Review

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Diagnostic accuracy of contrast-enhanced ultrasound for detecting renal cancer: a systematic review and meta-analysis

Renfan Xu[1], Yunqi He[1], Xianghuan Xie[2], Guangzhi Chen[2]

[1]Department of Medical Ultrasound, [2]Division of Cardiology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Abstract

Aim: This systematic review and meta-analysis was designed to evaluate the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) in distinguishing renal cancers from benign renal masses. **Material and methods:** Meta-regression evaluated the sources of heterogeneity across studies and subgroup analyses for individual clinical classifications were conducted. Subgroup diagnostic performance for solid vs. cystic masses was also performed. The methodological quality evaluation was performed using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2). Publication bias was assessed using the Begg funnel plot and Egger's test. **Results:** Thirty-six articles involving 4,530 renal masses (3,221 malignant, 1,309 benign) were included in the analysis. The pooled sensitivity, specificity, PLR, NLR, and DOR were 0.94 (0.91–0.96), 0.85 (0.79–0.89), 6.24 (4.54–8.56), 0.07 (0.04–0.11), and 89.46 (51.66–154.94), respectively. The accuracy was 0.95 (0.93–0.97). I^2 values of sensitivity (I^2=95.91%) and specificity (I^2=80.43%) were both >50%. Subgroup analyses demonstrated that CEUS had higher sensitivity for cystic renal masses than solid renal masses (0.99 vs. 0.88), but lower specificity (0.80 vs. 0.87). No publication bias was found (p=0.123). **Conclusion:** This meta-analysis demonstrated that CEUS could be an excellent tool for differentiating between malignant and benign renal masses, particularly for cystic renal masses.

Keywords: contrast-enhanced ultrasound; diagnosis; meta-analysis; renal masses

Introduction

Increasing incidence rates of renal cancer have been reported worldwide [1]. Renal cell carcinoma (RCC), the 14th most frequently diagnosed cancer worldwide, is the most lethal genitourinary malignancy; it accounts for 3% of all adult neoplasms and 90–95% of renal cancer [2]. Preoperative diagnosis of noninvasive or early invasive carcinoma remains challenging due to the absence of specific radiologic or biochemical markers. Additionally, these cancers are often asymptomatic or patients typically present with nonspecific symptoms, except in the advanced stages of the disease. [3]. In fact, one-third of patients with newly diagnosed RCC had metastasis without any clinical symptoms, and 20–40% of patients with localized RCC developed metastasis [4]. Studies indicated that for patients with renal masses <4 cm, partial nephrectomy can lead to a cancer-specific survival rate exceeding 94% for five years. However, the survival rate of patients with advanced or metastatic renal cell carcinoma is significantly lower. A combination of immune check point inhibitors with tyrosine kinase inhibitors are associated with a median overall survival period of 46–56 months [1]. Therefore, early differentiation between benign and malignant masses is crucial for guiding treatment and may improve patients' long-term survival.

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Corresponding author: Guangzhi Chen
Division of Cardiology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095# Jiefang Ave., 430030, Wuhan, China
E-mail: chengz2003@163.com

Renal cysts, with an incidence rate of 50% in patients over 50 years, are often encountered in clinical practice; they can be divided into simple cysts and complex cysts [5]. Although the radiological diagnosis of simple cysts and clearly suspicious masses is straightforward, characterizing complex cysts can be challenging. Approximately 10% of RCCs present as complex cysts, and some benign renal cysts may also appear complex due to infection, hemorrhage, or ischemic changes within the masses [6]. Therefore, the differential diagnosis of benign cysts, especially complex cystic masses and cystic renal cell carcinoma, still poses significant challenges.

Conventional ultrasound (US) is the primary diagnostic tool for early detection of renal diseases due to its convenience, real-time imaging, non-invasiveness, low cost, and safety with no radiation exposure [7]. In these cases, conventional US is more suitable than magnetic resonance imaging (MRI) and computed tomography (CT) in early screening for renal diseases. However, the diagnostic accuracy of US for RCC is reportedly low [7]. In addition, although color Doppler US can provide valuable information regarding lesion vascularity, its effectiveness is often limited by factors such as location, or low blood flow velocity, especially in patients with cysts or hypovascular tumors [8].

In recent years, contrast-enhanced ultrasound (CEUS) has been widely adopted and proven to be highly effective [9]. CEUS enables both qualitative and quantitative assessment of macro- and microvascularization patterns within renal tumors, as well as evaluation of the blood supply and septal thickness in cystic masses [10].

Some studies have pointed that CEUS combined with conventional US can greatly improve the diagnostic accuracy of RCC, similar to the functions of CT and MRI, but in real time and free from ionizing radiation [11]. However, the significance of the features of CEUS in diagnosing renal cancer is still controversial and requires more research. Till date, several studies have been conducted to investigate the diagnostic accuracy of CEUS in distinguishing between malignant and benign renal masses. However, these studies had limited sample sizes and reported broad sensitivity and specificity. Hence, we performed this systematic literature review and meta-analysis as a more comprehensive and reliable analytic technique to evaluate the diagnostic accuracy of CEUS in distinguishing between malignant and benign renal masses.

Material and method

Data source and literature search

Eligible studies were identified by searching the PubMed, MEDLINE Embase, Cochrane Library and Web of Science databases comprehensively from their inception through March 1, 2025. Open published studies about CEUS for renal cancer diagnosis were collected. The search terms included combinations of keywords such as “contrast-enhanced ultrasound” or “contrast-enhanced ultrasonography” or “contrast-enhanced US” or “CEUS” or “enhanced ultrasound” or “contrast enhanced Doppler ultrasonography,” with terms like “renal carcinoma” or “renal tumor” or “renal neoplasm” or “renal mass” or “kidney tumor” or “kidney cancer” or “kidney carcinoma” or “kidney neoplasm” or “kidney mass”. We also manually searched the bibliographies of selected studies for further eligible publications.

Selection criteria

The two authors (XRF and HYQ) independently conducted literature search and research selection. In case of disagreement regarding the inclusion of a particular study, these were resolved through group discussions with the third review author (CGZ) until a consensus was reached. The inclusion criteria were: (1) prospective studies or retrospective studies in human patients aged 18 years and above; (2) related research on the differential diagnostic value of CEUS for malignant and benign renal masses; (3) malignant renal masses confirmed through pathology examination; (4) pathological findings or follow-up observation (>6 months) were used as the reference standard for the final diagnosis of benign renal masses; (5) published data must be sufficient to calculate the true-positive (TP), false-negative (FN), false-positive (FP) and true-negative (TN); (6) each study consisted of at least 20 samples; (7) full articles were available and written in English. We also conducted literature review and manual search by searching for identified reviews and abstract articles to expand the scope of our research. For duplicated data, the latest data result was used.

The exclusion criteria were: (1) studies not published in English; (2) incomplete data or duplicated publications; (3) non-comparative studies; (4) reviews, conference abstracts, case reports and any other unpublished articles.

Data extraction

Relevant data regarding the study were retrieved by two observers independently (XRF and HYQ): 1) study characteristics: first author, country, publication year, research design, reference standard, blind method, and the number of observations; 2) patient characteristics: mean age, sex, patient number, lesion number, lesion size, and final diagnosis; 3) CEUS characteristics: US equipment and the type and dosage of the contrast agents; 4) diagnostic accuracy: TP, FP, FN, and TN published in the four-fold (2×2) tables were collected. Disagreements were independently checked by another observer (CGZ) and resolved through consensus.

Quality assessment

Two authors (XRF and HYQ) independently assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool; this tool evaluates the risk of bias for four key domains: patient selection; index test; reference standard; and flow and timing [12]. To evaluate the risk of bias, each part was assessed. Any disagreements were resolved by a third researcher (CGZ).

Statistical analysis

All the statistical analyses were performed using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA software, Version 14.0 (StataCorp LLC, College Station, TX, USA). The pooled sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratios (PLR), and negative likelihood ratios (NLR) were extracted or calculated from individual studies.

Heterogeneity across the included studies was assessed using the inconsistency index (I^2) and Cochran's Q statistic. When I^2 >50% or P <0.10, there exists substantial heterogeneity, and the random-effect model was conducted to pool the included studies. Otherwise, the fixed-effects model was used. Afterwards, the summary receiver operating characteristic (SROC) curve and areas under curve (AUC) were analyzed[13]. Meta-regression analysis and subgroup analysis were performed to explore potential sources of heterogeneity[14]. Publication bias was assessed using the Begg funnel plot and Egger's test [15].

Results

Study selection

By searching with the predefined key words, a total of 1719 potential studies were retrieved. Of these studies, 686 records were removed as duplicates, 770 were excluded after reviewing the title and the abstract and 143 articles were reviews, editorials or protocols. Therefore, 120 full-text articles were assessed for eligibility. Thirty-five studies were excluded due to incomplete data, 8 studies only published an abstract and 41 studies did not meet the inclusion criteria. Finally, 36 studies were included in this meta-analysis. The selection process is outlined in the PRISMA flow diagram (fig 1).

Study characteristics

The detailed patient characteristics of all 36 articles with 37 studies are listed in Table I. The included articles, published between 2007 and 2024, assessed a total of 4530 renal masses (1390 benign and 3221 malignant) in 4458 patients [16-51]. Eighteen studies included solid masses only [17,20-24,27,31-36,39,44,45,50,51], 8 studies included cystic masses only [16,25-27,40,42,46,47], and 11 studies included both solid and cystic masses [18,19,28-30,37,38,41,43,48,49]. Elbanna et al included two independent sections exploring the role of CEUS in both renal solid masses and renal cystic masses [27]. Eleven studies prospectively enrolled patients [16,23,25,26,29,30,32,38,42,43,51] and 26 studies used retrospective enrollment [17-22,24,27,28,31,33-37,39-41,44-50]. Twenty three studies were conducted in Asia [20-25,28,29,31-36,39,43-48,50,51] and 14 studies were conducted in Western countries [16-19,26,27,30,37,38,40-42,49]. Twenty one studies used histopathology as the sole reference standard [17,22-24,27,28,30,31,33-37,39,41,43,44,46,47,50], while 16 studies combined pathological findings with imaging follow-up as the true standard [16,18-21,25,26,29,32,38,40,42,45,48,49,51]. Thirty studies [16,19-26,28,30-42,44-48,50,51] used Sonovue only as the contrast agents, 5 studies used other contrast agents (Definity or Sonazoid) [17,18,27,29] and 2 studies used both Sonovue and other agent [43,49]. The mass numbers were more than or equal to 100 in 17 studies [18,21-24,27,30,33,35-37,41,43-45,47,50] and less than 100 in 20 studies [16,17,19,20,25-29,31,32,34,38-40,42,46,48,49,51]. The mean sizes were larger than 3cm in 18 studies [16,22,25-28,30,32,33,35,36,40,42,43,46,47,50,51] and smaller than 3cm in 13 studies [17,19,20,23,27,29,37-39,41,44,48,49]. The studies utilized a variety of ultrasound instruments, primarily consisting of General Electric (GE), Siemens, and Philips models, with most probes set at 1–5 MHz. The mean/median age of patients ranged from 31–77 years.

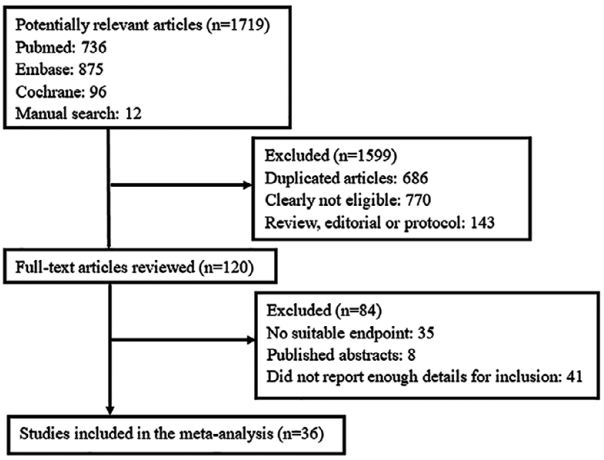

Fig 1. Study flow chart of the meta-analysis.

Study quality

All included studies were assessed using the QUADAS-2 tool (table II). In the domain of patient selection, one study was judged to be at high risk of bias due to the inclusion of nonconsecutive patients [35] an-

Table I. Characteristics of the studies included in this meta-analysis.

Author	Year	Country	Study design	No. patient	Mean age (y)	Male/ female	No. lesions	Mean size of lesions (cm)	Renal mass type	Contrast agent	Contrast Dosage (ml)	Instrument	Diagnosis standard
Ascenti	2007	Italy	prospective	40	31-77	23/17	44	3.5	complex cystic	SonoVue	2.4	Esaote	histopathology and follow up
Atri	2015	Canada	retrospective	91	62±14	56/35	94	2.7	solid	Definity	0.2	Acuson, Philips, Toshiba	histopathology
Barr	2014	USA	retrospective	265	NA	NA	306	NA	solid and cystic	Definity, Optison	0.3 3	Philips, Siemens	histopathology or follow up
Bertolotto	2015	Italy	retrospective	47	65±13	38 / 9	47	2.6	solid and cystic	SonoVue	1.2-2.4	Philips, Siemens, Esaote	histopathology or follow up
Cai	2014	China	retrospective	73	56.3±12.2	45/28	73	2.9	solid	SonoVue	1-1.8	Siemens	histopathology and follow up
Cai	2021	China	retrospective	519	55.3±13.1	278/241	519	>0.5	solid	SonoVue	1-2.4	Siemens, GE	histopathology and follow up
Cao	2020	China	retrospective	165	60.5 ±12.4	122/43	172	3.9	solid	SonoVue	1.6-2.4	Toshiba	histopathology
Chen	2015	China	prospective	99	56.6± 16.5	66/33	102	1.8	solid	SonoVue	1.2	Siemens	histopathology
Dai	2019	China	retrospective	163	59.2 ± 13.3	108/55	163	NA	solid	SonoVue	1.2	Toshiba	histopathology
Das	2023	India	prospective	40	49.5±2.7	32/8	40	3.1	complex cystic	SonoVue	2	Aixplorer	histopathology or follow up
Defortescu	2017	France	prospective	47	64.7(37-76)	30/17	47	3.8	complex cystic	SonoVue	1.2	Siemens	histopathology and follow up
Elbanna-a	2021	Canada	retrospective	29	NA	NA	29	3.5	complex cystic	Definity	0.2-0.3	Siemens	histopathology
Elbanna-b	2021	Canada	retrospective	158	58.7±15.2	101/57	161	2.3	solid	Definity	0.2-0.3	Siemens	histopathology
Fang	2021	China	retrospective	71	58.2±13.1	45/26	73	3.2	solid and cystic	SonoVue	1.5-2.0	Philips, GE, Siemens	histopathology
Hashimoto	2019	Japan	prospective	18	61.3±10.7	15/3	19	<2	solid and cystic	Sonazoid	NA	GE	histopathology or follow up
Ignee	2010	Germany	prospective	143	66±12	83/60	137	5.3	solid and cystic	Sonovue	2.4	Siemens	histopathology
Kuang	2024	China	retrospective	97	NA	NA	97	NA	solid	Sonovue	1.4	Philips	histopathology
Li	2008	China	prospective	71	53.6±11.2	41/30	72	3	solid	Sonovue	0.8	Siemens	histopathology and follow up
Li	2013	China	retrospective	91	62± 15.6	66/25	100	3.3	solid	SonoVue	1-1.2	Siemens	histopathology
Liu	2023	China	retrospective	67	60	48/19	69	NA	solid	SonoVue	1.2-1.8	Canon, Mindray	histopathology

Author	Year	Country	Study design	No. patient	Mean age (y)	Male/ female	No. lesions	Mean size of lesions (cm)	Renal mass type	Contrast agent	Contrast Dosage (ml)	Instrument	Diagnosis standard
Lu	2012	China	retrospective	123	48±18.4	74/49	123	4.4	solid	Sonovue	1.2,2.4	Philips Esaote	histopathology
Lu	2015	China	retrospective	174	47.2±20	106/68	174	3.6	solid	SonoVue	1.2	GE	histopathology
Marschner	2020	Germany	retrospective	255	62±13	NA	255	2.2	solid and cystic	SonoVue	1.0-4.8	Philips, GE, Siemens	histopathology
Nicolau	2015	Spain	prospective	72	64.2(34-85)	50/22	83	2.1	solid and cystic	Sonovue	2.4	Siemens	histopathology or follow up
Oh	2014	Korea	retrospective	49	61(37-83)	35/14	49	2.9	solid	SonoVue	NA		histopathology
Quaia	2008	Italy	retrospective	40	62±11	18/22	40	4.3	complex cystic	SonoVue	2.4	Siemens, Esaote	histopathology and follow up
Rübenthaler	2018	Germany	retrospective	255	62± 13	NA	255	2.2	solid and cystic	SonoVue	1.6-2.4	Philips,Siemens	histopathology
Sanz	2016	Spain	prospective	66	67.8	48/18	66	3.9	complex cystic	SonoVue	2.4	Hitachi	histopathology and follow up
Tian	2017	China	prospective	367	53.2±9.7	246/121	378	4.3	solid and cystic	Bracco and SonoVue	1.2	Siemens	histopathology
Wei	2017	China	retrospective	118	52.8 ± 11.2	73/45	118	2.8	solid	SonoVue	1.6-2.4	Siemens	histopathology
Xu	2010	China	retrospective	119	42.9± 11.9	80/39	126	NA	solid	SonoVue	2.4	Siemens, Toshiba	histopathology or follow up
Xu	2013	China	retrospective	87	45.3±17.5	51/36	87	4.9	complex cystic	SonoVue	1.2	GE	histopathology
Xue	2014	China	retrospective	103	50.7±12.1	67/36	103	4.7	complex cystic	SonoVue	1.2,2.4	Philips, GE, Esaote	histopathology
Yong	2016	Singapore	retrospective	63	62.4±14.5	39/24	74	2.8	solid and cystic	SonoVue	1.5	Philips, Toshiba	histopathology or CT/MRI or follow up
Zarzour	2017	USA	retrospective	41	58.6±12.7	NA	41	2.9	solid and cystic	Definity or SonoVue	0.8-2.4	Philips	histopathology or follow up
Zhao	2023	China	retrospective	181	54.4±11.2	140/41	184	3.8	solid	SonoVue	1.0-2.4	Mindray	histopathology
Zhou	2011	China	prospective	51	37(34-72)	17/34	51	3.4	solid	Sonovue	1.5-2.4	Siemens	histopathology or follow up

NA: not available ; No. : number.

done study was marked as having an unclear risk, because it did not explicitly report consecutive patients [51]. In the domain of the index test, eight studies were rated as "unclear" because blinding was not reported [17,18,29,33,36,37,39,42]. The reference standard domain posed challenges in 21 studies, as combining pathological results with follow-up findings may introduce a high risk of bias [16,18-21,23,25,26,29,32,33,38,40-45,48,49,51]. In the flow and timing domain, 17 studies were rated as having a high risk of bias due to the absence of specific information on the interval between the index test and the reference standard [16,18-21,23,25,26,29,32,38,40,42,45,48,49,51]. Regarding applicability concerns, all studies were judged to be at low risk across the domains of patient selection, index test, and reference standard.

Table II. Quality assessment of the studies according to QUADAS-2.

Author	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ascenti 2007	Low	Low	High	High	Low	Low	Low
Atri 2015	Low	Unclear	Low	Low	Low	Low	Low
Barr 2014	Low	Unclear	High	High	Low	Low	Low
Bertolotto 2015	Low	Low	High	High	Low	Low	Low
Cai 2014	Low	Low	High	High	Low	Low	Low
Cai 2021	Low	Low	High	High	Low	Low	Low
Cao 2020	Low	Low	Low	Low	Low	Low	Low
Chen 2015	Low	Low	High	High	Low	Low	Low
Dai 2019	Low	Low	Low	Low	Low	Low	Low
Das 2023	Low	Low	High	High	Low	Low	Low
Defortescu 2017	Low	Low	High	High	Low	Low	Low
Elbanna 2021	Low	Low	Low	Low	Low	Low	Low
Fang 2021	Low	Low	Low	Low	Low	Low	Low
Hashimoto 2019	Low	Unclear	High	High	Low	Low	Low
Ignee 2010	Low	Low	Low	Low	Low	Low	Low
Kuang 2024	Low	Low	Low	Low	Low	Low	Low
Li 2008	Low	Low	High	High	Low	Low	Low
Li 2013	Low	Unclear	High	Low	Low	Low	Low
Liu 2023	Low	Low	Low	Low	Low	Low	Low
Lu 2012	High	Low	Low	Low	Low	Low	Low
Lu 2015	Low	Unclear	Low	Low	Low	Low	Low
Marschner 2020	Low	Unclear	Low	Low	Low	Low	Low
Nicolau 2015	Low	Low	High	High	Low	Low	Low
Oh 2014	Low	Unclear	Low	Low	Low	Low	Low
Quaia 2008	Low	Low	High	High	Low	Low	Low
Rübenthaler 2018	Low	Low	High	Low	Low	Low	Low
Sanz 2016	Low	Unclear	High	High	Low	Low	Low
Tian 2017	Low	Low	High	Low	Low	Low	Low
Wei 2017	Low	Low	High	Low	Low	Low	Low
Xu 2010	Low	Low	High	High	Low	Low	Low
Xu 2013	Low	Low	Low	Low	Low	Low	Low
Xue 2014	Low	Low	Low	Low	Low	Low	Low
Yong 2016	Low	Low	High	High	Low	Low	Low
Zarzour 2017	Low	Low	High	High	Low	Low	Low
Zhao 2023	Low	Low	Low	Low	Low	Low	Low
Zhou 2011	Unclear	Low	High	High	Low	Low	Low

L: low risk of bias, H: high risk of bias, U: unclear risk of bias, QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies.

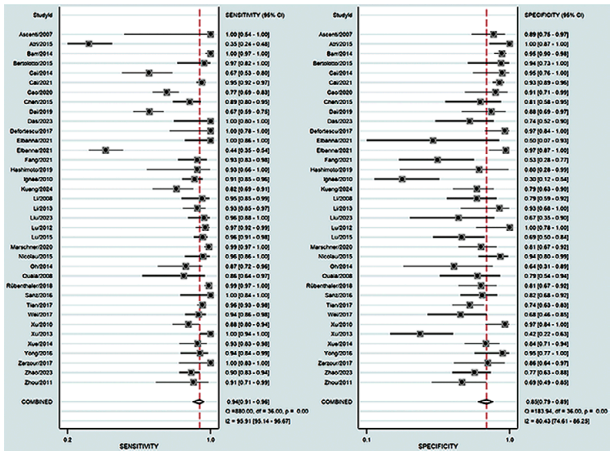

Fig 2. The forest plot showed pooled sensitivity and specificity of CEUS in the diagnosis of renal cancer: (A) The pooled sensitivity was 0.94 (95% CI, 0.91–0.96); (B) The pooled specificity was 0.85 (95% CI, 0.79–0.89). CEUS=contrast-enhanced ultrasound.

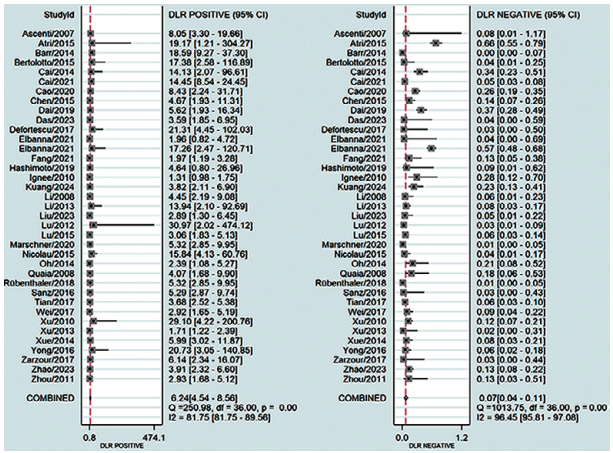

Fig 3. Forest plot showed positive likelihood ratios (PLR) and negative likelihood ratios (NLR) of CEUS in the diagnosis of renal cancer: (A) The pooled PLR was 6.24 (95% CI, 4.54–8.56); (B) The pooled DLR was 0.07 (95% CI, 0.04–0.11). CEUS = contrast-enhanced ultrasound.

Pooled analysis of diagnostic accuracy

Overall sensitivity of CEUS to detect renal cancer was 0.94 (95% confidence interval [CI], 0.91–0.96), specificity was 0.85 (95% CI, 0.79–0.89). Significant heterogeneity was found for sensitivity and specificity, and the I^2 values were 95.9% and 80.4%, respectively (fig 2).

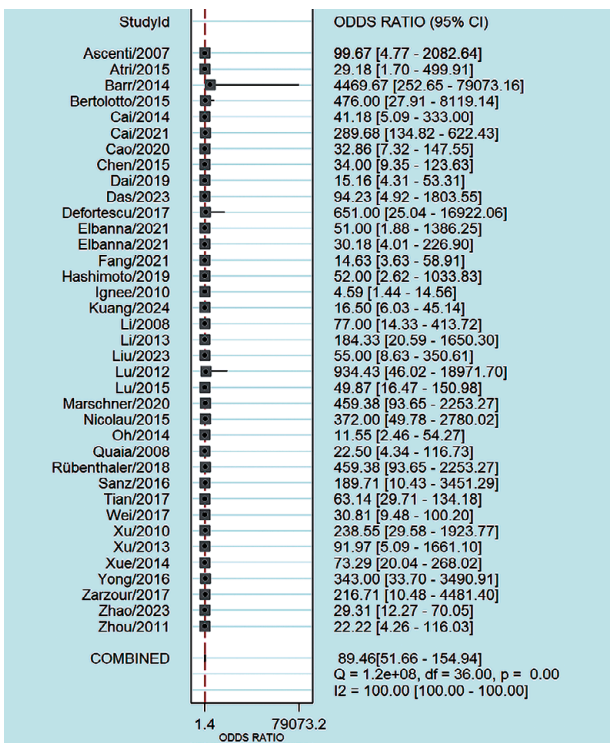

Fig 4. Forest plot showed diagnostic odds ratio 89.46 (95% CI, 51.66–154.94) of CEUS in the diagnosis of renal cancer. CEUS = contrast-enhanced ultrasound.

The pooled PLR, NLR, and DOR were 6.24 (95% CI, 4.54–8.56), 0.07 (95% CI, 0.04–0.11), and 89.46 (95% CI, 51.66–154.94), respectively. Significant heterogeneity was found for PLR (I^2=81.8%), NLR (I^2=96.5%) and DOR (I^2=100%) (fig 3, fig 4). The area under the subject receiver operating characteristic (SROC) curve was 0.95 (95% CI, 0.93–0.97) (fig 5).

Heterogeneity exploration

To explore the potential sources of heterogeneity in this meta-analysis, meta-regression analysis was con-

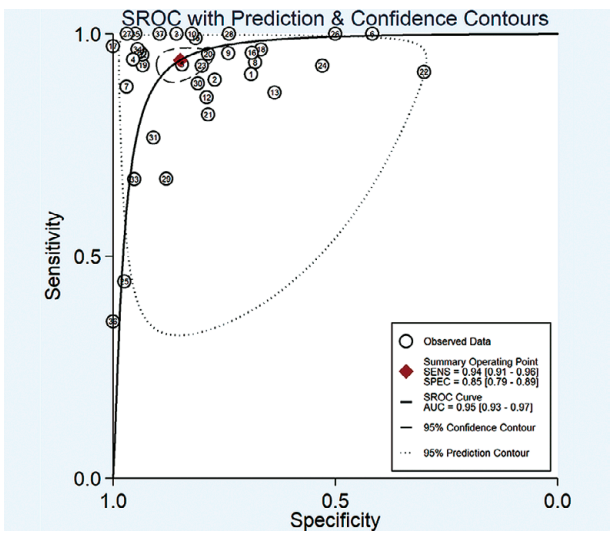

Fig 5. Summary receiver operating characteristic (SROC) curve for CEUS in the diagnosis of renal cancer (AUC 0.95 [95% CI, 0.93–0.97]). Each circle indicates one included study. AUC=area under the SROC curve; SENS=sensitivity; SPEC=specificity. Values in brackets are 95% confidence intervals.

ducted based on various covariates such as tumor nature (solid vs. non-solid), study design (prospective vs. non-prospective), continent of study origin (Western vs. non-Western country), diagnostic criteria (histopathology vs. non-histopathology), number of patients (⩾100 vs. <100), tumor size (≥3cm vs. <3cm), and contrast agent (SonoVue vs. non-SonoVue). According to meta-regression analysis, potential sources of heterogeneity were identified as including research design, tumor size, tumor nature, number of patients, diagnostic criteria and contrast agent (fig 6).

Sensitivity analysis was also performed to explore potential sources of heterogeneity by sequentially excluding one study at a time. This analysis showed no significant changes in heterogeneity for sensitivity, specificity, accuracy, or DOR. The detailed results of the sensitivity analysis are presented in Supplemental Table I (on the journal site).>

Subgroup analyses

Due to the existence of significant heterogeneity across the whole analyses, subgroups were analyzed depending on the tumor nature, predesign, country, diagnostic criteria, tumor number, tumor size, and contrast agent type. CEUS had higher diagnostic value when using histopathology and follow-up as the assessment criteria (sensitivity: 0.92, specificity: 0.96, AUC: 0.95), compared to when only histopathology was used as the criterion (sensitivity: 0.94, specificity: 0.72, AUC: 0.95). Subgroup analysis according to country revealed that CEUS was more powerful for diagnosing malignant renal masses in Western countries than in Asian countries (sensitivity: 0.98>0.92, specificity: 0.89>0.82, AUC: 0.97>0.94). CEUS for diagnosing nature of the tumor appeared to have higher accuracy in complex cystic masses than solid masses (sensitivity: 0.99>0.88, AUC: 0.96>0.94). Subgroup analysis according to the type of

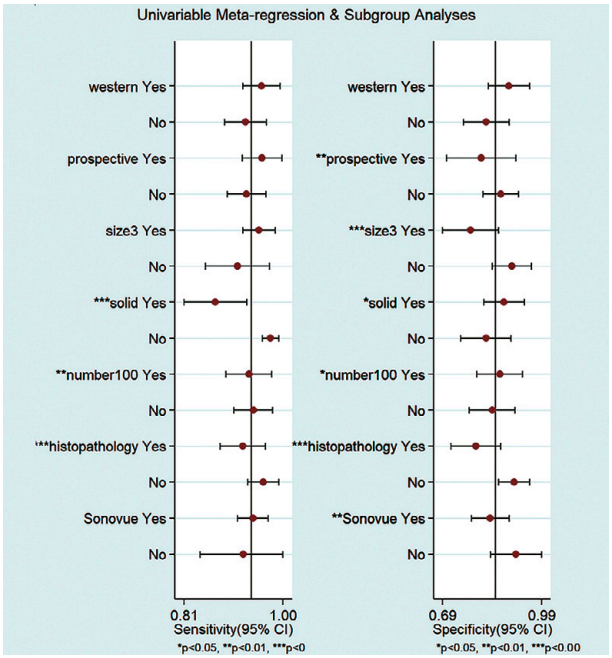

Fig 6. Univariable meta-regression analyses of the accuracy of CEUS in the diagnosis of benign and malignant renal tumors.

contrast agent revealed that CEUS was more powerful for diagnosing malignant renal masses when using a non-Sonovue agent than when using the Sonovue agent (sensitivity: 0.96>0.93, specificity: 0.95>0.86, AUC: 0.98>0.96). In addition, subgroup analysis results revealed that CEUS exhibited similar excellent diagnostic performance in the predesign, different tumor number, and tumor size subgroups. The results of these subgroup analyses are summarized in Table III.

Diagnostic accuracy of CEUS in solid lesions

Eighteen studies mentioned the diagnostic accuracy of CEUS in solid lesions. The summary of these studies generated a sensitivity of 0.88 (95% CI, 0.80–0.93,

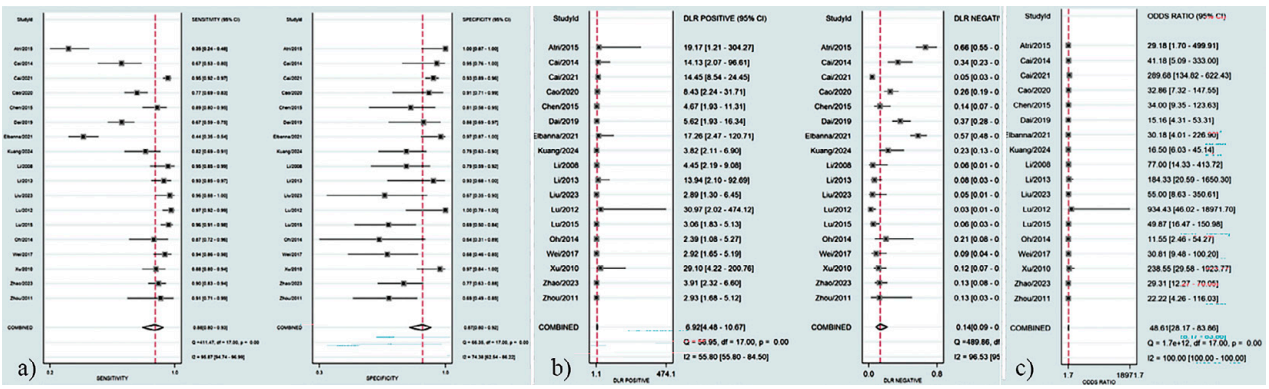

Fig 7. Forest plot showed pooled accuracy of CEUS in the diagnosis of renal cancer in the solid tumors: (A) The pooled sensitivity and specificity were 0.88 (95% CI, 0.80–0.93) and 0.87 (95% CI, 0.80–0.92); (B) The pooled PLR and DLR were 6.92 (95% CI, 4.48–10.67) and 0.14 (95% CI, 0.09–0.23); (C) The diagnostic odds ratio (DOR) was 48.61 (95% CI, 28.17–83.86)

Table III. Subgroup analyses of Sensitivity and Specificity for CEUS.

Subgroup	Study number	Number of participants	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PLR	NLR	DOR	I^2 for DOR
All combined	37	4530	0.94 (0.91-0.96)	0.85 (0.79-0.89)	0.95 (0.93-0.97)	6.24 (4.54-8.56)	0.07 (0.04-0.11)	89.46 (51.66-154.94)	100.00 (100.00-100.00)
Tumor nature									
Solid	18	2447	0.88 (0.80-0.93)	0.87 (0.80-0.92)	0.94 (0.91-0.95)	6.92 (4.48-10.67)	0.14 (0.09-0.23)	48.61 (28.17-83.86)	100.00 (100.00-100.00)
Complex cystic	8	456	0.99 (0.81-1.00)	0.80 (0.66-0.89)	0.96 (0.94-0.98)	4.93 (2.83-8.59)	0.01 (0.00-0.27)	353.97 (18.09-6926.05)	98.68 (98.29-99.07)
Solid and cystic	11	1627	0.98 (0.96-0.99)	0.82 (0.70-0.90)	0.98 (0.97-0.99)	5.56 (3.13-9.88)	0.03 (0.02-0.06)	185.91 (58.47-591.08)	100.00 (100.00-100.00)
Predesign									
Prospective	11	1039	0.95 (0.92-0.97)	0.80 (0.69-0.88)	0.96 (0.94-0.98)	4.79 (2.91-7.88)	0.06 (0.04-0.10)	77.77 (32.50-186.13)	100.00 (100.00-100.00)
Retrospective	26	3491	0.93 (0.88-0.96)	0.87 (0.80-0.91)	0.95 (0.93-0.97)	6.97 (4.69-10.34)	0.08 (0.04-0.14)	91.89 (48.54-173.95)	100.00 (100.00-100.00)
Country									
Asian	23	2966	0.92 (0.89-0.95)	0.82 (0.75-0.87)	0.94 (0.92-0.96)	5.07 (3.70-6.95)	0.09 (0.07-0.13)	54.19 (34.34-85.49)	100.00 (100.00-100.00)
Western	14	1564	0.98 (0.90-0.99)	0.89 (0.79-0.94)	0.97 (0.96-0.98)	8.86 (4.62-16.97)	0.03 (0.01-0.12)	329.79 (70.04-1552.89)	100.00 (100.00-100.00)
Diagnostic criteria									
histopathology only	21	2923	0.94 (0.92-0.96)	0.72 (0.61-0.82)	0.95 (0.92-0.96)	3.43 (2.37-4.95)	0.08 (0.05-0.11)	43.88 (25.10-76.72)	99.99 (99.99-99.99)
histopathology and follow up	16	1607	0.92 (0.86-0.95)	0.96 (0.89-0.98)	0.98 (0.96-0.99)	22.02 (8.44-57.41)	0.09 (0.05-0.15)	253.60 (98.25-654.59)	98.38 (98.03-98.73)
Lesion number									
≧100	17	3335	0.93 (0.88-0.96)	0.86 (0.78-0.92)	0.96 (0.93-0.97)	6.84 (4.27-10.96)	0.07 (0.04-0.14)	89.92 (40.30-200.61)	100.00 (100.00-100.00)
<100	20	1195	0.95 (0.89-0.97)	0.83 (0.75-0.89)	0.95 (0.93-0.97)	5.76 (3.73-8.62)	0.06 (0.03-0.13)	87.69 (40.37-190.49)	91.88 (89.30-94.45)
Tumor size									
≧3	18	1920	0.95 (0.92-0.97)	0.78 (0.68-0.85)	0.95 (0.93-0.97)	4.28 (2.93-6.24)	0.07 (0.04-0.11)	62.07 (32.34-119.15)	100.00 (100.00-100.00)
<3	13	1371	0.92 (0.87-0.97)	0.89 (0.82-0.94)	0.95 (0.93-0.97)	8.69 (5.21-14.48)	0.09 (0.04-0.21)	96.15 (41.31-223.81)	98.04 (97.54-98.54)
Contrast agents									
Sonovue only	30	3543	0.93 (0.90-0.95)	0.86 (0.78-0.91)	0.96 (0.94-0.97)	6.53 (4.09-10.42)	0.08 (0.06-0.12)	78.93 (45.85-135.88)	100.00 (100.00-100.00)
Non-Sonovue	5	568	0.96 (0.39-1.00)	0.95 (0.80-0.99)	0.98 (0.97-0.99)	19.60 (4.67-82.29)	0.04 (0.00-1.31)	485.89 (20.93-11279.87)	99.46 (99.30-99.61)

AUC= area under the curve; 95%CI=95% confidential ratio; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio.

I^2=95.87%) and a specificity of 0.87 (95% CI, 0.80–0.92, I^2=74.38%). The SROC with pooled AUC was 0.94 (95% CI, 0.91–0.95). The summary PLR and NLR were 6.92 (95% CI, 4.48–10.67, I^2=55.80%) and 0.14 (95% CI, 0.09–0.23, I^2=96.53%), respectively, while the DOR was 48.61 (95% CI, 28.17–83.86, I^2=100%) (fig 7, fig 8).

Diagnostic accuracy of CEUS in complex cystic lesions

Eight studies mentioned the diagnostic accuracy of CEUS in complex cystic lesions. The summary of these studies generated a sensitivity of 0.99 (95% CI, 0.81–1.00, I^2=70.94%) and a specificity of 0.80 (95% CI, 0.66–0.89, I^2=79.15%). The SROC with pooled AUC was 0.96 (95% CI, 0.94–0.98). The summary PLR and NLR were 4.93 (95% CI, 2.83–8.59, I^2=76.91%) and 0.01 (95% CI, 0.00–0.27, I^2=61.56%), respectively, while the DOR was 353.97 (95% CI, 18.09–6926.05, I^2=98.69%) (fig 9, fig 10).

Publication bias

According to Begg's funnel plot asymmetry test, there was no evidence of significant publication bias, as the included studies were symmetrically distributed (fig 11). This was further confirmed by Egger's linear regression analysis (t=1.58, p=0.123).

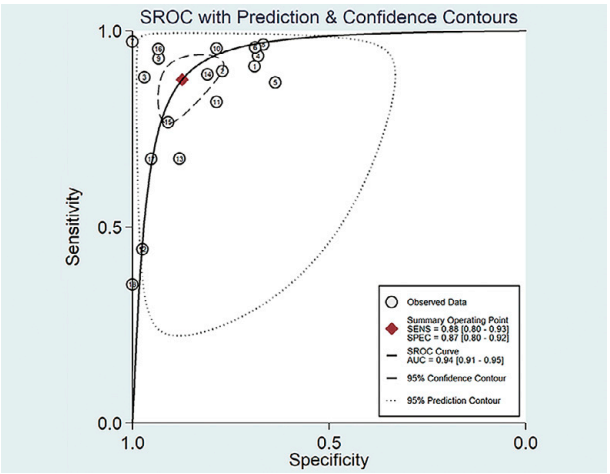

Fig 8. The summary receiver operating characteristic (SROC) curve for CEUS (AUC 0.94 [95% CI, 0.91–0.95]). CEUS = contrast-enhanced ultrasound.

Discussion

This systematic review and meta-analysis of 36 trials aimed at evaluating the diagnostic performance of CEUS in detecting renal masses. Overall, our meta-analysis revealed that CEUS has excellent performance with good sensitivity (94%) and specificity (85%) as well as a high diagnostic ability (AUC=0.95) in detecting renal cancer. Further analysis evidenced that CEUS has a high detection ability with a favorable DOR value 89.46 (95% CI, 51.66–154.94). This meta-analysis suggests that CEUS could be considered a valuable and reliable method for distinguishing and diagnosing renal masses.

In recent years, several systematic reviews and meta-analyses have evaluated the diagnostic performance of CEUS in accurately diagnosing renal masses [52-55]. The results of our study are consistent with those of most published studies. Liu et al demonstrated that CEUS has satisfactory diagnostic accuracy for clear cell renal cell carcinoma ≤ 4 cm [52]. Zhou et al evidenced that CEUS and MRI have good diagnostic performance for cystic renal masses. In addition, CEUS is more sensitive, but has less specificity than MRI [55]. Furrer et al concluded that CEUS may be at least as good, or even better, than CECT and CEMR for diagnosing renal masses [53] .

This review, which included only observational rather than comparative studies, represents a comprehensive synthesis conducted according to rigorous standards. However, some of the included studies lacked sufficient

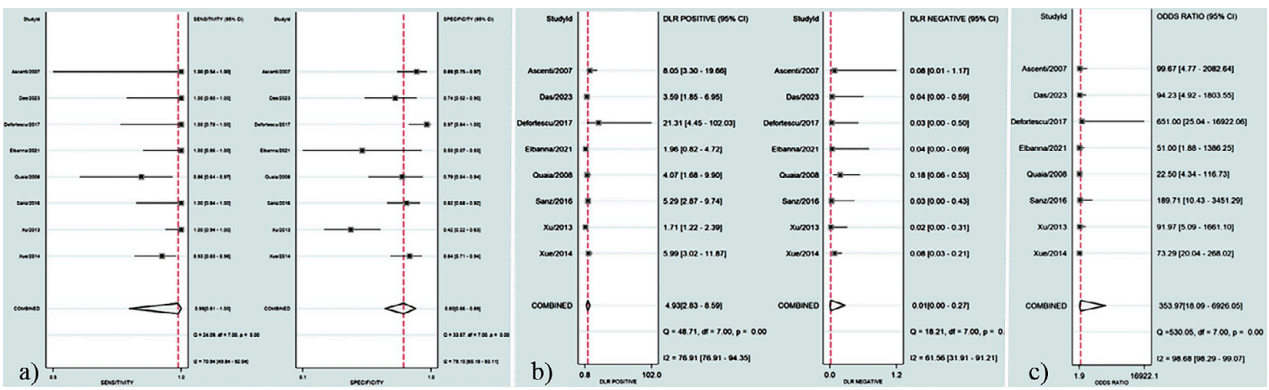

Fig 9. Forest plot showed pooled accuracy of CEUS in the diagnosis of renal cancer in the complex cystic tumors: (a) The pooled sensitivity and specificity were 0.99 (95% CI, 0.81–1.00) and 0.80 (95% CI, 0.66-0.89); (b) The pooled PLR and DLR were 4.93 (95% CI, 2.83–8.59) and 0.01 (95% CI, 0.00-0.27); (c) The diagnostic odds ratio (DOR) was 353.97 (95% CI, 18.09–6926.05).

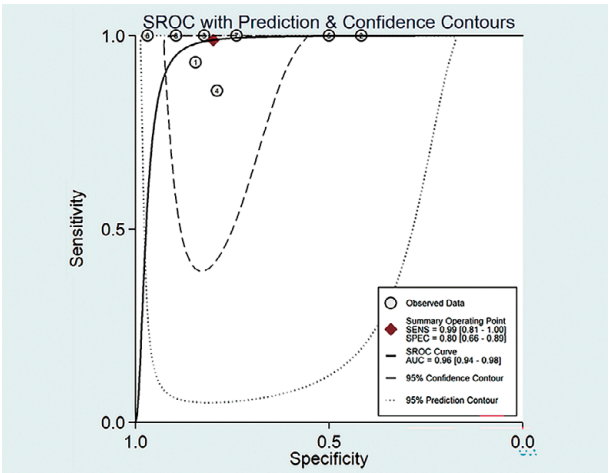

Fig 10. The summary receiver operating characteristic (SROC) curve for CEUS (AUC 0.96 [95% CI, 0.94–0.98]). CEUS = contrast-enhanced ultrasound.

methodological detail. For example, in the QUADAS-2 assessment, several studies were rated as "unclear" or "high" risk of bias due to issues such as combining histopathology and follow-up as reference standards or failing to report whether CEUS interpretation was blinded. These methodological limitations introduce potential bias that cannot be ruled out.

Although the funnel plot did not indicate statistically significant publication bias, some degree of bias was still present. Additionally, substantial heterogeneity was observed across the included studies, likely due to differences in patient characteristics, study design, and diagnostic protocols. This heterogeneity reduces the precision and reliability of pooled performance estimates. To explore these variations, we conducted meta-regression analysis. The analysis identified several key sources of heterogeneity, including tumor pathology (benign vs. malignant), study design, diagnostic criteria, sample size, and tumor size. Notably, studies conducted in Western countries demonstrated higher diagnostic accuracy than those from Asian countries (sensitivity: 0.98 vs. 0.92; specificity: 0.89 vs. 0.82), possibly reflecting regional differences in the etiologies and clinical presentations of renal masses. Given the known prognostic importance of tumor size in renal malignancies, we performed a subgroup analysis for lesions <3 cm. CEUS demonstrated comparable diagnostic accuracy for tumors <3 cm and ≥3 cm (sensitivity: 0.92 vs. 0.95; specificity: 0.89 vs. 0.78; AUC: 0.95 for both). These findings suggest that while larger tumors may increase sensitivity, they may also contribute to higher false-positive rates, reducing specificity. We also compared diagnostic performance based on the type of contrast agent used. Studies using Sonovue reported slightly lower diagnostic accuracy (sensitivity: 0.93; specificity: 0.86) compared to studies using other agents such as Sonazoid, Definity, or Optison (sensitivity: 0.96; specificity: 0.95). However, this finding should be interpreted with caution, as only five studies used non-Sonovue contrast agents, highlighting the need for further research. Finally, CEUS demonstrated better diagnostic performance in studies that used both histopathology and follow-up as reference standards (sensitivity: 0.92; specificity: 0.96) compared to those using histopathology alone (sensitivity: 0.94; specificity: 0.72). This may reflect reduced selection bias and inclusion of a broader range of benign and indolent lesions in the former group, thereby improving specificity.

Various conventional imaging modalities are used in the preoperative evaluation of renal masses, including US, CT, and MRI. CT exposes patients to ionizing radiation, and its iodinated contrast agents may cause allergic reactions or impair renal function [54] . MRI, while avoiding radiation, can be difficult to access due to the high cost and is contraindicated in patients with pacemakers or renal dysfunction [54,55]. CEUS has rapidly developed in recent years as a technique that objectively visualizes tissue perfusion. CEUS offers several advantages, including the absence of ionizing radiation, lack of nephrotoxicity, high temporal resolution, and superior signal-to-background ratio, enabling enhanced assessment patterns. It can accurately diagnose a variety of renal masses, such as complex cystic masses, solid renal tumors, focal inflammatory lesions, pseudotumors, and indeterminate masses, without requiring CT or MRI [56]. Furthermore, CEUS contrast agents, consisting of gas microbubbles, are eliminated through respiration and can be administered repeatedly without harming the kidneys [53]. However, CEUS has some limitations. It relies

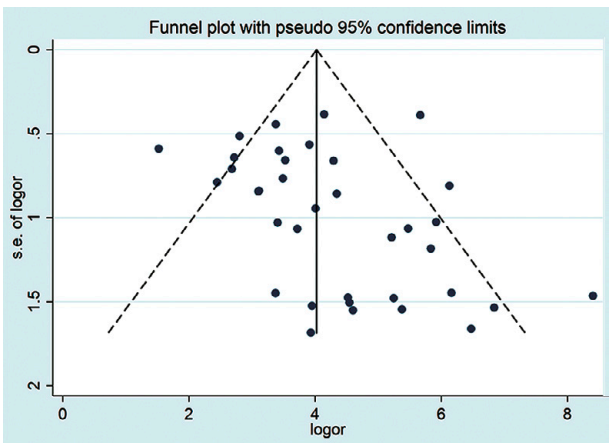

Fig 11. Begg funnel plot was described to show symmetric distribution of studies, indicating that there was no publication bias in meta-analysis.

heavily on the experience and skill of the operator, which may introduce subjective bias. Additionally, factors such as patient obesity, bowel gas, and imaging artifacts can affect the accuracy of CEUS results [57] .

Our analysis demonstrated that CEUS performs excellently in differentiating benign from malignant solid renal masses, with pooled sensitivity of 94%, specificity of 85%, and a high diagnostic accuracy (AUC=0.95). These findings align with those of previous meta-analyses [52,53]. CEUS can evaluate several tumor characteristics, including degree and pattern of enhancement, regression mode, enhancement uniformity, regression intensity, and the presence of a high-enhancement ring [11]. RCC typically appears as a heterogeneous mass with internal necrosis, hemorrhage, and calcification [1]. Variations in tumor size, pathology, and contrast agent type may result in some inconsistency in enhancement patterns across studies. Nonetheless, CEUS has distinct advantages over color Doppler US and CT, being more sensitive in detecting blood flow, especially in hypovascular lesions, and capable of identifying intralesional blood flow in nearly all solid masses [53,58].

Regarding cystic lesions, our analysis revealed high pooled sensitivity and specificity of CEUS (99% and 80%, respectively) and strong diagnostic performance (AUC=0.96), consistent with previous meta-analyses [54,55]. The Bosniak classification system, widely used for renal complex cystic masses, is primarily based on CT features such as cyst wall and septa thickness, lesion enhancement, calcifications, and solid components [59]. CEUS effectively detects contrast-enhanced features including the number of septae, wall thickness, and presence of solid cystic components due to its high sensitivity in detecting subtle enhancement of small blood vessels within masses [56]. Studies have also shown that CEUS outperforms contrast-enhanced CT and MRI in diagnosing complex cystic masses, particularly regarding these key diagnostic parameters [54,55].

This study has some important strengths: (1) this is a comprehensive review based on a large number of published studies, large sample sizes, and very strict criteria (such as reference standard), so our findings are more robust than previous individual studies (2) no significant publication bias was detected in our analysis, indicating that our research has high reliability and satisfactory quality. This also reflects the reliability of the inclusion criteria in this analysis.

Our meta-analysis also has some limitations. First, several included studies had relatively small sample sizes, which may reduce the reliability of the conclusions. Second, most studies were retrospective, with only a limited number of prospective studies, which could introduce potential selection bias and methodological limitations. Third, this meta-analysis included only studies published in English, potentially excluding high-quality research in other languages and introducing language bias. Fourth, although most renal cancers were confirmed by pathology, some studies used both pathological confirmation and follow-up as the reference standard, which may introduce selection bias. Fifth, significant heterogeneity was observed, which could affect the generalizability of our summary estimates. Although meta-regression was performed to explore sources of heterogeneity, these factors remain incompletely understood and may be influenced by various disease-related characteristics.

Conclusion

The results of this meta-analysis demonstrated that CEUS has excellent diagnostic accuracy as well as high sensitivity and specificity in distinguishing benign and malignant renal lesions. It provides additional diagnostic information, which is applied in clinical practice. These findings suggest that CEUS should be considered an important imaging tool for characterization of renal tumors. In summary, CEUS, as a new and constantly evolving adjuvant examination, has broad clinical prospects. Large-scale, well-designed trials are needed to evaluate its future clinical value.

Conflict of interest: none

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