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ORIGINAL ARTICLE

Contrast-enhanced US for characterization of focal liver lesions: a comprehensive meta-analysis

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Abstract

Objectives This meta-analysis was performed to evaluate the accuracy of contrast-enhanced ultrasound (CEUS) in differentiating malignant from benign focal liver lesions (FLLs).

Methods Cochrane Library, PubMed and Web of Science databases were systematically searched and checked for studies using CEUS in characterization of FLLs. Data necessary to construct 2×2 contingency tables were extracted from included studies. The QUADAS tool was utilized to assess the methodologic quality of the studies. Meta-analysis included data pooling, subgroup analyses, meta-regression and investigation of publication bias was comprehensively performed.

Results Fifty-seven studies were included in this meta-analysis and the overall diagnostic accuracy in characterization of FLLs was as follows: pooled sensitivity, 0.92 (95%CI: 0.91–0.93); pooled specificity, 0.87 (95%CI: 0.86–0.88); diagnostic odds ratio, 104.20 (95%CI: 70.42–154.16). Subgroup analysis indicated higher diagnostic accuracy of the second-generation contrast agents (CAs) than the first-generation CA (Levovist; DOR: 118.27 vs. 62.78). Furthermore, Sonazoid demonstrated the highest diagnostic accuracy among three major CAs (SonoVue, Levovist and Sonazoid; DOR: 118.82 vs. 62.78 vs. 227.39). No potential publication bias was observed of the included studies.

Conclusion CEUS is an accurate tool to stratify the risk of malignancy in FLLs. The second-generation CAs, especially Sonazoid may greatly improve diagnostic performance.

Key Points

- *CEUS shows excellent diagnostic accuracy in differentiating malignant from benign FLLs.*
- *The second-generation CAs have higher diagnostic accuracy than first-generation CAs.*
- *Sonazoid demonstrates the highest diagnostic accuracy among three major CAs.*

Keywords Ultrasonography · Contrast media · Liver neoplasms · Diagnosis · Meta-analysis

Abbreviations

CEUS	Contrast-enhanced ultrasound
FLLs	Focal liver lesions
CAs	Contrast agents
CA	Contrast agent
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
TP	True positive
TN	True negative
FP	False positive
FN	False negative
DOR	Diagnostic odds ratio
PLR	Positive likelihood ratio
NLR	Negative likelihood ratio
CIs	Confidence intervals

Menglin Wu and Liang Li are co-first authors.

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HSROC	Hierarchical summary receiver operating characteristic
AUC	Area under the curve
RDOR	Relative diagnostic odds ratio
UL	Upper limit
LL	Lower limit
HCCs	Hepatocellular carcinomas
RES	Reticuloendothelial system

Introduction

Accurate diagnosis focal liver lesions (FLLs) remains a dilemma [1, 2], whereas it is essential with regards to intervention and prognosis [3, 4]. The introduction of contrast-enhanced ultrasound (CEUS) with gas-filled microbubbles serving as contrast agents (CAs) has dramatically improved the characterization of FLLs when compared with conventional US (either B-mode or Doppler ultrasound) [5, 6].

All currently commercially available ultrasound CAs consist of an inert gas encapsulated by a shell molecule. The low-solubility gas component determines the major acoustic properties, while the shell mainly affects the stability and durability in blood [7, 8]. When employing an intravenous ultrasound contrast agent, CEUS makes it possible to observe the hemodynamic process in real-time. Advanced low mechanical index technologies along with sophisticated software provide high-resolution real-time contrast-specific imaging for detecting macro- and micro-vascularization in lesions [9]. Almost all malignancies show a contrast wash-out feature in the delayed phase compared to normal liver tissue; reversely benign lesions are typically iso- or hyper-enhancing. Consequently, many clinical studies have proved that CEUS is useful for characterization of FLLs based on the above characteristics [1, 10].

The US Food and Drug Administration finally approved the application of CEUS with SonoVue under the name of Lumason for liver examination in 2016 after years of off-label usage [11]. This license might result in a possible breakthrough in the field of CEUS study. Hence, we carry out a meta-analysis to present the diagnostic value of CEUS in the work-up of FLLs through summarizing the studies so far in order to give related researchers some reference. Additionally, there is a wide variety of contrast agents in the healthcare market, and sonographers are facing numerous choices. As there are still no comparative studies among different CAs published to date, CA selection was often done without any guidance from relevant theories. Therefore, the other aim of our study is to explore the diagnosis performances of different CAs, and then to offer a certain theoretical foundation for clinical practice.

Materials and methods

The systematic review was conducted according to the recommendations of the PRISMA guidelines.

Literature search

A comprehensive search was performed to identify suitable diagnostic studies from electronic databases (the Cochrane Library, PubMed and Web of Science) up to February 10th, 2017. The search terms used in this meta-analysis were as follows: (focal liver lesions OR FLL OR hepatocellular carcinoma OR cholangiocarcinoma OR metastatic hepatic carcinoma OR liver metastases OR liver tumor OR hepatic haemangioma OR focal nodular hyperplasia OR liver adenoma OR liver abscess OR liver neoplasms [Mesh]) AND (contrast-enhanced ultrasound OR contrast-enhanced US OR CEUS). The search had no language restriction, but only full articles written in English were further evaluated. The references of relevant reviews were also manually searched and screened to identify eligible studies.

Two reviewers selected eligible studies independently with disagreements resolved by consensus. The following inclusion criteria were utilized to recognize eligible studies: (1) human patients with suspected FLLs; (2) studies evaluated by CEUS in the differential diagnosis of FLLs; (3) only per-lesion or per-patient statistics had sufficient data to construct a diagnostic table (2×2 table); (4) each study consisted of at least 20 samples; (5) final diagnosis confirmed by histological or close clinical diagnosis with imaging follow-up for at least 6 months; (6) full articles were available and written in English.

Studies were excluded if: (1) types of literature such as reviews, letters, meta-analyses, case reports or editorial articles; (2) fewer than 20 patients; (3) could not provide sufficient data for diagnostic meta-analysis; (4) with FLLs after treatment. When data were presented in more than one study by the same authors, either the most recently published studies or the study with the largest sample size was included.

Data extraction

All selected studies were screened by two reviewers to retrieve the following data: first author's name, publication year, country of origin, the number of patients, the number of lesions, average age, gender ratio, final diagnosis standard, final diagnosis (the specific disease types and quantities), the number of benign and malignant lesions, average lesion size, CA, true

positive (TP), true negative (TN), false positive (FP) and false negative (FN).

Methodology quality assessment

The quality of eligible studies was evaluated by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool by the same reviewers who performed data extraction. Fourteen items (maximum score 14) were included to assess the overall quality of each study.

Statistical analysis

The estimates including sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), negative likelihood ratio (NLR) with corresponding 95% confidence intervals (CIs) are summarized for graphically represent the diagnostic value of CEUS in differentiating malignant from benign lesions in FLLs. Afterwards, the hierarchical summary receiver operating characteristic (HSROC) curve and the area under the curve (AUC) were calculated. The heterogeneity across the studies was assessed by a chi-square test and Q statistic. The random effects model (the DerSimonian Laird method) would be utilized if the heterogeneity was significant ($P_{heterogeneity} < 0.05$ or $I^2 \geq 50\%$); otherwise, the fixed effects model (the Mantel–Haenszel method) would be used. The Spearman correlation coefficient was used to investigate the threshold effect. Subgroup analysis and meta-regression analysis were also utilized to further explore the potential sources of heterogeneity. Bias in publication was tested by funnel plots. All statistical analyses were performed by Meta-Disc (version 1.4) and STATA (version 13.1).

Results

Study identification and selection

The initial databases search with the above strategy yielded a total of 4579 potentially relevant studies (29 from the Cochrane Library, 2642 from PubMed and 1908 from Web of Science). After 311 duplicated studies were deleted, 4268 potential studies remained. 4025 studies were further excluded according to the inclusion criteria by screening the titles and abstracts, and the remaining 243 studies were left for full text review. In accordance with the inclusion criteria, a further 186 records were excluded due to various reasons (seen in Fig. 1), leaving 57 eligible [1, 10, 12–66] studies selected in this meta-analysis. The detailed flow chart is shown in Fig. 1.

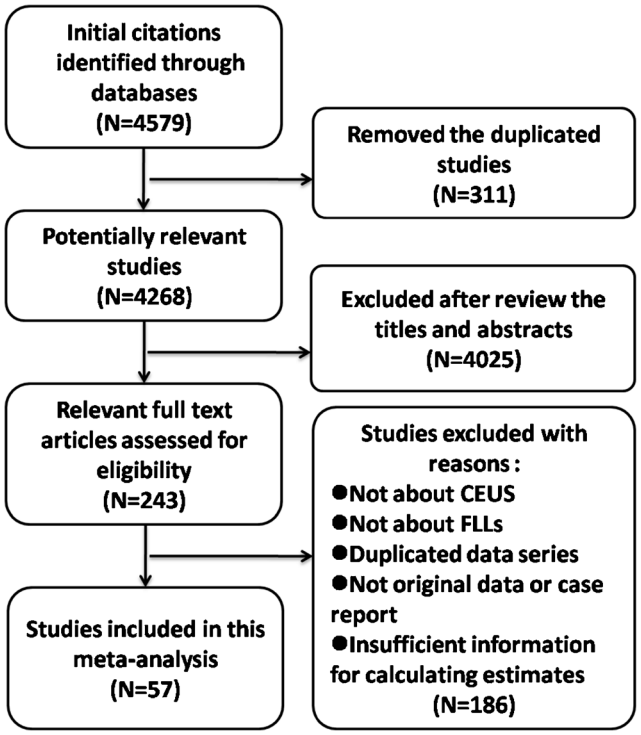

Fig. 1 Flow chart of the study selection process

Characteristics of eligible studies

Basic characteristics of eligible studies are presented in Table 1 with the publication year from 2001 to 2017 (Fig. 2A). 35 studies were conducted in Western countries (10 from Germany, 9 from Italy and 16 from other Western countries), and the remaining 22 studies were conducted in Asian countries (10 from China, 8 from Japan and 4 from other Asian countries; Fig. 2B). The numbers of both patients and lesions varied from 30 to 1328. The average age of the included patients ranged from 13 (one study conducted in paediatric patients) to 70. Most of the malignant lesions were hepatocellular carcinomas (HCCs) and liver metastases, and most of the benign lesions were haemangiomas and regenerative or dysplastic nodules. The first-generation contrast agent (Levovist) was used in 12 studies, and the second-generation contrast agents were utilized in the other 45 studies [39 studies used SonoVue, 4 studies used Sonazoid (a particular US contrast agent, which has late liver-specific phase) and the remaining 2 studies used Definity and Optison]. QUADAS scores are also summarized in Table 1.

Diagnostic accuracy

The pooled sensitivity and specificity of CEUS for characterization of FLLs were 0.92 (95%CI: 0.91–0.93), and 0.87 (95%CI: 0.86–0.88), respectively (Fig. 3). The pooled PLR and NLR of CEUS were 7.38 (95%CI: 5.86–9.31) and 0.09

Table 1 The characteristics of eligible studies

First author	Year	Country	Number of patients	Number of lesions	Gender (male/female)	Average age (year)	Average size (mm)	Final diagnosis (ML/BL)	Contrast agent	2×2 table				QUADAS score
										TP	TN	FP	FN	
Kondo [10]	2017	Japan	98	98	59/32	61	41	67/31	Sonazoid	63	27	4	4	10
Gatos [1]	2015	Greece	52	52	25/27	50	NA	22/30	SonoVue	20	27	3	2	10
Shan [13]	2015	China	83	83	62/21	52	ML (50); BL (39)	56/27	SonoVue	51	22	5	5	11
Quaia [14]	2014	Italy	46	55	20/26	55	20	22/33	SonoVue	21	30	3	1	8
Ryu [15]	2014	Korea	48	50	37/11	58	NA	44/6	SonoVue	37	5	1	7	9
Sporea [16]	2014	Romania	525	536	317/208	59	35	344/192	SonoVue	295	165	27	49	9
Zhang [17]	2014	China	NA	120	NA	NA	ML (34); BL (26)	112/58	SonoVue	104	52	6	8	10
Jacob [18]	2013	England	44	44	23/21	12	30	1/43	SonoVue	1	42	1	0	12
Hohmann [12]	2012	Switzerland	99	99	42/57	59	33	53/46	SonoVue	53	41	5	0	11
Streba [19]	2012	Romania	112	112	69/43	NA	NA	73/39	SonoVue	69	35	4	4	12
Anaye [20]	2011	Belgium	145	146	82/63	63	ML (50); BL (30)	113/33	SonoVue	110	3	3	30	10
Bartolotta [21]	2011	Italy	142	174	49/53	49	33	5/169	SonoVue	5	164	5	0	10
Giorgio [22]	2011	Italy	40	40	NA	60	NA	25/15	SonoVue	23	0	0	2	9
Strobel [23]	2011	Germany	318	329	NA	NA	NA	163/166	SonoVue	152	126	40	11	12
Beaton [24]	2010	UK	127	127	68/59	NA	NA	77/50	SonoVue	71	50	0.5	6	10
Ooi [25]	2010	Singapore	73	82	55/18	64	27	50/32	SonoVue	43	29	3	7	9
Rognin [26]	2010	Switzerland	NA	146	NA	NA	NA	113/33	SonoVue	110	30	3	3	9
von Herbay [27]	2010	Germany	317	317	204/113	59	NA	209/108	SonoVue	188	107	1	21	9
Inoue [28]	2009	Japan	50	50	38/12	67	27	42/8	Levovist	35	8	0	7	12
Jang [29]	2009	Canada	59	59	43/16	56	NA	30/29	Definity	26	29	0	4	11
Liu [30]	2009	China	388	388	272/116	49	20	186/292	SonoVue	170	195	7	16	11
Moriyasu [31]	2009	Japan	190	190	NA	NA	NA	164/26	Sonazoid	162	23	3	2	10
Quaia [32]	2009	Italy	106	121	68/38	70	NA	72/49	SonoVue	64	34	15	8	9
Sugimoto [33]	2009	Japan	137	137	NA	NA	HCC (25); metastasis (35); hemangioma (28)	107/30	Sonazoid	104	28	2	3	8
Trillaud [34]	2009	France, Belgium, Czech Republic & Poland	123	123	NA	NA	NA	55/68	SonoVue	54	60	8	1	10
Wang [35]	2009	China	148	164	106/42	40	NA	116/48	SonoVue	108	36	12	8	11
Zuber-Jerger [36]	2009	Germany	86	100	55/31	65	33	55/45	SonoVue	54	42	3	1	11
D'Onofrio [37]	2008	Italy	128	207	80/48	46	23	106/101	SonoVue	102	97	4	4	12
Hatanaka [38]	2008	Japan	74	113	47/27	70	17	108/5	Sonazoid	103	4	1	5	11
Shiraishi [39]	2008	Japan	97	103	NA	NA	NA	87/16	SonoVue	85	15	1	2	10
Strobel [40]	2008	Germany	1328	1328	NA	NA	NA	755/573	SonoVue	723	476	97	32	12
Wang [41]	2008	China	52	67	34/18	NA	41	12/55	SonoVue	11	50	5	1	9
Catala [42]	2007	Spain	77	77	45/32	62	35	57/20	SonoVue	52	18	2	5	9
Celli [43]	2007	Italy	125	171	NA	NA	NA	94/77	SonoVue	91	77	0.5	3	8
Dai [44]	2007	China	456	554	295/161	55	NA	346/208	SonoVue	314	172	36	32	11
Jung [45]	2007	Germany	100	100	57/43	57	NA	59/41	SonoVue	58	37	4	1	12
Quaia [46]	2007	Italy	215	236	151/64	62	NA	96/170	SonoVue	79	84	56	17	9
Xu [47]	2007	China	112	126	88/24	43	NA	48/78	SonoVue	45	74	4	3	12
Leen [48]	2006	UK	127	134	77/50	59	28	82/52	SonoVue	76	45	7	6	9
Nicolau [49]	2006	Spain	152	152	76/76	60	28	102/50	SonoVue	100	41	9	2	8
Wang [50]	2006	China	30	30	20/10	55	15	18/12	Levovist	17	8	4	1	9

Table 1 (continued)

First author	Year	Country	Number of patients	Number of lesions	Gender (male/female)	Average age (year)	Average size (mm)	Final diagnosis (ML/BL)	Contrast agent	2×2 table				QUADAS score
										TP	TN	FP	FN	
Wu [51]	2006	China	79	129	NA	NA	31	101/28	SonoVue	96	27	1	5	10
Xu [52]	2006	China	200	200	142/58	50	20	114/86	SonoVue	105	81	5	9	9
Kim [53]	2005	Korea	75	75	57/18	57	27	41/34	Levovist	31	27	7	10	12
Bryant [54]	2004	UK & Germany	142	142	67/75	58	NA	88/54	Levovist	80	47	7	8	11
Dietrich [55]	2004	Germany	174	174	94/80	54	NA	79/95	Levovist	79	88	7	0	11
Klein [56]	2004	Germany	39	42	25/14	56	46	29/13	Levovist	24	6	7	5	10
Peschl [57]	2004	Austria	62	62	NA	NA	NA	22/40	SonoVue	22	38	2	0.5	12
Quaia [58]	2004	Italy	452	452	253/199	64	NA	323/129	SonoVue	269	122	7	54	10
Suzuki [59]	2004	Japan	46	52	31/15	66	23	41/11	Levovist	37	10	1	4	9
von Herbay [60]	2004	Germany	124	126	65/59	59	NA	64/62	SonoVue	64	57	5	0	10
Isozaki [61]	2003	Japan	183	183	121/62	Male (65); female (64)	HCC (28); metastasis (34); hemangioma (41)	158/25	Levovist	157	22	3	1	12
Karabacakoglu [62]	2003	Turkey	45	57	21/24	NA	NA	35/22	Levovist	30	18	4	5	12
Strobel [63]	2003	Germany	90	101	NA	NA	NA	33/68	Optison	24	42	26	9	11
Beissert [64]	2002	UK & Germany	60	60	36/24	57	NA	40/20	Levovist	39	17	3	1	12
von Herbay [65]	2002	Germany	67	67	33/34	57	NA	40/27	Levovist	40	17	10	0	10
Fracanzani [66]	2001	Italy	41	41	30/11	62	NA	20/21	Levovist	19	15	6	1	10

TP true positive, *FP* false positive, *FN* false negative, *TN* true negative, *QUADAS* quality assessment tool for diagnostic accuracy studies, *NA* not available, *ML* malignant lesion, *BL* benign lesion, *HCC* hepatocellular carcinoma

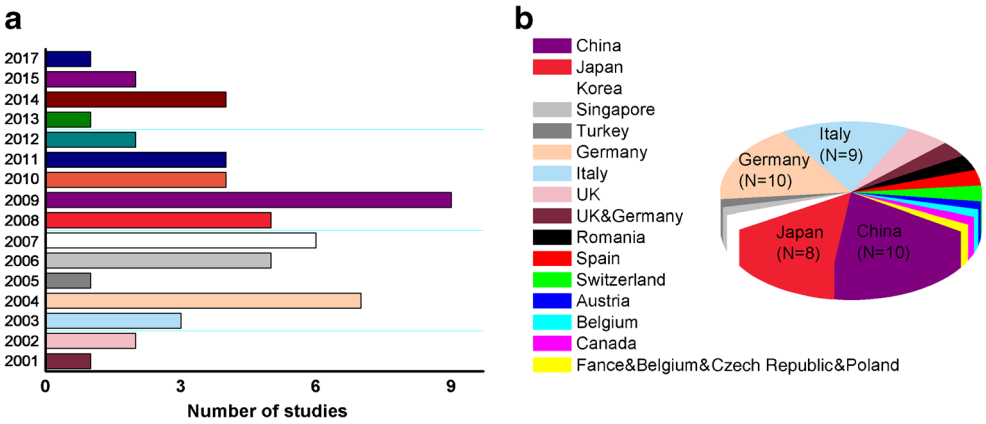

Fig. 2 Distribution of studies according to publication year (A) and country (B)

(95%CI: 0.07–0.11), respectively (Fig. S1). And the pooled DOR was 104.20 (95%CI: 70.42–154.16; Fig. S2). Figure 4 illustrates the SROC curve with AUC to be 0.9665. The Spearman correlation coefficient showed there was no significant correlation between sensitivity and specificity (r = -0.158, P = 0.242), which indicated no threshold effect.

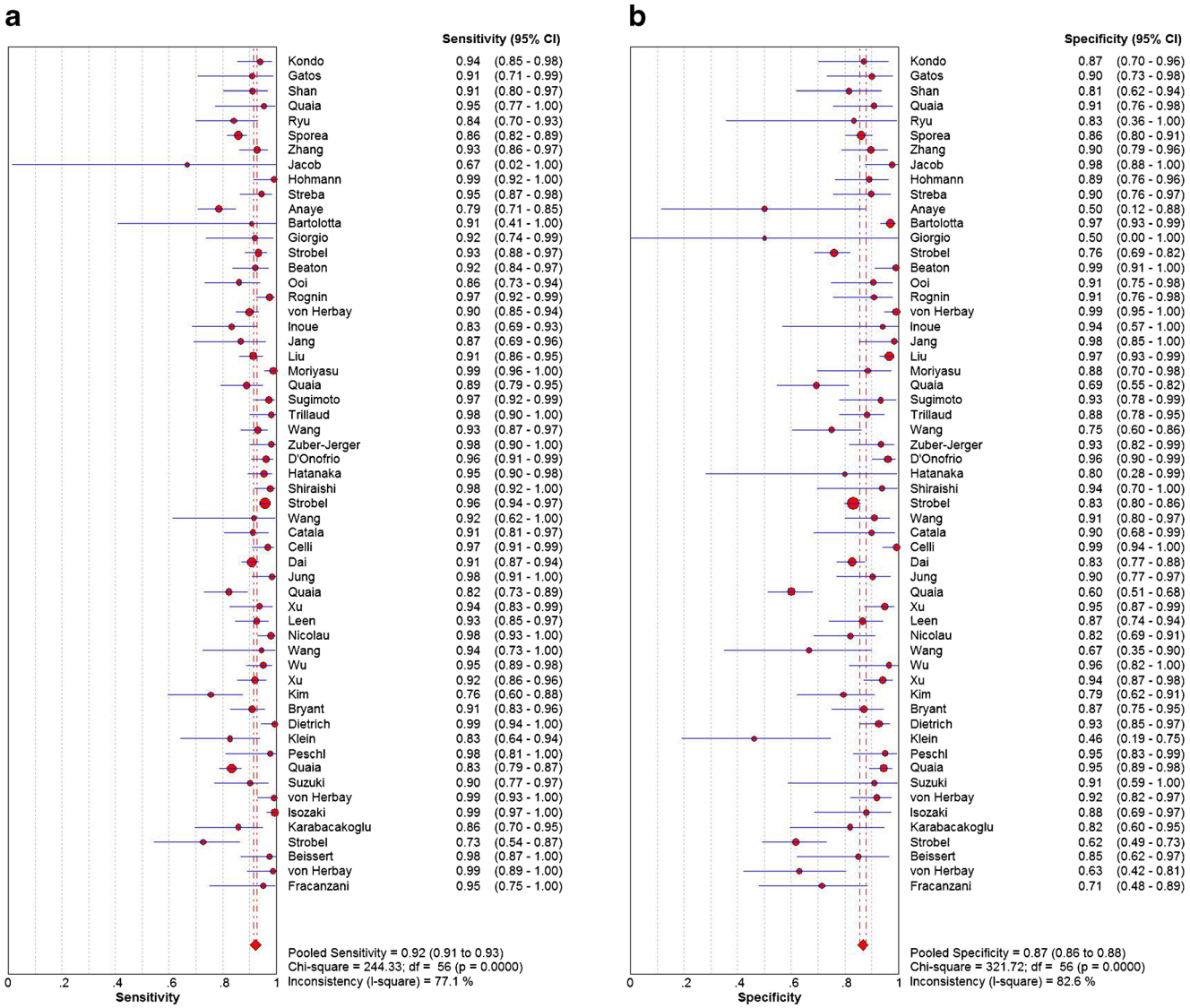

Fig. 3 Sensitivity (A) and specificity (B) for characterization of FLLs with CEUS

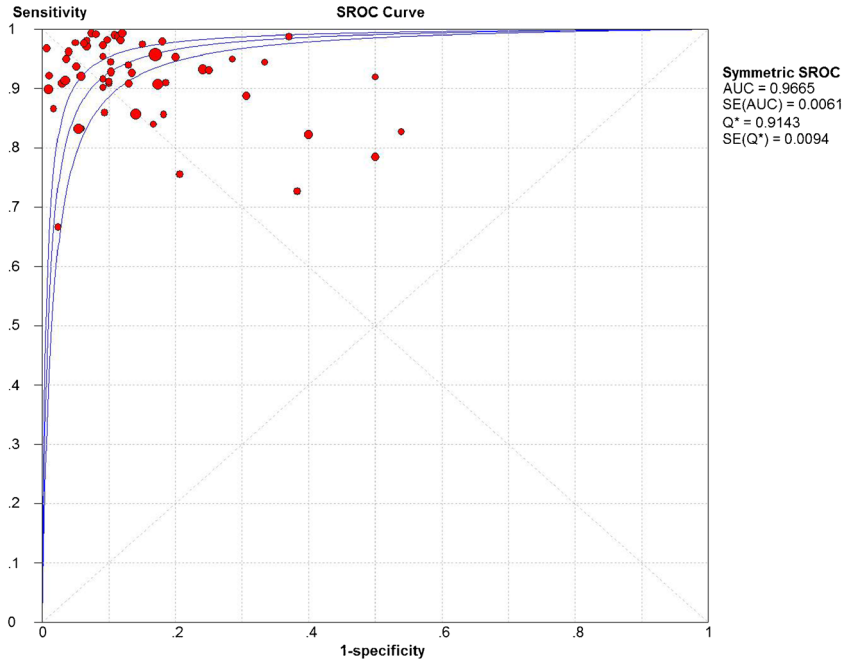

Fig. 4 Summary receiver operating characteristic curves

Subgroup and meta-regression analysis

Several potential factors were explored to illustrate their capabilities in affecting the diagnostic accuracy (Table 2, Fig. 5). Since the DOR is a single entity which combines the data from sensitivity and specificity, we calculated pooled DOR to present the diagnostic accuracy. As seen in Table 2, number of lesions and CA type used in CEUS both greatly influenced the diagnostic accuracy. The DOR value of the big-sample-size group (number of lesion ≥100) appeared more improved than the small-sample-size group (number of lesion < 100; 135.86 vs. 58.19). Heterogeneity was still observed in the big-sample-size group (I^2= 84.3%), while it was greatly reduced in the small-sample-size group (I^2= 39.1%). CA type also affected the diagnostic accuracy. Because Definity was only applied in one study, as was Optison, the pooled DORs of these CAs could not be calculated in subgroup analysis. After eliminating these two types, Sonazoid had the highest DOR (DOR = 227.39), while Levovist had the lowest DOR (DOR = 62.78). Even more remarkable was the fact that heterogeneity was almost eliminated in the Sonazoid group (I^2= 15.5%). Nevertheless, heterogeneity still existed in SonoVue and Levovist. When dividing the included studies according to different generations of CAs, the subgroup result demonstrated the second-generation CAs had higher diagnostic accuracy than the first-generation CA (Levovist; DOR: 118.27 vs. 62.78). However, heterogeneity still existed in both groups.

Meta-regression analysis was performed to take all the above factors into account. As shown in Table 3, none of the factors (including region, number of lesions and CA type) was the major source of heterogeneity.

Publication bias

Funnel plots were created to assess the publication bias of the eligible studies. As seen in Fig. 6, the plot was symmetric, indicating that there was no potential publication bias for the included studies (P = 0.630).

Discussion

The results of this meta-analysis showed that CEUS had excellent diagnostic capability in differentiating malignant from benign FLLs. The pooled sensitivity, specificity, DOR, PLR, NLR and AUC for CEUS in characterization of FLLs were 92%, 87%, 104.20, 7.38, 0.09 and 0.9665, respectively. Subgroup analyses demonstrated some factors might affect diagnostic performance such as number of lesions, CA generation and CA type.

Diagnostic performance of the big-sample-size group appeared greatly improved than the small-sample-size group (DOR: 135.86 vs. 58.19). The performance of CEUS is more strongly influenced by the experience of the sonographer compared with CT and MRI. The sonographers in large medical centers with adequate patients tend to have more professional experiences to distinguish FLLs for on-site reading in clinical practice [12].

Another major factor which greatly influenced the diagnostic accuracy of CEUS was the various kinds of CAs used in applications. Ultrasonic CAs have unique structures, consisting of inert gas and a shell molecule. Since the lifetime of air bubbles is very short, soft-shell materials are used to stabilize the

Table 2 Subgroup analysis of DOR of CEUS for the diagnostic performance of FLLs

Subgroup	Number of studies	Pooled DOR	95%CIs	I^2	*P* value
Region					
Western countries	35	108.53	62.22–189.32	82.6%	< 0.001
Asian countries	22	101.89	61.61–168.61	61.5%	< 0.001
Number of lesions					
< 100	22	58.19	33.28–101.74	39.1%	0.0322
≥ 100	35	135.86	82.51–223.71	84.3%	< 0.001
CA type					
SonoVue	39	118.82	76.85–183.72	77.6%	< 0.001
Sonazoid	4	227.39	84.73–610.30	15.5%	0.3143
Definity	1	-	-	-	-
Optison	1	-	-	-	-
Levovist	12	62.78	23.88–165.06	68.3%	0.0003
CA generation					
The first generation	12	62.78	23.88–165.06	68.3%	0.0003
The second generation	45	118.27	76.70–182.36	79.6%	< 0.001

CIs confidence intervals, *CA* contrast agent

CA, as well as improve the nonlinear oscillation. The terms "first- and second-generation ultrasound CA" are usually used to differentiate CAs, which are determined by different kinds of inert gas [7]. Though that's a bit of a simplification, in fact, the development of a second generation of ultrasound CAs leads to near complete disappearance of first-generation CAs on account of greatly improved image quality and effectiveness [7, 67]. In our study, the first-generation CA (Levovist) was used in 12 studies, and the second-generation CAs were utilized in the remaining 45 studies. The first-generation CA (Levovist) was used between 2001 to 2009; then the second-generation CAs replaced it entirely. Subgroup analysis indicated higher diagnostic accuracy of the second-generation CAs than the first-generation CA, Levovist (DOR: 118.27 vs. 62.78). The perfect DOR of second-generation CAs illustrated CA upgrade benefited diagnostic efficacies of FLLs.

Among the second-generation ultrasound CAs, Sonazoid is a particular kind. The unique feature of Sonazoid is the

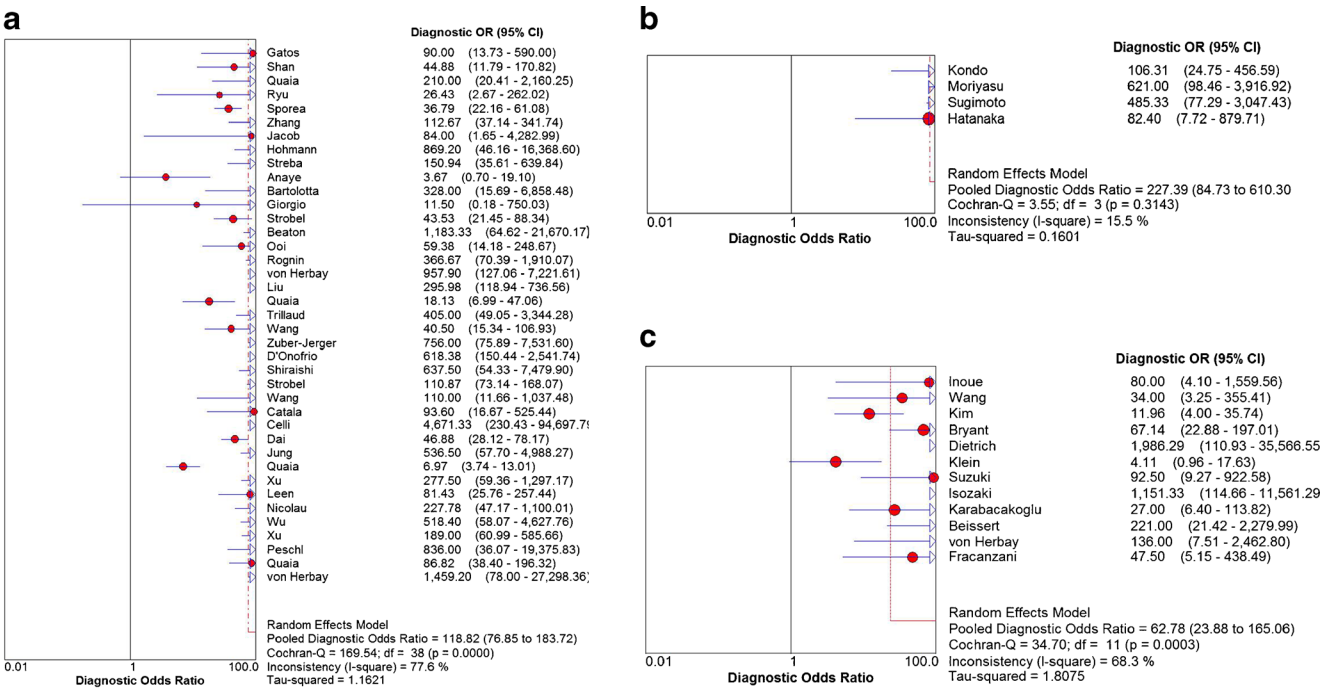

Fig. 5 Subgroup analysis of DOR for SonoVue (A), Sonazoid (B) and Levovist (C) in characterization of FLLs

Table 3 Meta-regression analysis of potential source of heterogeneity.

Potential sources	Coeff.	Std. err.	*P* value	RDOR	UL	LL
Region	0.125	0.4335	0.7737	1.13	0.47	2.71
Number of lesions	0.550	0.4736	0.2506	1.73	0.67	4.48
CA type	-0.339	0.2243	0.1366	0.71	0.45	1.12

Coeff. coefficient, Std. err. standard error, *RDOR* relative diagnostic odds ratio, *UL* upper limit, *LL* lower limit, *CA* contrast agent

accumulation property in the reticuloendothelial system (RES), such as liver and spleen [68]. This phenomenon might involve the Kupffer cells, which present in the hepatic parenchyma. As the Kupffer cells do not exist in malignant lesions, the contrast-enhanced images can easily elucidate the difference of contrast effect between the malignant lesion from normal parenchyma or benign lesion in the post-vascular phase (also known as Kupffer phase) [9, 69]. This late liver-specific phase lasts from around 6 to 10 min to over 60 min. The advent of Sonazoid has become a big breakthrough in CEUS practice of characterizing FLLs. However, it is only available in Japan, South Korea and Norway, so far [9]. SonoVue, another kind of second-generation CA, is widely used in most countries and regions [2]. In our meta-analysis, we evaluated the diagnostic value of CEUS in differentiating malignant from benign FLLs, meanwhile, different kinds of CAs were explored for their diagnostic capabilities. Since no comparative studies between Sonazoid and SonoVue are available at present, our study may offer an evidence-based basis for clinical practice. In our meta-analysis, the liver-specific contrast agent (Sonazoid) was only utilized in 4 studies, much less than SonoVue (utilized in 39 studies). Nevertheless, Sonazoid demonstrated the highest diagnostic accuracy among three major CAs (SonoVue, Levovist and Sonazoid) used in CEUS practice (DOR: 118.82 vs. 62.78 vs. 227.39). The above results revealed that Sonazoid was an outstanding CA; however,it still needs global research to verify its diagnostic ability. Marked heterogeneity was found among the different studies. To deal with this issue, the Spearman correlation coefficient, subgroup analyses and meta regression were combined to detect the sources of heterogeneity. Number of lesions and CA type might contribute to heterogeneity of included studies according to subgroup analyses. Heterogeneity was mainly observed in the big-sample-size group and non-Sonazoid group. However, synthetic regression analysis did not provide evidence supporting the above results. This might be due to the multivariate factors involved in this clinical diagnostic procedure we were unable to statistically analyse. For example, Fracanzani's [66] study indicated that the vascularity in a small nodule could not be easily assessed by CEUS. But since the data on small nodules couldn't be obtained in most of the eligible studies, the diagnostic value of CEUS for small FLLs could not be estimated. Given that, the heterogeneity within our study may have influenced the reliability of our results. There are some limitations in this meta-analysis. Firstly, the performance of CEUS is strongly influenced by the experience of the sonographer. Heterogeneity among studies might not be fully eliminated. Secondly, in obese patients, or when the lesion is very deep, the lesion might be difficult to assess. This intrinsic limitation of CEUS might decrease the diagnostic performance to some extent. Thirdly, US techniques have evolved over the last

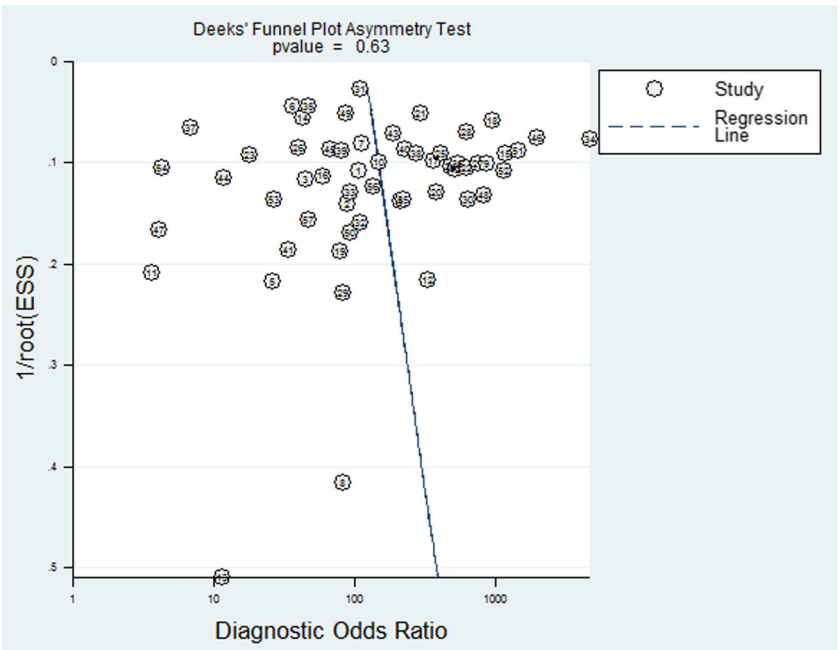

Fig. 6 Funnel plot for the evaluation of potential publication bias of included studies

decade; low mechanical index imaging along with phase inversion mode greatly improved spatial resolution [70]. This would result in significantly improved diagnostic capacity in recent studies compared to studies without these techniques. Lastly, meta regression failed to reveal the source of heterogeneity presented in this meta-analysis. The consequences might impact the credibility of this study, highlighting that further research is most pressing.

With regard to the above results, our meta-analysis indicates that CEUS has an outstanding performance in differentiating malignant from benign FLLs with both high sensitivity and specificity. The usage of second-generation CAs, especially Sonazoid, greatly promoted the diagnostic accuracy of CEUS. As CEUS becomes more widely available in the future, it's role will increase in managing patients with FLLs.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Xuening Zhang.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was not required for this study because the study concerns a meta-analysis.

Ethical approval Institutional review board approval was not required because the study concerns a meta-analysis.

Methodology
• diagnostic study
• performed at one institution

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