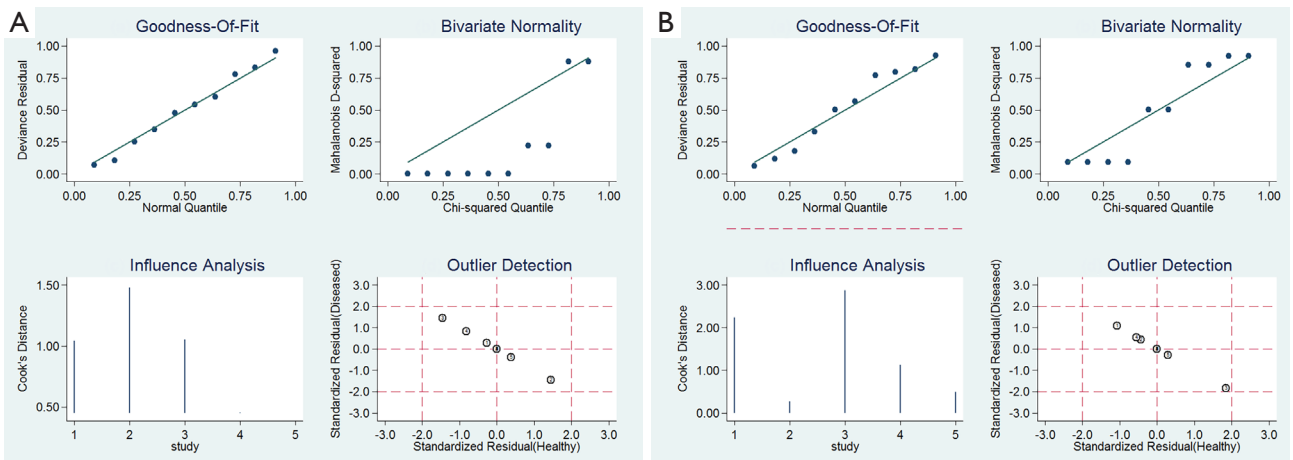

Figure S2 The result of the sensitivity analysis of LR-4/5. (A) CEUS LR-4/5; (B) CT/MRI LR-4/5. CEUS, contrast-enhanced ultrasound. CT/MRI, computed tomography/magnetic resonance imaging.

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Table S1 Results of meta-regression analysis of CEUS and CT/MRI LR-5

Variable	CEUS LR-5				CT/MRI LR-5			
	P	Std.Err	95% CI	RDOR	P	Std.Err	95% CI	RDOR
Country/sample size	0.8345	3.4492	0.00-1229161.46	0.44	0.8271	1.1396	0.01-101.52	0.75
Tumor size	0.9826	0.7355	0.04-24.11	1.02	0.2377	0.5081	0.26-20.74	2.33

CEUS, contrast-enhanced ultrasound; CT/MRI, computed tomography/magnetic resonance imaging; 95% CI, 95% confidence interval; RDOR, relative diagnostic odds ratios.

Table S2 Results of meta-regression analysis of CEUS and CT/MRI LR-4/5

Variable	CEUS LR-4/5				CT/MRI LR-4/5			
	P	Std.Err	95% CI	RDOR	P	Std.Err	95% CI	RDOR
Country/sample size	0.6593	0.4557	0.18-8.98	1.26	0.304	0.5332	0.21-20.5	2.08
Tumor size	0.2932	0.5755	0.19-26.83	2.26	0.2192	0.6787	0.18-61.54	3.32

CEUS, contrast-enhanced ultrasound; CT/MRI, computed tomography/magnetic resonance imaging; 95% CI, 95% confidence interval; RDOR, relative diagnostic odds ratios.

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